Addiction Biology

BRIEF REPORT: PRECLINICAL RESEARCH

doi:10.1111/j.1369-1600.2011.00337.x

Successful deep brain stimulation of the nucleus accumbens in severe alcohol dependence is associated with changed performance monitoring

Jens Kuhn[1]*, Theo O. J. Gründler[2,3]*, Robert Bauer[4], Wolfgang Huff[1], Adrian G. Fischer[2], Doris Lenartz[5], Mohammad Maarouf[5], Christian Bührle[5] Joachim Klosterkötter[1], Markus Ullsperger[2,6] & Volker Sturm[5]

Department of Psychiatry and Psychotherapy, University of Cologne, Germany[1], Max Planck Institute for Neurological Research, Germany[2], Department of Psychology, University of Trier, Germany[3], International Centre for Ethics in the Sciences and Humanities, Eberhard Karls University of Tübingen, Germany[4], Department of Functional Neurosurgery and Stereotaxy, University of Cologne, Germany[5] Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen, the Netherlands[6]

ABSTRACT

Following recent advances in neuromodulation therapy for mental disorders, we treated one patient with severe alcohol addiction with deep brain stimulation (DBS) of the nucleus accumbens (NAc). Before and one year following the surgery, we assessed the effects of DBS within the NAc on the addiction as well as on psychometric scores and electrophysiological measures of cognitive control. In our patient, DBS achieved normalization of addictive behavior and craving. An electrophysiological marker of error processing (the error-related negativity) linked to anterior mid-cingulate cortex (aMCC) functioning was altered through DBS, an effect that could be reversed by periods without stimulation. Thus, this case supports the hypothesis that DBS of the NAc could have a positive effect on addiction trough a normalization of craving associated with aMCC dysfunction.

Keywords Alcohol addiction, corticomesolimbic pathway, craving, deep brain stimulation, error-related negativity, nucleus accumbens.

Correspondence to: Jens Kuhn, Department of Psychiatry and Psychotherapy, University of Cologne, Kerpener Strasse 62, Cologne 50937, Germany. E-mail: jens.kuhn@uk-koeln.de

Chronic alcohol consumption elicits a diffuse pattern of neurochemical changes and is associated with a dysfunction in corticomesolimbic circuitry as well as pernicious cognitive impairments. The abstinent addicted brain is primed to return to drug use when triggered by a single use of a drug, contextual drug cues, craving or stress. The obsessive drive toward drug use (craving) is complemented by deficits in impulse control and decision-making, processes thought to be mediated by the nucleus accumbens (NAc), orbitofrontal cortex and anterior mid-cingulate cortex (aMCC). The chronic use of drugs therefore appears to affect higher order neuronal circuitry. Executive functions, such as planning, decision-making and attentional processes show an amplified response to drug-related stimuli and all subserve drug acquisition and ingestion (Kalivas & Volkow 2005).

The ability to monitor action outcomes and deriving appropriate adaptations in behavior, e.g. in the presence of craving-related cues, is based on the function of a performance monitoring system encompassing—among others—two key structures, namely the NAc and aMCC (Ridderinkhof *et al*. 2004). Activity of the aMCC can be estimated non-invasively by extracting the error-related negativity (ERN) from the scalp-recorded electroencephalogram (EEG). The ERN, an event-related brain potential associated with the commission of errors, is assumed to be generated in the aMCC and is a psychophysiological marker well-suited to assess the functional integrity of the performance monitoring system

*Equal contribution.

(Ullsperger 2006). Acute alcohol intake and chronic substance abuse are characterized by reduced aMCC activity and consequently, by attenuated ERN amplitudes (Ridderinkhof *et al.* 2002; but see: Schellekens *et al.* 2010).

Recently, we reported on a patient with alcohol dependence who showed a substantial reduction of his alcohol consumption after deep brain stimulation (DBS) of the NAc, even though the primary therapeutic aim, namely to improve his anxiety disorder, was not achieved (Kuhn *et al.* 2007). In addition, studies on animal models demonstrated that addictive behavior can also be ameliorated by application of DBS in the NAc (Vassoler *et al.* 2008; Knapp *et al.* 2009; Henderson *et al.* 2010). Lately, successful treatment with DBS of three cases with chronic therapy refractory alcohol dependence were reported from another center using a similar approach (Müller *et al.* 2009).

Here, we report on a 69-year-old male suffering from alcohol dependence for more than 30 years. The average daily consumption was estimated to be 200 g of vodka. Administration of the Alcohol Use Disorders Identification Test (AUDIT) yielded a score of 32 points, and the carbohydrate deficient transferring (CDT) value was 7.8 %. The severity of this disorder was further substantiated by the fact that the patient was only able to consume alcohol through self-injection in his percutaneous endoscopic gastrostomy probe after a laryngeal resection for an alcohol-associated larynx tumor in 1997. To date, he has received numerous detoxifications, withdrawal treatments and psychopharmacological interventions resulting only in short abstinence periods of some days up to a maximum of a few weeks.

Only after careful consideration and once the otherwise neurological and psychiatric healthy patient had given written informed consent, surgery was performed using quadripolar electrodes (Medtronic 3387; Medtronic, Inc., Minneapolis, MN, USA; for surgical details, see supporting information). Independent from the surgery, a separate written and informed consent by the patient, as well as approval from the ethics committee, was obtained for all electrophysiological measures.

To assess the extent of alcohol abuse, we used the following range of tests: Alcoholism Dependence Scale (ADS), AUDIT, the Craving Believe Questionnaire, the Inventory of Drinking Situation and the Obsessive Compulsive Drinking Scale (OCDS-G) (see supporting Table S1). Scores were obtained at different time points: immediately after admittance to the hospital (T-1), two weeks later and immediately before surgery (T0), two weeks (T1), four months (T2), eight months (T3) and one year (T4) after surgery. Additionally, at T0, T2, T3 and T4, EEG recordings were taken while the patient engaged in a task designed to elicit a sufficient number of errors to access cognitive control (Flanker task; see Fig. 1, Fig. S1 and

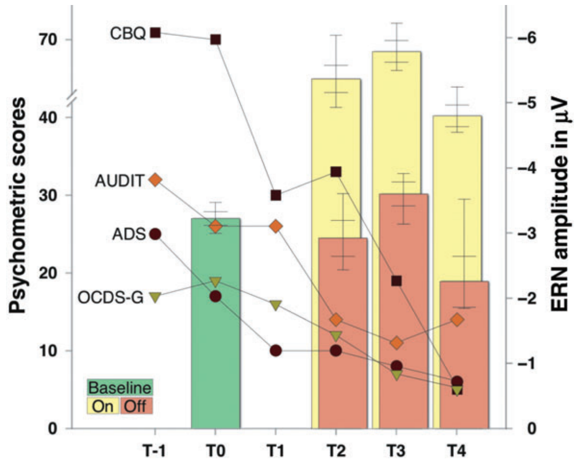

Figure 1 Psychometric scores and error-related negativity (ERN) amplitudes at different time points. T-1: Admittance to clinic; T0: prior to surgery; T1: two weeks after surgery; T2: four months after surgery; T3: eight months after surgery; T4 one year after surgery and continuous bilateral high-frequency deep brain stimulation (DBS) of the nucleus accumbens. Postsurgical ERN amplitudes are shown for conditions with and after 24-hour withdrawal of DBS. Error bars denote 99.73% (±3 SD) asymmetric confidence intervals and symmetric (more narrow) standard errors of the mean. Abbreviations (range): ADS = Alcoholism Dependence Scale (0–47); AUDIT = Alcohol Use Disorders Identification Test (0–40); CBQ = Craving Believe Questionnaire (0–120); OCDS-G = Obsessive Compulsive Drinking Scale (0–40); ERN = error-related negativity

Supporting Information). For that purpose, the participant has to press a left or right response button in line with the orientation of a briefly presented target arrow. Distracter arrows flanking the target arrow induce about 15–20% erroneous responses when pointing in the incongruent direction. The ERN can be observed in the EEG approximately 30–80 ms following errors of commission. To estimate the immediate effect of stimulation at T2, T3 and T4, the patient was tested both under stimulation and at the end of a 24-hour period without stimulation (see supporting information). The patient was not blinded to his condition and kept under close observation to prevent relapse during all follow-up measurements, the orders of which were alternated between time points

After initiation of DBS in October 2008, a considerable improvement of our patient's drinking behavior was reported. Eight months after commencing DBS, the patient only consumed alcohol occasionally and ceased to consume alcohol completely after one year. The CDT normalized to 1.9 %. Accordingly, there was also a marked reduction in all psychometric scores (Fig. 1 and supporting Table S1). Especially the ADS and the OCDS-G, as primary measures of alcohol dependence, fell below pathological scores.

The ERN amplitude increased over the year with DBS (from T0: –3.2 µV to T4: –4.8 µV). Most remarkably, the

ERN amplitude was also significantly enlarged during all postsurgery measurements compared with the respective 24-hour off-DBS recordings (see Fig. 1 and supporting Fig. S1 and Table S2). The error rate dropped from 23.4% presurgically to a range between 12.3% at T4 and 14.7% at T2 in postsurgical measures. This change in error rates was independent of whether DBS was switched on or off, which might possibly indicate an effect of attention. Reaction times did not vary systematically across time points (supporting Table S2).

Performance monitoring is a key feature in adaptive control since it regulates both short- and long-term adjustments to environmental cues as well as behavioral alterations. The ERN is known to be a stable and reliable index of functional integrity of the aMCC and the connected executive function network. In externalizing disorders such as addiction, the ERN is found to be attenuated. The ability to monitor ongoing processes for erroneous outcomes is a prerequisite for adequate performance. The brain's possible attenuated capability to detect action slips before surgery, expressed in the much lower ERN amplitude, and its consistent and reliable restoration with neural stimulation in our tests might implicate regained cognitive control as an outcome of DBS of the NAc in addictive behavior leading to the suppression of craving and consequently, less alcohol consumption. This promising hypothesis deems further clinical trials.

In conclusion, we found that in our case, DBS of the NAc led to a significant reduction of drug consumption and modulated associated deficits in cognitive control as reflected in an electrophysiological marker. Although the exact mechanisms by which DBS achieves therapeutic effects remains currently unclear, it seems reasonable to suggest that NAc DBS may achieve therapeutic effects by normalizing the function of a neural circuit that shows aberrant activity in addiction. Finding that neural stimulation is able to increase cognitive control might be an interesting hint at underlying mechanisms of craving and abuse. This hypothesis clearly demands further investigations expanding the validity of our single case study.

FINANCIAL DISCLOSURES

JK, RB, MU, JK, WH, TOJG and AGF reported no biomedical financial interests or potential conflicts of interest. DL reports having received financial assistance for travel to congresses from Medtronic AG. MM has occasionally received honoraria from Medtronic for lecturing at conferences and consulting. VS disclosed financial support for studies and travel to congresses and lecture fees from Medtronic AG and Advanced Neuromodulation Systems Inc. He also reported to be coholder of patents on desynchronized brain stimulation and joint found of ANM-GmbH Jülich, a company that intends to develop new stimulators.

Authors Contribution

JK, TOJG, MU, VS and JK were responsible for the study concept and design. AGF, DL, MM, CB assisted with acquisition of the data. JK, WH, TOJG, AGF and MU were responsible for data analysis and interpretation of findings. JK, TOJG, RB and MU drafted the manuscript. All authors have critically reviewed content.

References

Henderson MB, Green AI, Bradford PS, Chau DT, Roberts DW, Leiter JC (2010) Deep brain stimulation of the nucleus accumbens reduces alcohol intake in alcohol-preferring rats. Neurosurg Focus 29: E12.

Kalivas PW, Volkow ND (2005) The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry 162:1403–1413.

Knapp CM, Tozier L, Pak A, Ciraulo DA, Kornetsky C (2009) Deep brain stimulation of the nucleus accumbens reduces ethanol consumption in rats. Pharmacol Biochem Behav 92:474–479.

Kuhn J, Lenartz D, Huff W, Lee S, Koulousakis A, Klosterkoetter J, Sturm V (2007) Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? J Neurol Neurosurg Psychiatry 78:1152–1153.

Müller U, Sturm V, Voges J, Heinze H-J, Galazky I, Heldmann M, Scheich H, Bogerts B (2009) Successful treatment of chronic resistant alcoholism by deep brain stimulation of nucleus accumbens: first experience with three cases. Pharmacopsychiatry 42:288–291.

Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S (2004) The role of the medial frontal cortex in cognitive control. Science 306:443–447.

Ridderinkhof KR, de Vlugt Y, Bramlage A, Spaan M, Elton M, Snel J, Band GPH (2002) Alcohol consumption impairs detection of performance errors in mediofrontal cortex. Science 298:2209–2211.

Schellekens AFA, De Bruijn ERA, van Lankveld CAA, Hulstijn W, Buitelaar JK, de Jong CAJ *et al.* (2010) Alcohol dependence and anxiety increase error-related brain activity. Addiction 105:1928–1934.

Ullsperger M (2006) Performance monitoring in neurological and psychiatric patients. Int J Psychophysiol 59:59–69.

Vassoler FM, Schmidt HD, Gerard ME, Famous KR, Ciraulo DA, Kornetsky C, Knapp CM, Pierce RC (2008) Deep brain stimulation of the nucleus accumbens shell attenuates cocaine priming-induced reinstatement of drug seeking in rats. J Neurosci 28:8735–8739.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Approach to measure executive functioning and resulting event-related potential. (a) Schematic diagram of the speeded modified flanker task. The participant has to respond rapidly to the central (target) arrow by pressing the left or right response button according to the direction indicated by the target. The flanking arrows, which in 50% of the trials are incongruent with the target, i.e. point in the opposite direction, were introduced to induce response conflict and resulted in more frequent erroneous responses. (b) Average waveform of the error-related negativity (ERN) at midline electrode FCz. The ERN amplitude was increased under neural stimulation as compared to baseline and off-stimulation measurements. Gray shading indicates the analyzed time-window

Table S1 Questionnaire data.

Table S2 Electrophysiological and behavioral data.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.