Bial

Effect of Deep Brain Stimulation of the Nucleus Accumbens on Affective Picture Processing

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ABSTRACT

Background:

The Nucleus Accumbens (NAc) is involved in emotional processing and Deep Brain Stimulation (DBS) of the NAc could affect this processing.

We report an approach to find stimulus parameters for DBS of the NAc to ameloriate the attenuation of mood, emotions and motivation of a 64 year old male after anterior capsulotomy (AC).

Differences in Valence and Arousal based on Self-Assessment-Manikins (SAM), the event-related potentials (ERP), skin conductance response (SCR) and cardiac activity (ECG) have been reported following presentation of pictures from the International Affective Picture Scale (IAPS).

Objective/Hypothesis:

We expected to be able to optimize stimulation. Our secondary objective was to assess the feasibility of this approach.

Methods:

30 pictures from the IAPS were selected and presented to the subject in several runs. Stimulation parameters were changed for every run to a combination of high (i.e. 6.5V) or low (i.e. 2V) voltage with location (0-, 1-, 2- and 3-) plus OFF and regular setting. We measured EEG, ECG, SCR and SAM ratings.

Results:

We were able to successfully filter out stimulation artifacts introduced by DBS. We found significant differences in EEG, SCR and SAM ratings and were able to derive optimized stimulation parameters. Yet, the patient did not perceive an improvement in the affective attenuation. We believe this is due to the AC.

Conclusion(s):

Although we were not able to improve the affective attenuation, we could show that our approach is feasible to systematically derive DBS settings in psychiatric care.

INTRODUCTION

Bilateral anterior capsulotomy (AC), i.e. ablation of the anterior limb of the Capsula Interna is one possible intervention for treatment-refractory social phobia. AC affects the superolateral Median Forebrain Bundle connecting the Ventral Tegmental Area (VTA) with the Nucleus Accumbens (NAc) (1). The NAc is involved in emotional and motivational circuits (2), especially when it comes to the basic aspects of liking and wanting (3). The severing of afferent dopaminergic connections from the VTA to the NAc via AC can therefore lead to the attenuation of emotions and motivation.

This was the case with a 64 year old male patient presented to us with a history of Social Phobia. After AC, which was successful in treating his Social Phobia, he developed a general attenuation of mood, emotions and motivation and was in succession treated by Deep Brain Stimulation (DBS) of the NAc in an attempt to ameliorate this anhedonic state (s. fig. 1). All this happened before he was presented to us and asked about possibilities to improve his stimulation parameters.

Various psychiatric disorders have successfully been treated by DBS of the NAc (4) and DBS of the NAc can lead to acute emotional responses (5). It is therefore plausible to expect that DBS of the NAc might have an effect on the described anhedonic state. Yet, the patient complained that so far no stimulation settings lead to any improvement. We therefore attempted to develop optimized stimulation parameters in a systematic way based on physiological and psychological correlates of affective picture processing.

The International Affective Picture System (IAPS) is an established research tool. Different ratings of Valence and Arousal based on Self-Assessment Manikins as well as changes in event-related potentials (ERP), skin conductance response (SCR) and cardiac activity (ECG) have been reported following presentation of pictures from the IAPS and two-factor solutions discerning between Arousal and Valence have been established for physiological and psychological measures (6). It has also been suggested that the NAc is activated separately

for both Valence and salience of affective cues (7), further highlighting the role of the NAc in emotional processing.

Insert Figure 1 about here

OBJECTIVE

Our main objective was to improve the affective status of the patient. To do so, we developed a method to derive stimulation parameters in a systematical way. Especially as the patient complained about a general attenuation of his emotions, we were therefore less interested in variance caused by differences in Valence or Arousal. Instead, to measure the effects various stimulation parameters have on his profile of physiological and psychological correlates of affective picture processing, we were more interested in the general effect for a broad range of different pictures. Our secondary interest was the feasibility of the approach.

MATERIALS & METHODS

Patient

The patient is a 64 year old male. He has a history of social phobia. The phobia was successfully treated with AC, but he reports a severe attenuation of emotions, mood and motivation immediately after AC. In an attempt to counter the side-effects of AC, he was being treated by bilateral DBS of the NAc, but without success. Chronic stimulation parameters as he was presented to us were 6.5 V, 1-2-3- vs. case, 120μs, 140Hz.

Stimulus selection

30 pictures from the International Affective Picture System were selected based on their general rating scores for males (8) to get a battery of 12, 6 and 12 pictures of positive, neutral and negative Valence.[1] Pictures include various contents from erotic images to landscapes, animals, food, household items, mutilations, injuries and various social

[1] The codes of the selected stimuli are 1120, 1201, 1463, 1560, 1710, 1811, 1931, 1945, 2030, 2053, 2070, 2100, 2170, 2205, 2550, 2700, 2750, 2900, 3150, 3179, 3220, 3550, 4210, 4669, 6313, 6550, 7090, 7470, 7545, 9417

situations. The mean Valence rating according to the normative sample is 4.94, spanning from 1.17 to 8.25. The mean Arousal rating is 5.16, spanning from 2.3 to 7.8. One additional picture (code 2791) was selected to serve as the introductory stimulus for every run. It was not used for interpretation.

Presentation

Stimuli were projected on a wall for 5 seconds in a dark and sound attenuated room. The subject was sitting comfortably in a chair and the images were projected ≈ 2.3 m from the participant's eyes (26° of visual angle). To promote a stable mental set, before every stimulus a command to relax was presented for 7 seconds and after each stimulus a white cross on black ground for 5 second. After each set of relax - stimulus - cross a Self-Assessment-Manikin was presented for 8 seconds, during which the patient rated the stimulus. The order of stimuli was pseudorandomized for each run of a session with the exclusion of the introductory stimulus. Stimuli were presented by BCI2000 software.

Session Procedure

There were four sessions, each separated by a break of six days. During each session, the subject was presented seven runs. After each run, DBS was turned off for 10 minutes. After this wash-out period DBS settings were changed to a setting undisclosed to the subject. After a 5 minutes waiting period for wash-in, a new run started. The stimulation parameters were pseudorandomly allocated to runs with the exclusion of the first run of each session, which always used the stimulation setting used during the week. Two runs with faulty data due to equipment or handling error were discarded and repeated in one of the other sessions.

Stimulation parameters

Stimulation parameters were changed for every run. All settings were bilateral with 120µs and 140 Hz and vs. case. We included stimulation off (OFF), regular stimulation setting, i.e. 6.5V at 1-2-3- and reduced regular stimulation setting, i.e. 6V at 1-2-3-. The other runs were combinations of high (i.e. 6.5V) or low (i.e. 2V) voltage with location (0-, 1-, 2- and 3-). Stimulation OFF and regular stimulation were measured four times, all others settings were repeated twice, resulting in 60 to 120 trials per stimulation setting.

Control

We used a 29 year old healthy male subject to control whether the setup influenced the measurement. For the control subject we measured EEG and SAM Ratings in five runs during one session.

Psychophysiological Recording and Analysis

Electroencephalogram (EEG) signals were recorded with a sampling rate of 1000Hz from 64 sites using BrainAmpDC amplifiers and Visionrecorder software routed through BCI2000 software. For the optimization of stimulation parameters we only analyzed results for Fz. Data was analyzed with MATLab 7.10.0 and EEGLab 8.0.3.5b, digitally filtered to exclude frequencies above 35Hz, and finally re-referenced to TP7 (6). Trials were automatically rejected based on kurtosis and large amplitude, resulting in a loss of 0 to 2 trials per stimulation parameter. ERPs were averaged for every stimulation parameter to improve signal-noise-ratio. A floating average filter with a window of 100ms was used for further smoothening. Baseline was set to the first millisecond after stimulus onset. ERP waveform and early peak mean power were statistically analyzed by comparison of confidence intervals.

Electrocardiogram (ECG) data was recorded from Ag/AgCl electrodes on the left and right elbow with a sampling rate of 1000Hz using BrainAmpDC amplifiers and Visionrecorder software routed through BCI2000 software to automatically add markers. Peaks were automatically detected using in-house code running on MATLab 7.10.0. Data was statistically analyzed by comparison of confidence intervals.

Skin Conductance Response (SCR) was recorded using Varioport with a sampling rate of 16Hz with electrodes affixed to the hypothenar and thenar eminence of the left palm. Data was analyzed with LEDAlab 3.2.6 running on MATLab 7.10.0. Conductance response magnitude was scored as the amplitude sum (in µSiemens) from 0 to 5 seconds after stimulus onset after Discrete Decomposition Analysis with six optimization runs. As SCR

shows rapid habituation (9), results were corrected assuming a linear habituation process. 3 trials had to be rejected due to measurement errors. Data was statistically analyzed with paired t-tests.

Valence and Arousal ratings were obtained using a graphic version of the Self-Assessment Manikin (SAM), scaled from 1 to 9, which was presented to the subject during the runs after each stimulus presentation and statistically analyzed with paired t-tests.

RESULTS

ECG

The average number of heartbeats per 5 seconds after stimulus onset spans from 4.17 to 4.49 (M=4.31, SD=0.09). No difference in Heartbeat rate for stimulation settings could be found.

Rating of valence and arousal (SAM)

Mean ratings of Valence span from 4.17 to 4.49 (M= 4.31, SD= 0.09). Ratings of Valence were lower than for the normative sample for every stimulation setting (average Δ= 1.15, $p<0.01$). No differences in Valence rating by setting were found. Mean ratings of Arousal span from 4.96 to 6.71 (M= 6.38, SD= 0.5). Arousal was rated higher by the subject compared to the ratings of the normative sample (M= 5.16) in every setting (in average Δ=1.22, $p<0.001$). Stimulation with 2V at 3- (M= 6.66, SD= lead to higher Arousal ratings than 2V at 1- (Δ= 1.15, $p<0.001$). Compared to OFF, when stimulated with 6.5V at 1-2-3-, Arousal rating was also significant higher (Δ= 0.64, $p<0.001$).

EEG

The subject did not show the waveform expected for healthy subjects, i.e. a negative peak between 150 and 300ms. Note that we were able to obtain such a waveform from our healthy control subject. Instead, the average ERP results indicate a significantly positive peak (compare figure 2). This highlights the importance of analyzing effects on the early peak. We found significant differences between stimulation settings for early peak mean power (compare figure 3).

The most pronounced finding is that 6.5V at 1- (M= -5.8, CI99%= -22.77 to 11.17) differs significantly from 6.5V at 0- (M= 60.39, CI99%= 41.75 to 79.03, Δ= 66.19) and 6.5V at 2- (M=51.14, CI99%= 25.03 to 77.25, Δ= 56.94). Other noteworthy results are that settings with 2V are not significantly different from each other and that (M=18.05, CI99%= 3.1 to 33.0) is significantly different from 6.5V at 0- (Δ= 42.34). In addition, 6V at 1-2-3- is different from 6.5V at 0- (Δ= 62.35) and 6.5V at 2- (Δ= 53.08).

Insert Figure 2 & 3 about here

Skin conductance response (SCR)

For any single electrode, stimulation with 6.5V was significantly different from 2V at the same electrode ($p<0.001$). SCR was increased when stimulated with 6.5V instead of 2V at 0- (Δ= 1.22), 2- (Δ= 2.18), 3- (Δ= 1.72) and decreased at 1- (Δ= 0.76). 2V at 3- yielded significantly lower SCR ratings than at 0-, 1-, 2-, (average Δ 0.83, $p<0.001$).In the group of stimulation with 6.5V all locations but one combination were significantly different from each other. Only 6.5.V at 0- was not different from 6.5V at 3- (compare figure 3). Additionally, out of all stimulation settings, only stimulation with 6.5V at 0-, 2- or 3- was significantly different from OFF or 6.5V at 1-2-3- ($p<0.001$). Compared with OFF, stimulation with 6.5V at 0- (Δ= 1.17) at 2- (Δ= 2.08) or 3- (Δ= 0.87) resulted in an increase in SCR. Compared with 6.5V at 1-2-3-, stimulation with 6.5V at 0- (Δ= 1.05) at 2- (Δ= 1.96) or 3- (Δ= 0.75) resulted in an increase in SCR. Note that 6.5V at 1-2-3-, 6V at 1-2-3- and OFF did not differ significantly from each other. Figure 4 shows the average SCR for different locations under identical voltage.

Insert Figure 4 about here

DISCUSSION

The most prominent result is that the subject produced a positive early peak instead of the expected negative peak could be explained besides. The P300 is sensitive to top-down cognitive processes (10), and the subject reports that since his AC, he lost his ability for intuitive bottom-up experience of emotions and has to rely on a cognitive appraisal of stimuli to come to socially acceptable evaluations. An anchoring effect followed by appraisal based on memory retrieval could explain why ratings of Valence and Arousal differed from the normative sample and showed little variance. We assume therefore that DBS was, most likely due to the AC, not able to sufficiently affect the cognitive processes that govern psychological outcomes like the SAM.

Fitting this interpretation, the results suggest that effects on a less conscious physiological level exist, especially for higher voltage. Varying location while stimulating with 2V seems to have only a limited effect on correlates of emotional processing. Instead, for 6.5V significant differences of location could be found. This is especially noteworthy, as it is generally assumed that higher voltage leads to stimulation of areas overlapping with other electrode locations, implying reduced distinction of effects, and our findings contradict this idea. Stimulation with 6.5V at 1- is in comparison with other stimulation settings followed by attenuation of SCR and the early peak mean power, while stimulation with 6.5V at 0- and 2- lead to an increase of SCR and the early peak mean power. Interpreting this results, we advised to continue stimulation with high voltage and only for 0- and 2-. Sadly, the patient reports that this stimulation change did not affect the conscious experience of his affective attenuation.

Even without leading to an obvious success, we believe that this or similar approaches are useful tools to assess the effects of DBS of the NAc. Especially for psychiatric cases, where there is no simple motor symptom, an intense psychophysiological assessment could improve stimulation parameter finding. Stimulation artifacts induced by DBS posed no large problems and it was possible to filter them out sufficiently well for data analysis. While the

patient complained at times about the long duration of the sessions, and grew tired, he was able to conclude all sessions. We advise to reduce to limit the amount of stimulation parameters tested or spread the runs over more, but shorter sessions.

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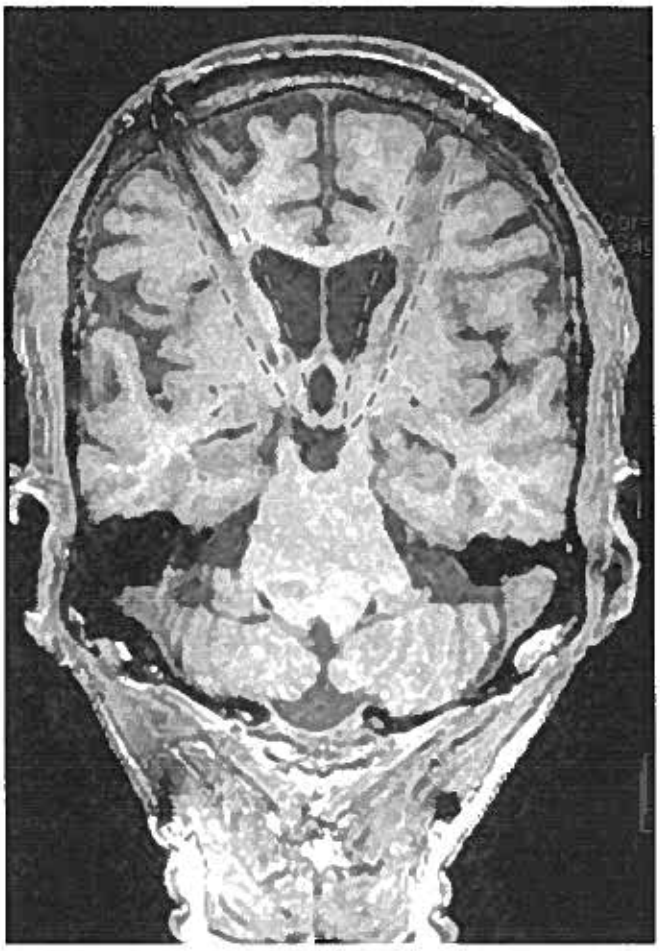

Fig. 1. Magnetic resonance imaging showing the position of the deep brain stimulation electrodes. Bilateral stimulation of the nucleus accumbens (NAc).

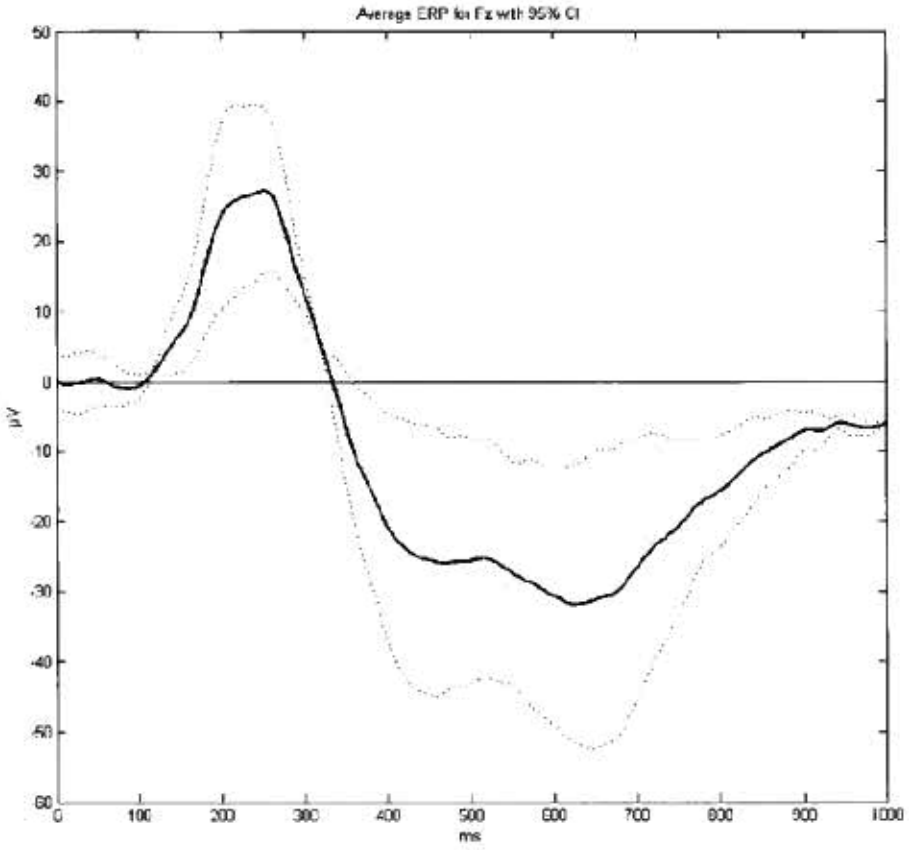

Fig. 2. ERP averaged over for all settings with 95% confidence intervals

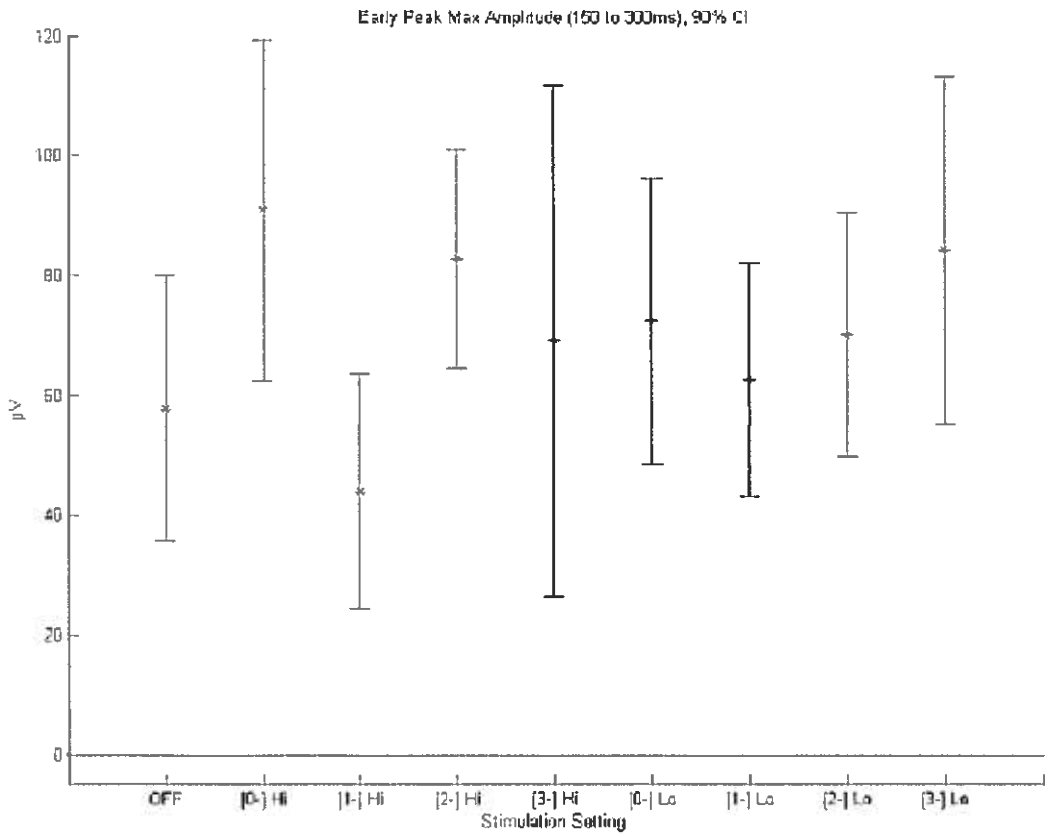

Fig. 3. 90% confidence intervals of early peak amplitude from 150 to 300ms for different settings, each electrodes and voltage setting (OFF: no stimulation, Hi: 8.5 V; Lo: 2V)

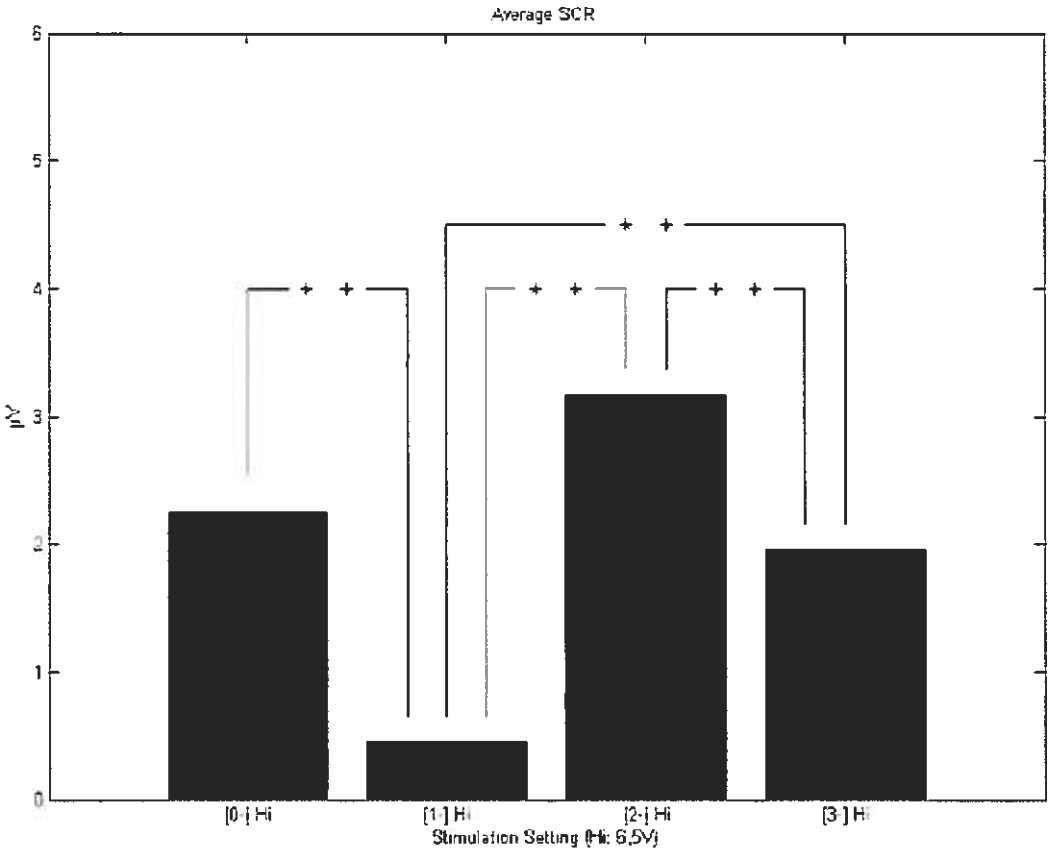

Fig. 4. Average SCR for different locations under identical voltage