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Intracranial EEG

A Guide for Cognitive Neuroscientists

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Chapter 39
What Are the Contributions and Challenges of Direct Intracranial Electrical Stimulation in Human Cognitive Neuroscience?

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Abstract Direct electrical stimulation (DES) is an old and powerful technique to causally inform about the localization of human brain function for clinical and research purposes. However, DES faces important challenges particularly in research: poorly known mechanisms and localization of the effects, methodological limitations due to clinical settings, etc. Through contributions of DES studies performed in the ventral occipito-temporal cortex, in particular to understand human face recognition, this chapter illustrates how future DES studies can overcome these challenges. At the methodological level, increasing the value of DES in cognitive neuroscience will depend on the use of well-controlled and diverse experimental paradigms across enough trials and stimulations to objectively evaluate DES effects. The combination of DES with independent or simultaneous measurements with functional magnetic resonance imaging and intracranial electroencephalography, particularly with frequency-tagging, offers new promises for causal objective mapping of brain function. Single or multiple subjects' studies are both well suited to this purpose, depending on the evaluated function and the frequency of observed effects. At a theoretical level, since it is now well established that DES affects remote brain regions, future DES studies should focus on assessing the connectivity of the critical sites to identify the network affected by the stimulation.

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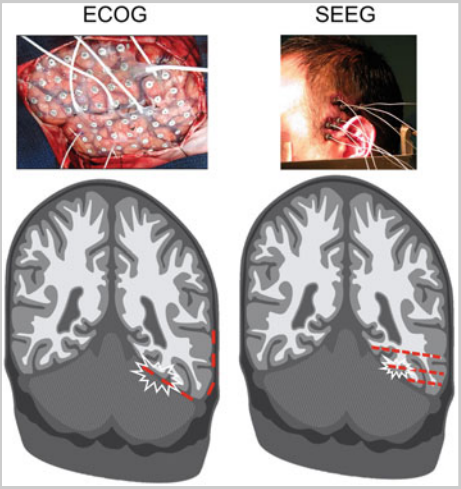
39.1 Introduction

Localizing and understanding sensorimotor and cognitive functions of the human brain are major goals in cognitive neuroscience. Among functional mapping techniques, the application of electrical current with an electrode to brain nuclei, to the cortex or white matter tracts, i.e., direct electrical stimulation (DES), holds a special place. Together with lesion studies, DES was one of the first methods used to investigate brain function, well before the advent of neuroimaging. Historically, DES provided to establish some of the foundations of modern neuroscience, such as the electrical nature of the brain, the localization of brain functions, and the functional anatomy of the sensorimotor cortex [1–3].

DES has also provided some of the most fascinating observations in human neuroscience (e.g., out-of-body experience [4]; self-face hallucination [5]). Most importantly for the purpose of this chapter, since it offers to draw a causal link between a specific brain region and a given function [6, 7], DES is often considered as the gold standard for functional localization, in particular for clinical purposes. That is, the rationale of DES is that applying an electrical current to the brain allows to temporarily disrupt the specific function of the stimulated region and therefore simulates what would be the behavioral effect if this region was removed or lesioned ("virtual lesion").

In practice, DES can be delivered extraoperatively via two types of intracranial electrodes in epileptic patients refractory to medication (Box 39.1): either intracerebral "depth" electrodes inserted inside the brain (stereo-electroencephalography, SEEG) or subdural electrodes applied onto the cortex after removing a part of the skull (electro-corticography, ECOG). DES can also be performed intraoperatively, mostly during brain tumor resection, by applying electrical currents over the cortex or the white matter via handheld probe electrodes [8]. In this chapter, we will focus on DES applied extraoperatively in epileptic subjects, i.e., through electrodes implanted intracranially for several days or weeks to define the localization and extent of epileptic seizures, allowing more carefully controlled stimulation procedures and concomitant electrophysiological recordings (intracranial EEG or iEEG).

Box 39.1: Two Types of Intracranial Approaches for Extraoperative DES in Epileptic Patients



ECOG consists in applying electrodes onto the cortical surface after craniectomy (i.e., subdural electrodes). Subdural electrodes have a circular shape and are spatially arranged as grids or strips with typically 5–10 mm inter-electrode spacing (center-to-center). SEEG consists in inserting needle electrodes inside the brain through small holes in the skull (i.e., depth electrodes). The current intracerebral electrodes are thin cylinders (e.g., 0.8 mm diameter) typically containing 8–15 contiguous individual recordings sites (or contacts) separated by an insulating material (3.5 mm spacing, center-to-center). From the point of view of fundamental research, each technique has its own advantages: while ECOG offers a more extensive spatial coverage, SEEG provides recordings and stimulations directly inside the grey matter and allows the specific exploration of cortical sulci, white matter, and deep structures (e.g., amygdala, hippocampus). The usual variables of electrical stimulation parameters are intensity, waveform, duration and frequency of the pulses, total duration and montage (bipolar or monopolar). The commonly used parameters of these techniques have been reported in previous reviews [9–14]. While the stimulation settings are similar between ECOG and SEEG, current intensities are lower in SEEG (0.5–5 mA compared to 1–20 mA in ECOG) in order to deliver similar charge density, and pulse duration is usually longer in SEEG. DES parameters in clinical practice remain insufficiently standardized with significant variations across epilepsy centers [15], which is an issue for DES

functional mapping (risk of false negatives and false positives, lack of reproducibility across centers and studies, etc.). In order to streamline DES procedure, French epilepsy centers published recommended stimulation parameters for SEEG [11]: bipolar and biphasic square wave current delivered either in low-frequency DES (frequency: 1 Hz, pulse duration: 0.5–3 ms, intensity: 0.5–4 mA, total duration: 20–60 s) or high-frequency DES (frequency: 50 Hz, pulse duration: 0.5–1 ms, intensity: 0.5–5 mA, total duration: 3–8 s). These 2 types of DES are recommended for functional localization, with low-frequency DES particularly well-suited for the primary cortices (especially the primary motor cortex) and to study functional connectivity, and high-frequency DES for the associative cortex. However, varying these parameters, beyond the usual recommendations but within the safety limits, produces differential neural effects that help to understand the physiology of the DES (e.g., [16]) and highlight some behavioural effects which may have been missed with standard settings; [17–20]; see also [21]). For example, a promising avenue for DES in the future would be to adapt stimulation parameters on the known physiology of the stimulated region or on individual electrophysiological analyses performed before DES (e.g., stimulation frequency matching the main endogenous oscillations of the stimulated site, [18]; theta burst stimulation parameters in the medial temporal lobe, [20], see also [22] for microstimulations).

Since cognitive functions are localized (to some extent) in specific brain regions and networks, stimulating discrete brain regions to observe behavioral consequences in real time represents a unique way to understand human brain function. Over several decades of investigation, DES with SEEG or ECOG has provided unique information about the anatomico-functional organization of the human brain [10, 13, 14, 23–26]. However, as early as the first DES studies on the motor cortex of dogs and non-human primates [1, 2], the relevance of DES effects to map and understand brain function has been debated, mainly because of the unknown effect of DES at local and distant sites. While it is sometimes claimed that "*if its rules of use are rigorously applied, the sensitivity of DES for detection of cortical and axonal eloquent structures is 100%*" [6], these claims have been criticized [27–29]. These criticisms are based on the fact that the physiology of DES is far from being fully understood, that DES effects could be due to the involvement of a large brain surface (both local and distant) and that these effects may be unpredictable, depending on local and remote factors. In sum, the danger of ignoring the complexity of DES may lead to oversimplistic and equivocal conclusions about the role of the stimulated region [29]. Moreover, since DES investigations in humans are performed in clinical settings with inherent limitations (e.g., limited testing time, limited number of experiments and trials, electrode positions based on clinical factors, patients with epilepsy or brain tumor, etc.), they are sometimes considered as anecdotical compared to other neuroscientific approaches, in particular recordings and stimulations performed in non-human primates [30, 31]. Therefore, despite the "gold standard" label for mapping brain function that is

still attributed to human DES nowadays in clinical settings, the technique faces a substantial number of challenges that need to be addressed.

In the present chapter, we first illustrate these challenges with DES studies applied to the human ventral occipito-temporal cortex (VOTC), one of the most explored regions in temporal epilepsy patients. Then, we illustrate how DES could overcome these challenges and provide a unique body of knowledge about the functions of the VOTC and the human brain in general. To do so, we build upon a specific research program with SEEG DES that aims at understanding arguably the most complex recognition function for the human brain, *face identity recognition* (FIR). In a last section, we survey the methodological and theoretical issues necessary for DES to overcome these challenges and to be considered as a key technique to understand the neural basis of human brain function.

39.2 Challenges of DES Studies in the VOTC

In humans, the VOTC supports many cognitive functions including visual recognition (through the ventral visual pathway), semantic memory (through the anterior temporal lobe), episodic and spatial memory (through the medial temporal lobe), and some language-related functions (mainly reading and naming through the left lateralized ventral visual pathway and the basal temporal language area, i.e., BTLA, respectively).

Recognition based on vision (considered as the dominant sensory modality in primates, humans in particular; see [32]) is of one most complex human brain functions, enabling us to quickly and automatically behave adaptively in a rich, dynamic and fundamentally ambiguous sensory environment. This function is supported by a network of brain regions in the VOTC, forming the ventral visual stream [33]. The ventral visual stream emerges from low-level (i.e., retinotopic) visual areas in the occipital lobe (e.g., V1, V2, V4, etc.) and continues through the ventral temporal lobe where higher-level category-selective areas (e.g., for faces, scenes, letters/words or other categories such as body parts) have been identified in neuroimaging studies over the past three decades [33, 34].

DES performed in the VOTC evokes either visual hallucinations (simple such as phosphenes or complex such as faces or scenes), illusions (e.g., distortions of the face being perceived during stimulation) or recognition impairments (for reviews, see [25, 35, 36]). These DES studies have supported the hierarchical organization of the ventral visual pathway [37–39] and showed the causal role of some category-selective areas in the recognition of their preferred category (faces: [40, 41]; written words: [42–44]; scenes: [45]). However, these latter studies are mostly considered as confirming the utmost importance of these regions in the dedicated functions that were already defined by neuroimaging or lesion studies. For example, recent ECOG DES studies have shown a causal link between the most studied and well-known face-selective area, i.e., the Fusiform Face Area (FFA, [46]; Fig. 39.1) in the lateral section of the middle fusiform gyrus (LatMidFG), and face perception

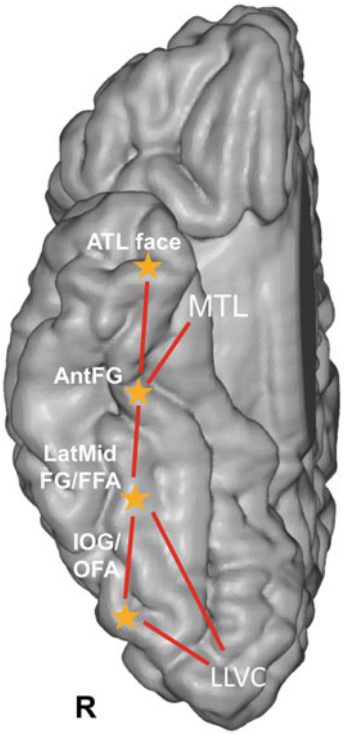


Fig. 39.1 Schematic illustration of the main VOTC face-selective regions (IOG/OFA, LatMidFG/FFA, AntFG and ATL face area) in the right hemisphere and of their hypothetical patterns of reentrant connectivity. FMRI and iEEG studies have recorded robust face-selective neural activity in these regions, except in the AntFG, in which face-selectivity has been disclosed only in iEEG recordings because of a strong BOLD signal drop-out affecting this region, making this region almost invisible in fMRI (see [97]). SEEG DES of the right IOG/OFA and AntFG have induced transient FIR impairment while SEEG DES to the LatMidFG has led to perceptual face distortion or palinopsia. According to a recent hypothesis [25], transient changes of the currently experienced face stimulus during SEEG DES of the right IOG and LatMidFG would be due to reentrant direct (i.e., monosynaptic) connections between these face-selective posterior regions and low-level (i.e., retinotopic) visual cortex (LLVC). In contrast, the face-selective AntFG is not directly connected to the low-level visual cortex (LLVC), but has direct connections with the medial temporal lobe (MTL), mainly the hippocampus, such that stimulation of the AntFG leads to transient failures to encode the visual stimulation experience in memory [98, 99]. Face-selective regions are shown at their approximate locations—considering a wide interindividual variability—as schematic yellow stars on a reconstructed cortical surface of the Colin27 brain

[30, 31, 40, 41]. By electrically stimulating the FFA in the right hemisphere, these studies reported either face-related perceptual changes (i.e., subjective change in the visual appearance of a face, usually a distortion of the experimenter's face in front of the subject) and face or face-part hallucinations. Although these studies showed that the FFA is causally involved in visually processing the category of faces, they provided no information about the specific role of the FFA in face recognition. Most

strikingly, while lesion studies, neuroimaging and intracranial recordings point to an important role of the (right) FFA and its neighboring VOTC face-selective areas in face *identity* recognition (e.g., [47–51]), impairment at this function during DES to the FFA has never been demonstrated (see [25]). Moreover, these ECOG DES studies were performed without well-controlled experimental set-up, essentially requiring subjects to passively look at real faces or objects in the room and describe their subjective experience, thus reinforcing the anecdotal reputation of DES studies in neuroscientific research. For this reason, these studies have offered no or very little contribution to neurofunctional models of human face recognition, which are somewhat paradoxically more influenced by findings in non-human primate recording studies [52]. In the same vein, observations of transient deficits in written word reading (alexia) during DES to a region of the left VOTC (potentially the so-called Visual Word Form Area, VWFA; [53]) have been rather anecdotic, i.e., reported without quantitative analyses of the behavioral effects and independent functional mapping [42, 44], or only briefly described in the context of extensive iEEG recording investigations [43, 54].

Another example of the limited impact of DES in the definition of VOTC functions is the study of the so-called BTLA, a functionally defined region based on DES effects observed at the interface between the ventral visual stream, the semantic system in the anterior temporal lobe (ATL) and the perisylvian language system [55]. DES performed on the left VOTC (inferior temporal gyrus, fusiform gyrus and parahippocampal gyrus) has consistently elicited deficits in naming (in both visual and authority modalities) but also in reading and comprehension [56–59] (for review see [10]). However, beyond the clinical community, the concept of BTLA and the information derived from DES of this region have so far generated little interest in fundamental neuroscience research, and the outcome of these studies is not included in theoretical frameworks of the anatomo-functional organization of language (e.g., [60, 61]). Despite relatively frequent effects of DES observed in this region, two factors at least have been brought forward to reduce interest in the BTLA. First, post-operative language deficits are either weak, inconsistent, or transient following resection of this region [57, 62, 63]. Second, DES studies have recorded distant post-discharges or cortico-cortical evoked potentials (CCEP), suggesting strong anatomico-functional connections between the BTLA and perisylvian language regions [64–66]. These two observations suggest that language-related deficits observed upon BTLA stimulation are due to remote rather than local effects of DES [29]. In short, studies on the BTLA provide a good example of the type of arguments raised against the validity of the information derived from DES and its ability to precisely map brain regions that are critical for cognitive functions.

39.3 DES to Understand Human Face Identity Recognition

39.3.1 Why Studying Face Identity Recognition with DES?

In its interaction with the environment, the brain is primarily a biological recognition system: it needs to provide selective/specific responses to sensory stimuli, these responses being generalizable across a wide variety of viewing conditions and temporal contexts. In primates and particularly in humans, the recognition[1] of faces is particularly rich and socially relevant, allowing to rapidly e.g., tell apart males and females, decode others' emotional states from their expression, estimate their age, infer their ethnical origin, their attention from head and gaze orientation, attractiveness and even make social judgments of dominance or trustworthiness [68, 69].

For several reasons, recognizing someone's *identity* from their faces, i.e., face identity recognition (FIR), is arguably the most challenging human recognition function, across the board. First, while individual human faces, even in a genetically homogenous population, appear to differ more than in other animal species [70], they nevertheless look similar in their basic features and configuration, requiring relatively fine-grained visual discrimination processes. Second, a given face identity can vary substantially in appearance across viewing conditions [71], requiring high level generalization abilities. Third, in most modern societies, the number of facial identities to recognize is very large, usually from several hundreds to thousands of individual faces [72]. Fourth, the number of identities to recognize is often undetermined, i.e., changes across different contexts and over time, with familiar faces mixed up among unfamiliar faces in various contexts.

Considering the challenge at stake, human adults' FIR is impressive, i.e., with up to thousands of face identities recognized accurately [72], automatically and at a glance (e.g., [73]). Yet, this challenge also explains why there is so much natural interindividual variability in this ability in the normal population [74], an ability that is easily disrupted in many neurological, neurodevelopmental and psychiatric disorders [75].

For long, knowledge of the neural basis of FIR relied on the localization of lesions in patients with prosopagnosia (a category-selective impairment in FIR; [76, 77]), these lesions being consistently found in the VOTC, with a right hemispheric dominance [49, 78–81]. However, cases of prosopagnosia are rare (at least when properly diagnosed to exclude general visual object agnosia or semantic memory disorders; see [77, 82]) and have usually large lesions that limit the spatial resolution of these investigations. Functional magnetic resonance imaging (fMRI) studies have shown reduced

[1] The term 'Recognition' is often used in psychological research to refer to the judgment of previous occurrence [67]. However, the term is used here in a general biological meaning to refer to the production of a selective (i.e., discriminant) response to a given sensory input, a response that can be reproduced (i.e., generalized) across variable viewing conditions. Defined as such, even the decision or response signaling that a visual stimulus is a face is a recognition function (i.e., generic face recognition).

neural activity when repeating (unfamiliar or familiar) pictures of the same facial identities as compared to different identities in several face-selective (i.e., responding more to faces than non-face objects) VOTC regions, most notably the FFA in the LatMidFG and the occipital face area (OFA, Fig. 39.1) in the inferior occipital gyrus (IOG) [50, 83–86]. However, fMRI studies analyzing pattern variations of neural activity across voxels for different face identities have only reported small and/or inconsistent effects across experiments, sometimes outside face-selective regions, casting doubt on the contribution of the FFA and other posterior face-selective regions of the VOTC to FIR and pointing instead to the ATL [87–91]. Moreover, directly contrasting pictures of unfamiliar and familiar faces rarely leads to consistent differences in face-selective VOTC regions, and may instead recruit widespread unspecific regions in the brain, probably because of the richness of semantic information linked to familiar faces [50, 89, 92].

In this context, DES of face-selective VOTC regions, which are largely specific to humans or hominoids [93, 94] and largely inaccessible to transcranial magnetic stimulation (TMS), may provide invaluable information regarding the neural basis of this complex FIR function. Moreover, the human face recognition function is thought to be highly specialized and localized but also supported by a vast network of bilateral VOTC regions (Fig. 39.1; [95, 96]), making it particularly amenable to DES.

Below we briefly describe the contribution of DES studies performed in the last decade in the context of SEEG as an example case of promises and challenges of human DES in cognitive neuroscience.

39.3.2 DES of the Right Face-Selective IOG Impairs FIR

The first case of transient FIR impairment with DES (i.e., "transient prosopagnosia") was reported ten years ago [100]. During stimulation of a right IOG region (Fig. 39.2a), subject KV reported various subjective experiences (e.g., *"the face does not appear to me as a single entity"*, *"the facial elements were mixed"*) although some stimulation trials on the same contacts did not lead to perceptual changes. Regardless of her perceptual experience, DES to the right IOG caused a sudden inability for KV to recognize the face identity in front of her (i.e., the neurologist, or photographs of famous faces). This effect was transient, in fact ending as soon as the stimulation stopped, and highly consistent across trials [100] (see also [25], with all videos of the stimulation trials).

At the time of this original observation, only relatively limited behavioral observations could be performed on the case of KV, all with familiar faces. However, about a year later, KV underwent a second SEEG to perform radiofrequency-thermolesions of the epileptic focus. An intracerebral electrode was again inserted in KV's right IOG, near the location of the previous critical stimulation site (Fig. 39.2b; [101]). A behavioral paradigm with simultaneously presented pictures of unfamiliar face identities appearing on a computer screen next to each other at each trial was designed,

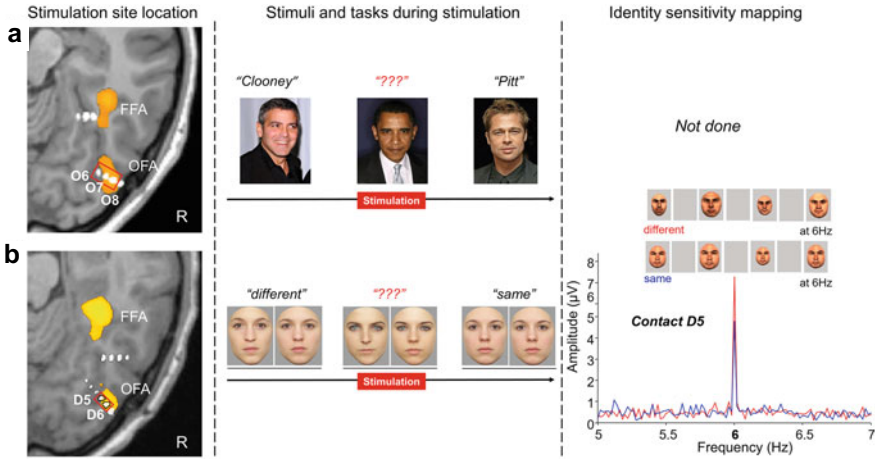


Fig. 39.2 Stimulating the face-selective right IOG induces transient prosopagnosia (subject KV). **a** Reprinted with permission from [100]. **b** [101]. In both studies, the left panel shows the fMRI face-selective activations in the right VOTC (axial slices) with the SEEG electrodes superimposed (white dots); the middle panel shows the stimuli presented during the stimulation procedure; the right panel shows SEEG recordings during a FPVS paradigm measuring sensitivity to face identity. In [100], the eloquent contacts O6, O7 and O8 (in the red rectangle) were located in the right face-selective IOG ("OFA") as shown by fMRI (shown here) and face-selective ERPs recorded on these contacts. Stimulation of these contacts induced a transient inability to recognize famous faces while object recognition was preserved. In [101], stimulating two contacts located within the right face selective IOG (D5/D6) evoked a transient inability to discriminate unfamiliar face identities. During SEEG, KV was tested with a FPVS adaptation paradigm measuring sensitivity to face identity at a fast rate of 6 Hz, with either identical faces or different faces [102]. The significantly largest difference for different versus same faces for upright faces was found on the critical contact D5 (right panel shows responses to different and same faces at 6 Hz in the frequency domain)

asking KV to determine whether they were of the same identity or not (Fig. 39.2b). To adjust the task to KV's excellent FIR ability (as pre-assessed with neuropsychological tests), faces that differed only by 40% along a morphed continuum were selected. While KV performed this task extremely well outside of stimulation, DES inside the face-selective right IOG led to systematic errors (i.e., answering "same" when different unfamiliar face identities were presented). She stated: *"I had a feeling of a strong resemblance*", "*there were two identical faces*", as if DES inside the right IOG interrupted her ability to grasp the physical differences between the two unfamiliar face identities. There was no visual distortion or rearrangement of facial elements reported ([101]; with videos of the stimulation trials). Sensitivity to unfamiliar face identity of each intracerebral contact was quantified independently in SEEG with a frequency-tagging approach (or Fast Periodic Visual Stimulation, FPVS) adaptation paradigm (fast periodic presentation of either different or same face identities; [102]) (see also Chap. 31 on frequency tagging in iEEG studies). Strikingly, among all electrode contacts implanted in KV's brain (N = 27), the largest face identity adaptation effect was recorded on the critical stimulation site (Fig. 39.2b).

These two successive reports of DES performed in the same brain region of the same patient [100, 101] at a one-year interval are not only unique to our knowledge, but they serve well to illustrate the progress that can be made in methodological control and systematicity as well as the refinement of hypotheses and correlations with independent electrophysiological measures to enrich the contribution of DES to our understanding of the neural basis of cognitive functions.

39.3.3 DES of the Right Face-Selective Anterior Fusiform Gyrus Impairs FIR

The anterior fusiform gyrus (AntFG) is located anteriorly to the LatMidFG/FFA but posteriorly to the ATL face area usually found in fMRI close to the temporal pole (Fig. 39.1). Unfortunately, little is known about its role in FIR mainly because this region is affected by a large BOLD signal drop-out arising from magnetic susceptibility artifact [97, 103, 104]. Consequently, only a handful of fMRI studies identified this region as face-selective (e.g., [105–107]). In contrast, large face-selective activity has consistently been reported with SEEG in this region [108, 109].

Transient impairment to recognize facial identity during right AntFG stimulation was reported initially a few years ago in a single case, CD (Fig. 39.3a; [98]). Upon DES to the right AntFG, CD was transiently unable to recognize any famous face picture presented. Visual object recognition was intact upon stimulation. As for subject KV, her behavioral impairment was clear, massive, and highly reproducible. After stimulation, CD said that she did not recognize the face identity, as if the face was shown for the first time. She did not report any perceptual change in the structure of the face. Subsequently, CD was unable to remember which were the face pictures presented during the stimulation, as if they did not enter her memory [98] (see also [25], with all videos of the stimulation trials).

As for the two successive observations on subject KV described above, this unique observation on CD was subsequently—recently—reproduced and extended by a behavioral investigation during right AntFG stimulation in another subject, ND (Fig. 39.3b; [99]). Based on the initial observation, multiple tasks that did not require a verbal output were designed, both with familiar and unfamiliar faces, quantifying performance in terms of both accuracy rates and response times. Upon stimulation of the right AntFG, DN was impaired at pointing out a familiar face among unfamiliar faces and at matching different pictures of the same identity, either familiar or unfamiliar. However, he had no difficulty at pointing famous names, and naming common objects and famous buildings. As for subject CD, DN never reported visual face-related changes, stating for example: "*I don't' know who he is*"; "*I don't know the 3 faces you showed me*", "*I had difficulties recognizing her*", "*I didn't recognize the face immediately*". DN also failed to remember all the visual items presented (face and non-face-items) during the stimulation. Sensitivity to unfamiliar face identity of each contact were measured independently with a FPVS paradigm [110, 111]. Again,

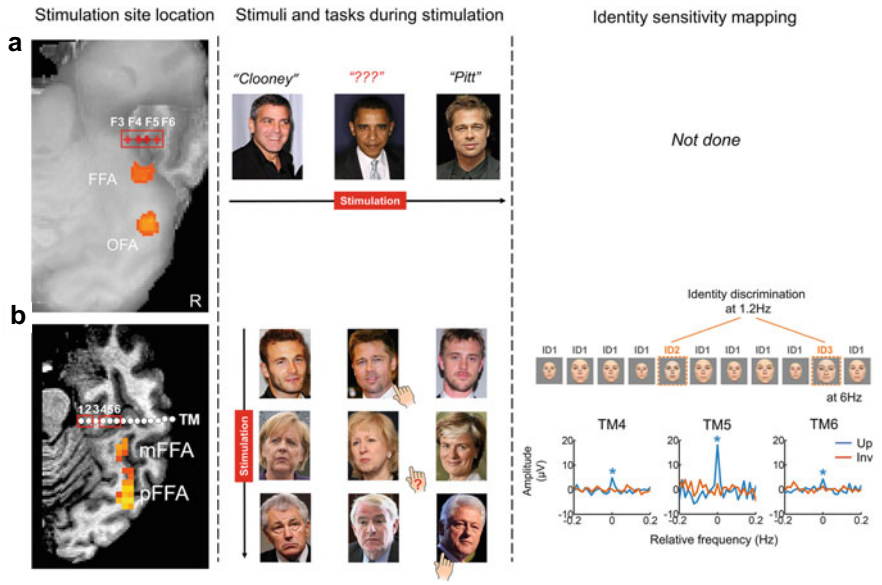


Fig. 39.3 Stimulating the right AntFG induces transient prosopagnosia. **a** Subject CD [98]. **b** Subject DN [99]. In both studies, the left panel shows fMRI face-selective activations in the right VOTC (axial slices) with SEEG electrodes superimposed (red crosses or white dots); the middle panel shows the stimuli presented during DES; the right panel shows SEEG recordings during a FPVS paradigm measuring sensitivity to face identity (for subject DN only, [110, 111]). **a** In subject CD, DES of contacts F3 to F6, located in the right AntFG, anteriorly to the FFA, induced a transient inability to recognize famous faces. Despite large face-selective responses in SEEG on these contacts, fMRI face-selective activations were not found because of a severe signal drop-out affecting the right AntFG (the left panel displays the raw functional images in light grey, showing the critical contacts being located in a region with very low fMRI signal). **b** In subject DN, DES of the same region (contacts TM1 to TM2 and TM4 to TM6) induced a transient inability to point out the familiar faces among unfamiliar faces (along with the inability to matching the identity of either familiar or unfamiliar faces). Again, no fMRI face-selective activations were found in the vicinity of the stimulation sites despite large SEEG face-selective responses recorded on these contacts. Of all the 141 recorded contacts in DN's brain, one of the critical contacts (TM5) recorded the largest face identity discrimination response amplitude in the upright condition (as well as the largest face inversion effect, i.e., upright-inverted) as measured by a FPVS paradigm (right panel shows the sum of identity discrimination responses at 1.2 Hz and harmonics centred on 0 Hz, in both upright and inverted conditions)

one of the few critical contacts recorded the largest neural face identity discrimination response (Fig. 39.3b; [99]).

39.3.4 DES to the FFA: Subjective and Objective Effects

The case studies presented above concern face-selective VOTC regions that are located posteriorly (IOG) and anteriorly (AntFG) to the FFA, which is not only, by far, the most studied and well-known face-selective human brain region [112], but also the right hemisphere region showing the most consistent and largest face-selective activity [108, 113]. However, to date, there has been no clear case of transient prosopagnosia following DES applied to this region. That is, DES with ECOG electrodes positioned over the right (but not the left) FFA have reported face-related perceptual changes and face or face-part hallucinations [30, 31, 40, 41, 114] (see also [115]) but without an objective FIR impairment (as only behaviorally tested by [40]; without any effect). With ECOG, these perceptual phenomena have been observed consistently enough to report studies in (small) groups of subjects (N = 8, [30]; N = 5, [114]), allowing to statistically demonstrate the prevalence of perceptual effects when stimulating on face-selective as compared to non-face-selective sites in the LatMidFG.

Importantly, two group studies have related DES to this region of the FFA (bilaterally) with objective face-related behavioral effects. Chong et al. [116] showed their participants (N = 8) ambiguous visual displays of a face and a house image superimposed in different transparency levels (Fig. 39.4a), asking them to recognize the images as face or nonface stimuli. This generic face recognition performance significantly decreased with brief (550 ms) electrical stimulation of the bilateral LatMidFG relative to no stimulation. The DES effect was small but significant thanks to the inclusion of several subjects and electrode contacts in the study. Moreover, subsequent analyses showed that this impairment by DES was confined to face-selective electrodes, with the amount of interference being positively correlated with the degree of face-selectivity of the electrodes as determined with iEEG (event-related potentials, ERPs).

Extending these findings, [117] applied DES to electrophysiologically face-selective sites of the bilateral LatMidFG in six subjects, and showed significant increases in response time at detecting whether a face stimulus was (slightly) distorted or not (Fig. 39.4b) (see also Chap. 40). The effect was also confined to face-selective sites defined independently, with no effect found for DES to neighboring non-face-selective (i.e., place-selective) regions. Importantly, response times were increased only when DES was applied 100 ms after visual onset (compared to 200 ms before or 500 after this onset), a latency that corresponds remarkably well to the onset time of face-selective activity in this region [117] (see also [118, 119]).

Unlike most of the above-cited studies reporting face-related perceptual changes (e.g., [31, 40]), these latter two studies did not localize the FFA in fMRI, measuring instead face-selectivity with independent electrophysiological recordings. Moreover, they used only brief stimulation durations. However, both of these studies provide a more systematic methodologically controlled approach to the effect of DES in the VOTC on human face recognition, here limited to the recognition of a visual stimulus as a (normal) face.

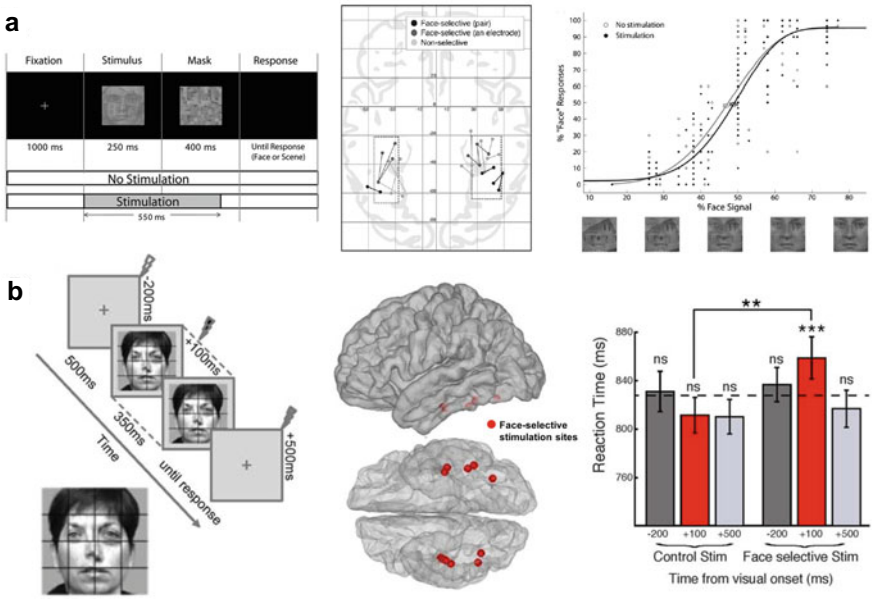


Fig. 39.4 Objective generic face recognition impairment during DES of the LatMidFG as assessed by quantitative measurements. For the 2 studies illustrated here, the left panel shows the experimental computerized paradigm during DES, the middle panel the location of the stimulated electrodes and the right panel the quantitative behavioral measurements across subjects. **a** Adapted from [116] with permission. Subjects (N = 8) had to decide whether compound stimuli mixing a certain percentage face and scene images were a face or a house while brief DES (550 ms) was applied to LatMidFG sites. Compared to no stimulation or stimulation of non-face-selective sites, DES of face-selective sites of the LatMidFG electrodes impaired categorization of the stimulus as a face, as shown by a small but significant increase of the point of subjective equality. **b** Adapted from [117] with permission. Subjects (N = 6) had to decide whether a face stimulus was distorted or not with DES applied to either face-selective and control (non-face selective) regions at −200, 100, and 500 ms with respect to the face presentation (face-selective sites are shown in red in a brain template). Only DES to face-selective sites and applied 100 ms after the face presentation induced a response time increase at the judgment of face distortion

How about face *identity* recognition linked to the FFA? To date, only one case of DES to the FFA apparently affecting FIR has been reported, with SEEG: subject MB who, during stimulation in this region of the right hemisphere experienced facial *palinopsia*, i.e., hallucinations of facial elements appropriately incorporated in the face identity in front of her [120]. MB experienced this phenomenon for the faces of a clinician or of an experimenter in front of her ("*I saw you with eyes and ears which were not yours*"). Although she stated that the superimposed features were those of a familiar face, she was unable to determine the identity of that face. She was also tested more systematically with photographs, stating, for example, that "*the photograph of Sarkozy* [former French president, first presented face picture during stimulation] *was transposed onto the other face identity* [second presented face picture during

stimulation]". MB never reported aberrant facial configurations, and reproducibly stated that the facial structure was preserved ("*it was a normal face*"). Although MB was not tested behaviourally with unfamiliar faces during DES, the sensitivity to unfamiliar face identity of each contact was also measured independently with a frequency-tagging paradigm [110, 111]. Again, strikingly, of all the 137 recorded contacts, the critical contact in the right LatMidFG recorded, by far, the largest neural face individuation response [120].

39.3.5 What Can Be Learned from DES in Face-Selective VOTC Regions?

In summary, following anecdotal observations of the effect of DES on face-selective VOTC regions in the context of extensive and detailed reports of iEEG recordings [121, 122], a number of studies performed over the last decade (since [100]) have focused on the effects of DES on perceptual experience, behavior, and even electrophysiological activity evoked by concurrent face stimulation.

Collectively, these studies show first that category-selectivity, i.e., face-selectivity, is a key predictor of the effect of DES. Indeed, the effective cortical sites are almost systematically located in highly face-selective regions, either shown by independent iEEG recordings (using standard ERPs or a frequency-tagging approach) or a face-localizer in fMRI. Moreover, across all recorded contacts, the contacts leading to DES effects are generally the most face-selective [40, 41, 99, 100, 116, 120].

Second, while DES to bilateral face-selective cortical sites in the LatMidFG can affect even the simple classification of a visual stimulus as a (normal) face, spectacular phenomena such as a change of percept or a complete interruption of face identity recognition have been observed following stimulation in the right hemisphere only (with the exception of one left handed subject in [123] and one in [30]; see [124] for the role of handedness in face recognition lateralization). Altogether with the lack of FIR impairment when stimulating corresponding regions of the left hemisphere, as regularly tested in our clinical center, this suggests that the right hemisphere is both necessary and sufficient for FIR. This conclusion is an agreement with the long-standing view of the right hemispheric predominance of human face (identity) recognition, as supported by a wealth of evidence in cognitive neuroscience [125].

Third, while (small) group studies have been performed with DES in ECOG, they have restricted their investigation to stimulation over face-selective contacts of the LatMidFG (i.e., the FFA, including sometimes two functional regions, pFus-faces and mFus-faces; e.g., [30]), focusing either on spontaneous perceptual reports or on a single behavioral task. In contrast, DES effects with SEEG have been rarer, but concerned more extensively studied single cases, with stimulation effects observed beyond the (right) FFA. Specifically, the 4 SEEG cases (5 explorations) summarized above (i.e., KV 2 times; CD; DN; MB) show that intracerebral stimulation of spatially different regions, i.e., the right IOG, LatMidFG and AntFG can evoke highly

reproducible transient impairments of FIR, both in terms of subjective reports and quantified behavioral measures, while the recognition of non-face images (common objects, famous buildings, famous names) is preserved [98–101, 120]. While the two posterior face-selective regions (IOG/OFA and LatMidFG/FFA) were already well identified (which does not mean that their critical role was established before DES), SEEG DES therefore extended the neural basis of FIR to the face-selective right AntFG (Fig. 39.1), a region with very little evidence of relationship to FIR (although see [126]), mainly because it is almost invisible in fMRI due to a large magnetic susceptibility artefact [77, 103]. Importantly, in all cases in which these tests were performed (KV second SEEG, MB, ND) the largest neural measures of sensitivity to the visual individuality of unfamiliar faces (i.e., independently from long-term familiarity) were also recorded on the very same contacts eliciting the transient FIR impairment.

Finally, while slight alterations of performance can be due to DES to several spatially dissociated contacts in the same patient, a FIR impairment appears to be restricted to the stimulation of one to three adjacent pairs of contacts, i.e., these sites being spatially confined. This does not imply that the effect of DES is limited to the stimulated contact, as demonstrated in some of these studies [117] and discussed below.

39.4 Interpretations, Practical and Theoretical Considerations for Future DES Studies

Based on the specific DES observations described above, in this last section of the chapter, we discuss practical and theoretical issues that are important to take into consideration to increase the value of DES in cognitive neuroscience.

39.4.1 Bringing the Lab into the Clinical Room

As mentioned in the introduction, the impact of DES studies in cognitive neuroscience has been limited in part because the experimental set-up is often less controlled than the experimental standards usually accepted in research laboratories worldwide. This gap is of course due to the fact that DES data is acquired in a clinical context, with limited testing time and experimental resources (for a description of the practical challenges of iEEG research and how they may be addressed, see also Chaps. 4 and 5). DES effects are sometimes unexpected and the time to adapt the experimental set-up is also limited in this context. As a consequence, DES studies usually include a restricted number of stimulations and trials, rely on retrospective clinical data, or are based only on the observation of the subjects' spontaneous behavior or subjective reports. Yet, in recent years, there has been an effort to bring the lab into the clinical

room to match as much as possible the lab experimental standards, and this effort should be pursued in the future. As illustrated in the present chapter for FIR, some DES studies have used well-controlled experimental paradigms specifically designed to test specific hypothesis regarding the potential function of the stimulated brain region (e.g., [22, 99, 101, 116, 117, 127–130]; see Figs. 39.2b, 39.4). Ideally, critical sites should be tested with a sufficient number of different paradigms, including control tasks, in order to isolate as much as possible the nature of the function of the stimulated region. For these tasks, objective measurements in terms of accuracy rates and response times should be recorded. Moreover, for all of these tasks, a sufficient number of stimulations, i.e., trials, should be performed in order to objectively (i.e., statistically) define the DES effects relative to trials without stimulation or stimulation to non-critical sites.

The experimental set-up during DES can be computerized to better control the delay between the stimulation and the trial onsets [101], to facilitate the recording of accuracy and response times and to promote multicenter DES studies thanks to easily sharable testing software (e.g., NeuroMapper; [26]). These computer-based paradigms promote innovative testing methods (e.g., video, virtual reality), providing a deeper understanding of usually targeted functions but also expand the range of tested functions (episodic memory, socio-emotional cognitive function, spatial memory, e.g., [26, 131, 132]). At the same time, computer-based approaches are not always possible in the clinical context and may lack flexibility (e.g., quickly removing problematic trials with low accuracy outside DES, or quickly showing impaired trials again after the stimulation procedure to test the subject once more or to let the subject comment about what happened during DES). Moreover, using only computer-based approaches may prevent subjects from reporting phenomenological experiences that are not available in non-human animal research and may be particularly useful in understanding the nature of the affected brain function and/or guiding further experiments.

39.4.2 Group or Single Case Studies?

The general principle of DES group studies is to perform stimulations across several subjects with the same test(s). Such studies are particularly suitable to map critical sites for a given brain function across a large area of cortex, as long as this function can easily be disrupted by DES to reach a sufficient number of subjects with critical sites (e.g., naming across the left ATL). They enable for example to report the percentage of positive and negative sites across regions and to compute proportion maps of positive sites (e.g., [58, 59, 101]). When DES results are projected into a standard brain space, the individual anatomy and functional organization is blurred, a caveat that can be avoided by grouping DES results according to their location based on the individual anatomy (e.g., [58]). By focusing on a specific brain region, these studies can also reveal subtle DES effects, such as increases of average error rates or response times (e.g., [116, 117, 132]; Fig. 39.4). Multiple critical sites across multiple subjects allow

such studies to correlate DES results with independent variables to better understand why some sites elicit positive effects while others do not (e.g., [116, 117]). Although they have the advantage to group subjects stimulated with similar cognitive tests and stimulation procedures, these tests are usually limited in number, usually one or two, restraining the full comprehension of the disturbed function. This limitation is usually due to practical reasons, either because a streamlined procedure is required to test all subjects the same way or because some studies rely on retrospective data acquired in a clinical context.

Other studies report in-depth explorations of a small number of subjects in the same article (e.g., [117, 129]). This type of study provides limited spatial sampling but deeper investigation of each subject and of the studied function. While our research group benefits from a large number of SEEG investigations per year at the University Hospital in Nancy (France) and has been able to map the neural basis of face, object and visual word recognition with large samples for SEEG recordings [108, 109, 133], the rarity of FIR impairments observed during DES (i.e., 5 cases in 10 years) has constrained us to report single case studies only. Despite this obvious limitation in number of cases and reproducibility of effects, this approach offered us the opportunity to report in-depth DES investigations of each subject, along with extensive multimodal explorations beyond DES (behavior, fMRI, SEEG recordings). First, well-controlled behavioral paradigms were specifically designed to test a specific function (e.g., [99, 101]). DES during these paradigms was repeated as often as possible to objectively measure DES effects with quantitative variables (error rates and/or response times increase during versus outside DES). Control tasks were also designed to isolate as much as possible the nature of the disturbed cognitive function. Second, beyond these objective measures, subjective reports and the semiology of these visual hallucinations or illusions were also investigated and clearly reported (e.g., facial palinopsia; [120]). Third, subjects were all tested with behavioral tasks before the DES procedure to ensure integrity of the tested function. In fact, subjects were even tested with the exact same tasks used subsequently during the DES procedure to ensure that their accuracy at these tasks was very high or even at ceiling, such that every failed trial during DES could be unambiguously classified as a stimulation-induced impairment (e.g., [99]). Finally, DES effects were interpreted in light of independent measures in every single case, mainly fMRI and SEEG recordings, either to map the whole network (e.g., the face network with face-selectivity measurements) or a specific function (e.g., sensitivity to face identity) (see also e.g., [41, 117, 129]).

As described above, all FIR impairments during DES were evoked by stimulating face-selective sites (as shown by both fMRI and SEEG recordings) and, when tested, by stimulating the regions with the highest sensitivity to unfamiliar face identity (as shown by SEEG recordings, [99, 101, 120]). The support of these independent measures is essential for DES studies for several reasons. They allow additional evidence of the critical role of the simulated region when DES and independent measurements evaluate the same function (e.g., face identity; [99, 101, 120]). When DES investigations remain ambiguous about the nature of the disrupted function because of a limited testing time or number of trials, these independent measures can tilt the balance in favor of one hypothesis according to the type of responses recorded

on the critical contacts. For instance, when the largest iEEG amplitude is recorded specifically on a critical site, it helps interpreting this stimulated site as a key node in the cortical network (e.g., entry point, highly connected node, etc.). In our DES studies specifically, we greatly benefited from the frequency-tagging approach for SEEG measurements, not only for its high sensitivity but also for enabling us to objectively identify, quantify and classify response amplitudes on each contact in the frequency domain rather than in an inherently ambiguous and subjective time-domain representation [99, 101, 120].

In summary, group and multiple case studies both have their own advantages and drawbacks, and the choice of one rather than the other approach should be based on the aim of the study, the frequency of observations and the nature of the tested cognitive function. A single case approach is inevitable if the observed phenomena and effects are extremely rare or if the patient's characteristics are unique. When such DES single case reports are well conducted (sufficient number of DES with adapted paradigms, multimodal investigations with independent measurements), they should not be considered as anecdotal or as "case reports" with their associated pejorative connotation, but as opportunities to perform in-depth investigations of a cognitive function, generate and evaluate new hypotheses [134–137]. Hence, as illustrated in the present chapter, we firmly believe that these types of studies have a key role to play in the future of DES.

39.4.3 A SEEG Advantage Over ECOG for DES?

As described above, transient impairment of FIR has been reported so far in 4 cases with DES using depth electrodes (i.e., SEEG). In contrast, DES with subdural electrodes, i.e., ECOG, has been much less successful and limited to anecdotal reports without quantification in early studies [121, 122]. Subsequent ECOG studies applying DES to face-selective regions of the VOTC (mainly the FFA) evoked changes of the face percept (i.e., face distortions) in several cases [30, 31, 40, 41, 114]; see also [115], but never reported a FIR impairment. One potential reason is that ECOG DES studies rarely tested for such impairments with behavioral tasks (with the exception of [40], in which no effect of DES on naming of celebrity pictures was found). Moreover, while complete category-selective impairment of FIR following brain damage, i.e., prosopagnosia, remains extremely rare, the prevalence of significant drops in recognition accuracy rates or increases in response times during FIR tasks in right posterior brain-damaged patients is high [138, 139]. Hence, in addition to subjective perceptual reports, the effect of DES to face-selective regions of the VOTC with subdural electrodes may be objectively identified in future studies with behavioral FIR tasks measuring accuracy rates and response times (as performed during generic face recognition tasks; [116, 117]; Fig. 39.4).

Alternatively, it could be that depth electrodes as used in SEEG, thanks to the position of the stimulated contacts within the brain tissue and often within the cortex as well as to the small intercontact spacing (see Box 39.1), allow for more focal

stimulation effects compared to subdural electrodes. In contrast, DES with the latter approach probably involves a relatively large cortical zone beyond regions specifically involved in FIR, explaining why visual distortions sometimes extend to non-face objects [40, 41] and can be experienced when stimulating non-face-selective sites [30]; see also [122].

Compared to the relatively low risk profile associated with the small burr holes of SEEG, ECOG requires a partial craniotomy. SEEG is therefore a safer surgical procedure with fewer post-operative complications such as hemorrhages and infections [140]. Specifically for DES to understand the neural basis of cognitive function, compared to ECOG, SEEG is also likely to leave the subject more alert cognitively to accurately report his/her perceptual experiences and to perform explicit behavioral tasks.

Despite a lower spatial coverage compared to ECOG, SEEG also has the advantage to access deep and medial structures that are inaccessible to ECOG (e.g., the medial temporal lobe, [141]; the precuneus, [5]; the cingulate gyrus, [142]; the transverse temporal gyrus, [143]; the insula, [144]). SEEG also allows one to specifically stimulate sulci, where critical effects are often found, sometimes more frequently than in the adjacent gyri [5, 42, 58, 99]. For example, the second highest rate of induced anomia in the left VOTC was found in a sulcus, the occipito-temporal sulcus [58], and the VWFA is also located primarily within this sulcus [145], making it particularly amenable to DES with SEEG [42]. SEEG DES enables also to independently stimulate grey and white matter [130].

While SEEG is already predominant in European clinical centers, these advantages, along with other clinical advantages not developed here, explain the recent rise of SEEG in the US compared to ECOG [13, 146]. For example, SEEG became the most frequently performed iEEG procedure in the US Medicare population in 2016 [13, 146]. While the selection of an iEEG procedure does not depend on advantages to answer fundamental research questions, we think that the increasing use of SEEG internationally will allow for more focal DES, targeting cognitive functions more specifically in the years to come.

39.4.4 Functional Specificity of Local and Remote DES Effects

As illustrated in the present chapter, several pieces of evidence show that DES effects are specific to the functional role of the stimulated region. Indeed, strikingly, almost all DES effects interfering with face perception (i.e., the subjective experience of seeing faces) were reported after stimulating cortical sites defined independently as face-selective [30, 31, 40, 41, 98, 100, 101, 114, 115, 120–122, 147]. Moreover, there is generally a highly positive correlation between the frequency or magnitude of DES effects and the amplitude of the face-selective [41, 99, 101, 116, 120] or face

identity-sensitive [99, 101, 120] electrophysiological activity. Along these observations, numerous stimulations of (sometimes weak) face-selective sites do not lead to face recognition/perception effects [30, 38, 114, 117].

The SEEG DES studies described in the chapter allowed for a clarification of the functional characteristics of the critical sites, beyond their high-level of face-selectivity. Specifically, only the stimulation of cortical sites that share common characteristics could elicit behavioral effects (in the case of FIR: right-lateralized, anatomically restricted, located from the IOG to the AntFG, highly face-selective, highly sensitive to unfamiliar individual faces). In our experience, DES of face-selective sites located in the left hemisphere or anteriorly to the AntFG located in classical semantic ATL regions [51, 148] never produced FIR impairments. This shows that the stimulation current does not spread indifferently across the whole bilateral cortical face-selective network and that the function—FIR—is impaired only if, within the specialized network, a key node is *directly* stimulated.

At first glance, these observations could be interpreted as evidence for a strictly localized function, suggesting that DES effects on face recognition/perception are due exclusively to interference with the function of a highly functionally specific local region (e.g., [31]). However, given the high density of connectivity between brain regions [149] and our current knowledge of DES effects, viewing these effects as being strictly focal seems outdated [6, 29, 150–152]. Instead, DES effects may arise when directly stimulating a key node of a functionally specialized network, i.e., a dense population of highly specialized neurons with increased connectivity to other sites of the network ([117, 153]; Fig. 39.5a). Nevertheless, a current crucial issue for DES studies is to assess the functional *specificity* of the current propagation and remote effects (i.e., that DES remote effects specifically concern the functional network to which the stimulation site belongs).

Regarding human face recognition, several pieces of evidence show the functional specificity of the remote effects. SEEG DES showed that a FIR impairment could be evoked by stimulating several distant sites (right IOG, LatMidFG and antFG), all part of the network supporting (unfamiliar) FIR as evidenced in electrophysiology [51]. There were also subtle differences in DES effects across regions probably due to these regions' own connectivity pattern with other nearby networks/regions (Fig. 39.1). Yet, that did not prevent us from highlighting the main functional role of these regions. For instance, face-perceptual changes (i.e., changes in the phenomenological experience of faces) have been found when stimulating posterior face-selective regions (OFA, FFA) [100, 101, 120]; see also [40, 41], i.e., regions that are known to be directly connected with low-level visual areas [154], but never when stimulating the more anteriorly located AntFG [98, 99]. In contrast, direct stimulation of the right AntFG only led to a generic deficit in encoding the stimulation episode in memory, interpreted as reflecting a remote effect of DES to the connected medial temporal lobe episodic memory system [25].

The cortical face network view of DES effects, which is supported by independent evidence of tight anatomo-functional connectivity within this network [155], is also well illustrated by the study of [117]; (Fig. 39.5b), in which the effect of DES to the LatMidFG (affecting behavioral performance) spreads anteriorly and posteriorly to a

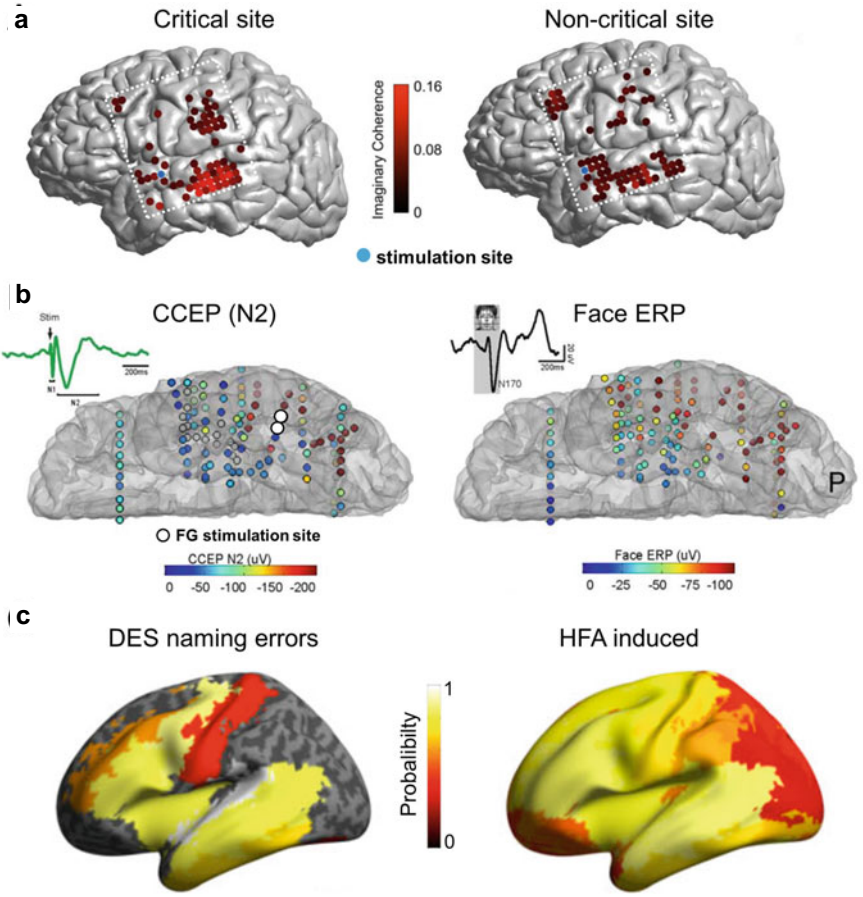


Fig. 39.5 Assessing the connectivity of critical DES sites. **a** Adapted from [153] with permission. A critical DES language site showed increased functional connectivity (left panel) compared to a non-critical DES site (right panel), as measured by imaginary coherence in the alpha band (example in one subject). **b** Adapted from [117] with permission. Single-pulse DES over the LatMidFG induced increase reaction time at detecting face distortions as well as distant CCEP along the VOTC (left panel, example in one subject). Interestingly, there was an amplitude correlation across electrodes between the N2 CCEP (left panel) and the face N170 recorded independently (right panel), showing that the stimulation current propagates preferentially within the face-selective network. **c** Adapted from [152] with permission. Critical DES naming sites (left panel shows the probability of evoking a naming impairment in the left hemisphere across 29 subjects) induced high-frequency activity (HFA) at distant sites, whose probability of occurrence is shown on right panel

number of recorded contacts along the VOTC but also to more distant regions of the temporal lobe and prefrontal cortex in some patients, as shown by distant recorded CCEP (see Chap. 40). Importantly, in that study, there was a strong amplitude correlation between the CCEP and the face-selective N170 potential in each patient and

in a group average, showing that the spread of activity reflects the intrinsic organization of a functional network. Even if cortical face networks of humans and monkeys differ substantially in anatomical substrates, region size, lateralization and cortical distance between the nodes of this network [94, 156], such findings are in line with the observation that focal electrical microstimulation of a face-selective region in the monkey brain also spreads selectively within the cortical face-selective network [150].

39.4.5 Assessing the Connectivity of the Critical Sites

Once it is admitted that DES is likely to affect a network linked to the stimulated site rather than only an isolated functional brain region, the next step for future DES studies is to identify and characterize this network. A first approach consists of identifying the critical sites using DES and subsequently assessing the functional connectivity of these sites using independent connectivity measures. In particular, high-frequency DES has been combined with CCEP, especially in studies stimulating language regions. Critical language sites identified with high-frequency DES either in Broca's area, Wernicke's area or the BTLA showed strong connectivity within the language network, i.e., elicited CCEP in the 2 remaining regions [65, 66, 157], see also [158]. DES could also be combined with various measures of functional connectivity using iEEG recordings acquired independently (e.g., coherence, phase-locking values, debiased phase lag index, etc.; see Chaps. 32 and 33). Several studies have shown increased functional connectivity of critical DES sites with distant regions [17, 153, 159, 160]; Fig. 39.5a). Finally, DES could be also combined with structural connectivity methods [158, 161]. For example, with diffusion tensor imaging, it has been shown that critical BTLA sites were structurally connected to the temporal pole, medial temporal lobe, lateral temporal, and occipital cortex through the inferior longitudinal fasciculus [161].

A second approach consists of using the DES effect itself to study the connectivity of the critical sites by *simultaneously* combining DES and iEEG recordings. Using this approach, a number of studies have identified remote power spectral changes in various frequency bands induced by DES evoking behavioral effects [152, 160]; see also [162, 163]). For instance, Perrone-Bertolotti and colleagues [152] found induced high frequency activity by critical language DES in remote sites belonging to the language system (Fig. 39.5c). Interestingly, they found similar results using remote after-discharges, indicating that these discharges could also be used to index the connectivity of DES sites. When single-pulse DES was sufficient to evoke a behavioral effect, it could be used at the same time to study the effective connectivity of the stimulated region using a CCEP approach (e.g., [19] for low-frequency DES in the fornix inducing memory improvement along with CCEP in hippocampus and posterior cingulate).

Other approaches have proposed to identify the distant spectral lines corresponding to the stimulation waveform of high-frequency DES evoking clinical effects

[164] or to measure the functional connectivity change just after DES [165]. Finally, a promising approach has recently been introduced in human research: DES while simultaneously recording fMRI to map evoke distant BOLD activation [166, 167].

Overall, connectivity analyses should be highly promoted in future DES studies not only to avoid the simplistic interpretation of strictly focal DES effects but to better characterize the neurofunctional organization of the critical network. However, there are at least two avenues for improvement. First, studies will need to show the specificity of the connectivity pattern of critical sites (both qualitatively and quantitatively), for example by comparing the connectivity of critical and non-critical DES sites ([117, 153, 163, 165]; Fig. 39.5a). Second, all connectivity methods listed above are designed to identify the overall connectivity of a region, independently of the various functional sub-networks linked to the stimulated region. Our investigations of single cases showing FIR impairments during DES strongly suggest that the stimulation could be specific enough to only affect a sub-network (see also [6]). Future studies will need to identity the particular sub-network affected by DES, using more specific connectivity measures. For example, functional responses (e.g., low- and high frequency neural activity to specific stimuli) could be recorded with and without concomitant DES, with the local and distant modulation of these responses reflecting the specific functional network affected by DES [117, 168].

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