Neuronal Correlates of Obsessions in the Caudate Nucleus

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Background: Metabolic overactivity of corticosubcortical loops including the caudate nucleus (CN) has been reported in obsessive-compulsive disorder (OCD) using functional imaging techniques. However, direct proof of a modification of neuronal activity within the CN of OCD patients is still lacking. We tested the hypothesis that obsessions or compulsions might be associated with particular features of neuronal activity in the CN of OCD patients.

Methods: Single unit recordings were performed peroperatively in the CN of three patients with severe forms of obsessive-compulsive disorder (OCD) who were candidates for deep brain stimulation of the CN. Severity of obsessions was assessed preoperatively with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) and peroperatively with a subjective obsession score based on a visual analog scale (VAS).

Results: Frequency of CN discharge and variability of interspike intervals were found to be abnormally high in two patients with a high VAS score during surgery but not in one with a low VAS score. Lateralization and depth of recording influenced neuronal activity variably among patients.

Conclusions: Because the three patients had high Y-BOCS scores before surgery, these findings suggest that caudate hyperactivity in OCD is concomitant with the occurrence of the obsession process.

Key Words: Caudate nucleus, neuronal recording, OCD, physiopathology

Obsessive-compulsive disorder (OCD) is one of the most disabling psychiatric disorders owing to the intensity of symptoms and the resulting functional disturbance (1). Obsessions may be defined as the eruption in the mind of uncontrolled thoughts considered by the subject as senseless or of unpleasant content. They are generally accompanied by a feeling of urgency or catastrophe, leading to grouped repetitive behaviors known as compulsions (2).

The pathophysiology of OCD remains hypothetical, but data from neuroimaging studies and phenomenological considerations have recently shed light on the putative brain regions involved in this psychiatric disorder. First, increased metabolism has been reported in the orbitofrontal (3–5) and anterior cingulate (5–7) cortices but also in the caudate nucleus (5,8) and thalamus (6,9,10). These observations suggest a disruption of information processing in frontosubcortical pathways involving the basal ganglia (for review, see references 11 and 12). Second, phenomenological evidence favors a particular role of the caudate nucleus (CN) in the pathophysiology of this anxiety disorder (2). This is supported by the therapeutic effect of neurosurgical procedures in patients with medically intractable forms of OCD. Subcaudate tractotomy and anterior capsulotomy, which interrupt the connection between the CN and the mesial frontal cortex, have proved to be of significant benefit in the treatment of refractory OCD (11). Moreover, a dramatic improvement in OCD has been reported with chronic deep brain stimulation (DBS) of either the ventral CN (13,14) or the anterior capsule (15). The rationale for DBS derived from a presumably excessive activity within these regions that could be tentatively reduced by this approach. However, direct proof of neuronal overactivity in the CN of OCD patients is still lacking. Indeed, there is a discrepancy between metabolic data obtained with functional imaging and the direct recording of neuronal activity. The question is to know whether particular features of neuronal activity potentially responsible for obsessions or compulsions might be found in the CN of OCD patients.

Here, we present data of electrophysiological unit recordings performed peroperatively in the CN of three patients who underwent DBS for a severe form of OCD resistant to medical treatment and who were candidates for DBS. Recordings were performed before the implantation of a chronic DBS electrode in the CN region. Parameters of neuronal activity were related to the presence or absence of obsessions during surgery as assessed with a subjective obsession score using a visual analog scale (VAS).

Methods and Materials

The three patients had suffered from a severely disabling and refractory form of OCD that was largely unresponsive to 1) maximally tolerated doses of 5 out of 6 serotonin reuptake inhibitor (SRI) antidepressants (i.e., clomipramine, fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram) for 10 weeks or more and 2) two drugs combined with an SRI (buspirone and lithium carbonate or clonazepam) for 1 month. They simultaneously received cognitive-behavioral therapy, which proved unsuccessful. Subjects’ OCD coexisted only with a lifetime history of recurrent major depression. Unlike OC symptoms, depressive manifestations often responded favorably to the multiple antidepressant regimens used.

To monitor OCD symptom severity, first the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was used, completed by an independent psychiatric OCD expert 1 week before surgery;
second, a 10-point VAS was filled in by the patient during peroperative electrophysiological recording.

Patient 1 (P1) was a 56-year-old man who for more than 4 decades had experienced somatic obsessions concerning potential disturbances in body functioning, especially his arms, fingers, legs, and gastrointestinal tract, and his mental capacities, with compulsive verification of functioning, comprising repetitive voluntary movements, controlled intake of foods according to their purgative properties, and repetitive mental acts of questioning. Aggressive obsessions with fear of embarrassing thoughts about his children also occurred, although considerably less frequently. His Y-BOCS and VAS scores were 25/40 and 7/10, respectively. Treatment with fluvoxamine in addition to lithium carbonate was discontinued 2 weeks before surgery.

Patient 2 (P2) was a 46-year-old man who for 27 years had exhibited an urgent need to know and remember, as well as fear of losing things or of not saying, understanding, writing, or reading just the right thing, coupled with repetitive ritualistic activities, especially rereading or rewriting and the need to ask for things to be repeated. Anecdotal obsessive thoughts of aggressive content were noted with a particular fear of hit-and-run automobile accidents because he felt he was not careful enough. His Y-BOCS and VAS scores were 25/40 and 2/10, respectively. Treatment with the antidepressant drug clomipramine was discontinued 2 weeks before surgery.

Patient 3 (P3) was a 45-year-old woman who for 28 years had had prominent contamination obsessions with disgust of bodily secretions (urine, feces) and concerns with dirt leading to recurrent compulsive cleaning and washing. She also reported the need to know and remember, along with fear of not saying, understanding, writing, or reading just the right thing. These symptoms were also associated with repetitive checking compulsions such as rereading or rewriting and requiring things to be repeated. Hoarding obsessions with collecting compulsions were also present, with the special need to check carefully that any postal envelope received did not contain any informative letter. Her Y-BOCS and VAS scores were 31/40 and 7/10, respectively. The patient was given a combination of sertraline with clonazepam, which were not discontinued before the intervention. Daily dosage of each medication remained unchanged during the 2 weeks before surgery.

Deep brain stimulation of the CN produced a 35%–60% reduction in Y-BOCS scores in the three patients at 1 year postoperatively.

Ethical Considerations

The local ethics institutional review board approved the study. A committee of independent French experts including two psychiatrists, a neurologist, and a neurosurgeon was consulted, and they examined the relevance of the cases. Following a detailed explanation of the study, written informed consent was obtained from the patients before participation.

Surgical Procedure

Stereotactic three-dimensional T1-weighted magnetic resonance imaging (MRI) was performed using a 1.5-Tesla unit, which was equipped with a Leksell G stereotactic frame support and adjusted to reduce image distortion to a minimum. The target was determined on the lower axial slice showing the ventral part of the putamen and that of the CN, 10 mm in the front of the nucleus accumbens. There is no anatomic border between the ventral part of the CN and the nucleus accumbens (NA). Targets were defined as the center of the ventral part of the CN and NA on this slice. On the coronal slice reconstructed through the targets, we determined the trajectories passing through the head of the CN in such a way that the two lower contacts were located within the ventral part of the CN (CNv) and the two upper contacts within the dorsal part (Cnd) of the CN defined as a horizontal line located 10 mm from the target (i.e., the inferior limit of the caudate; Figure 1). The targets and entry point coordinates were then calculated with regard to the anterior commissure–posterior commissure (AC-PC) line reference system (16). At the end of the procedure, the electrode locations were controlled by MRI and reconstructed with regard to the AC-PC line reference system. The electrode tips were located at a mean 2.5 ± 0.5 mm under the AC-PC line, 33.4 ± 2.3 mm anterior to PC and 8 ± 0.7 mm laterally to the AC-PC line.

Under local anesthesia, peroperative electrophysiological recordings were performed using five parallel microelectrodes (FHC, Bewdleyham, Maine) with an Alpha-Omega system (Nazareth, Israel) as previously described (17). The recordings required 90 min on each side. Neuronal activity was amplified (×10 K), filtered (300 Hz–3 KHz) and stored for 3 min each time a neuron with a single unit activity was encountered. Neuronal recordings began 20 mm from the target (i.e., the inferior border of the CN). At the end of each track, microstimulations were performed through the same microelectrodes with a current intensity up to 10 mA to detect the peroperative occurrence of adverse effects. No side effects were observed during this procedure. The final implantation sites of the definitive electrodes for chronic stimulation (DBS–3387 Electrode, Medtronic, Minneapolis, Minnesota) were guided by neuronal discharge frequency. The track with the highest activity was chosen for implantation. A cerebral CT scan was performed three days after electrode implantation to control electrode positioning and images were combined with pre-operative T-weighted 3D MRI (16). Electrodes were then connected to a pulse generator (Kinetra, Medtronic) 5 days after implantation under general anesthesia.

Analysis of Electrophysiological Data

Neuronal data obtained with Alpha Omega system (.map files) was then exported as compatible files (.text) to a PowerLab system (ADI instruments, Phymep, Paris, France) and analyzed using Chart 5.0 software (AD Instruments Inc., Colorado Springs, Colorado). Single-unit activity was identified on the basis of constant width (msec) and amplitude (μV). Spikes were retained for data analysis if the spike-to-noise ratio was at least 250%. Spike discrimination was based on both amplitude (ordinate) and duration (abscissa) plotted on a graph. Thereafter all Chart files were exported as NeuroExplorer compatible files (.nev) allowing analysis of frequency and pattern of discharge. The average of the interspike intervals (ISI) and discharge frequency (MDF) of each neuron was calculated with Neuroexplorer software (Nex Technology, Littleton, Massachusetts). The discharge pattern was initially studied by using a burst detection method (18), but the discharge frequencies in the striatum were too low to allow statistical analysis in most cases. Consequently, we used a variability index (VI) corresponding to Σ (ISI SD/ISI) in which ISI is the mean ISI for each neuron (19).

Results

The activity of 477 neurons was studied in the six CN (269 on right and 208 on left) of the three OCD patients (Figure 1). Typical examples of single unit neuronal activity recorded in the CN (Figure 1A and 1B) and in the CNv (Figure 1C and 1D) of the first patient are shown in Figure 1. Low discharge frequencies usually showed a discontinuous pattern (i.e., neurons exhibited
low discharge frequencies or bursts of moderate intraburst discharge frequencies separated by pauses of variable duration (Figure 1A and 1B). Neurons with higher discharge frequencies exhibited a more sustained activity or periods of long burst duration (Figure 1C and 1D).

The mean discharge frequency (MDF) was, respectively, 4.96 spikes/sec (SD = 4.20) in patient 1 (P1), 2.26 spikes/sec (SD = 3.71) in patient 2 (P2), and 5.50 spikes/sec (SD = 4.33) in patient 3 (P3). P2 had a lower MDF than P1 and P3 (Figure 2A). Differences in the variability index (VI) were also found between the patients. P2 had a much lower VI (mean VI = 1.76; SD = 1.70) than P1 (3.00; SD = 1.75) and P3 (2.26, SD = 1.16) (Figure 2B). A clear relation was noted between MDF and VI values and the VAS score obtained during surgery (Figure 2A and 2B). P2, who was particularly relaxed during surgery with few obsessions, had the lowest MDF and VI. Neurons with low frequencies generally showed an irregular discharge pattern (Figure 2C), whereas those with high frequencies were characterized by bursts of activity separated by pauses (Figure 2D).

We then examined whether lateralization and recording depth influenced neuronal activity. Differences emerged between patients. In P1, MDF was higher in the CNv than in the CNd without any effect of lateralization. In P2, there was no effect of lateralization or depth on MDF except for the left CNv, where the frequency was slightly higher. In P3, MDF was lower only in the right CNv (Figure 3). For VI, values were higher on the right side in P1 without any clear effect of depth. In P2, there was no effect of lateralization or depth. In P3, there was a higher VI on the left side but no effect of depth (Figure 3).

**Discussion**

To our knowledge, this is the first attempt to record single neuronal activity in the CN of human subjects. There was a clear relation between the patients’ self-evaluated obsessions during surgery and neuronal activity. It is unlikely that these differences were treatment related. Indeed, patients 1 and 2, who were receiving no medication at least 2 weeks before surgery exhibited different firing rates, whereas there was no difference in frequencies between patients 1 and 3, although the latter was being treated at the time of surgery. The features of neuronal activity in these patients cannot be compared with those in normal subjects because no direct recording has been performed in this region in the latter. However, several lines of evidence based on neuronal recording in subhuman primates suggest that the striatum is a silent region (20,21). In patients 1 and 3, we found a high discharge frequency...
and high variability of ISI, whereas these parameters were low in patient 2. All three patients had a severe form of OCD, as attested by their respective Y-BOCS score before surgery, but profoundly differed in their subjective obsession scores assessed during surgery. Patients 1 and 3 showed high VAS scores contrasting with the low VAS score in patient 2.

These findings therefore suggest that high discharge frequency and an irregular pattern are concomitant with the occurrence of the obsession process. These data are in accordance with the reported overactivity within the CN in OCD patients using functional imaging techniques (5,8). However, several patterns of neuronal activity are observed in the CN. Usually, two main types of cells are characterized electrophysiologically: 1) neurons with a low base firing rate (0.2–1 Hz) activated in short bursts of a few spikes; these neurons are thought to correspond to the medium spiny cells (MSC; i.e., the striatal output neurons);

Figure 2. Features of neuronal activity within the caudate nucleus. Mean discharge frequency (A) of the caudate nucleus (dorsal and ventral parts) and mean variability index (B) of the caudate neuronal activity for the three patients (P1–P3). The superimposed red line corresponds to the subjective obsession score obtained for each patient during surgery on a visual analog scale. This score was lower for the P2 who had the lower mean discharge frequency and the lower variability index. (C and D) Examples of raster displays (upper traces) and instantaneous neuronal frequencies (lower traces) illustrating the two main types of discharge pattern observed within the caudate nucleus (CN). These two cells (C and D) were recorded within the left ventral CN of P3. (C) This neuron had a low discharge frequency with a discontinuous pattern. (D) This neuron exhibited bursts of activity separated by pauses of variable duration.

Figure 3. Effect of lateralization and depth recordings on caudate neuronal activity. The mean discharge frequency expressed as spikes/sec and the variability index (VI) are represented for patients P1–P3. For each side (i.e., right and left caudate nuclei [CN]), data were obtained from recordings of the ventral and dorsal part of CN and expressed as mean ± SEM.
2) neurons with a medium firing rate (5–15 Hz) discharging in bursts of short duration separated by pauses, which likely correspond to the tonically active neurons (TANs; i.e., the cholinergic interneurons of the striatum (21–23). From our data, it is not possible to determine whether neurons with relative high frequencies and irregular pattern correspond to MSC or TANs. Although some authors have proposed a particular role for TANs in the pathophysiology of OCD on the basis of phenomenologic arguments (2), it is noteworthy than MSCs are quantitatively much more numerous (24). Increased activity of these striatal output neurons could be involved in the modification of cortical activation through striato-pallido-thalamo-cortical projections. Indeed, CN hyperactivity could result in an overactivation of the direct striatopallidal $\gamma$-aminobutyric acid–ergic pathway responsive for the disinhibition of the thalamocortical glutamatergic pathway. The net result would be a disruption of information processing at the cortical level (ie, orbitofrontal and cingulate cortices).

Previous imaging studies have reported contradictory results with regard to the lateralization of metabolic activity in the CN. Some authors reported increased activity in the right CN (5) and thalamus (3), but others have noted a bilateral activation (11). The CN is a complex structure encompassing several territories. The dorsal associative part (CNd) is thought to process cognitive information whereas the ventral limbic part (CNv) is involved in the processing of emotion-related information (25–29). Hence, OCD is associated with both cognitive and emotional disturbances. We found different features of activity in the CN of patients 1 and 3 regarding the side and depth of recordings. On the basis of these electrophysiologic results, we postulate that the pattern of neuronal activity within the caudate nucleus probably depends on the features of obsessions that are specific to each patient. This data could explain why variations in metabolic activation have been reported in OCD with functional imaging techniques.

These data raise the crucial question of how hyperactivity in the caudate might play a role in the phenomenology of OCD. As described previously, the CN is closely connected via the pallidum and medial thalamus to the orbitofrontal and cingulate cortices, both of which play an important role in error detection monitoring (11). If they do not function correctly, the error detection system may be disrupted. Obsessions and compulsions may be seen as an overfunctioning of the error detection process, which is activated repeatedly and inappropriately in specific situations. The clinical manifestation of this hyperactivity might be the internal feeling that “something is wrong,” a basic perception reported by OCD patients (2). This would result in the emergence of intrusions and pathologic thoughts leading to compulsions. However, alternative explanations should be considered. A failed CN stop signal resulting in an inability to delay responding in the context of reinforced habit learning could result from a disruption of the indirect striatal pallidal pathway. This impairment would in turn favor transmission through the direct striatopallidal pathway. Such a phenomenon could explain the cognitive functioning in loops and the repetitive eruptions in the mind of intrusive thoughts (facilitated but not refrained). Furthermore, the motivational system might fail, leading to repetitive behaviors (compulsions) to decrease the subject’s anxiety level. Indeed, compulsions occur as behavioral responses aiming to relieve the tensions or anxiety generated by the situation. If obtained, this relief may be felt to be a form of reward. Nevertheless, it is only transient, thereby creating a feeling of considerable anxiety. This leads to immediately repro-ducing the behavior in a cyclic manner on the basis of an internal motivational state through an expectation of the reward (for review, see reference 11). Finally, within these cortico-subcortical loops, OCD could also be associated with abnormal glutaminergic synaptic transmission from the cortex to the caudate. This is suggested by 1) high levels of glutamate in the lumbar cerebrospinal fluid of OCD patients (30); 2) elevated concentrations of glutamate in the CN of pediatric OCD patients on proton magnetic resonance spectroscopy (31); and 3) the antiobsessional effect of antiglutamate agents when added to antidepressants (32).

Conclusion

In this study, the clear relation between patients’ self-evaluative obsessions during surgery and abnormal activity within the CN supports the view that OCD is associated with overactivity in the CN. These data provide direct evidence for considering this subcortical region as a putative target for DBS in the treatment of refractory OCD.

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