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LETTERS TO THE EDITOR

DISCovery in psychiatric genetics

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The Guest Editorial by Sullivan[1] on DISC1 reflects not only his limitations in understanding biology, but more broadly reflects those of a group of statistically trained non-biologists who are currently very active (and vocal) in psychiatric genetics. Illness works through alterations in biology. Biology works at a gene level and not at a single-nucleotide polymorphism (SNP) level. Biologically important genes such as *DISC1* (or *BDNF* or *COMT*) have more SNP heterogeneity and diversity in the population[2] likely owing to the need to evolutionarily adapt and fine-tune the interface between organism and environment.[3] Integrative approaches at a gene level clearly demonstrate their involvement and show reproducibility[4] as opposed to the statistically driven SNP-focused Genome-Wide Association Study (GWAS) approaches of Sullivan and colleagues[5] that have identified primarily housekeeping genes to date (such as *ANK3*, *CACNA1C* and *ODZ*). In fact, SNP-focused GWAS approaches miss the boat on their own data. The overlap between GWAS studies is 100-fold greater at a gene level than at a nominally significant SNP level[4]. Moreover, what non-biologists do not understand is how the brain (or for the matter, the body) works. Schizophrenia, like other complex disorders, is a broad entity overlapping with other disorders. Genes and their products are building blocks that in different combinations, and in different environmental contexts, give different psychiatric and non-psychiatric syndromes. In the sporting tradition of years past in science, before things became rather boring and politically correct, I would like to wager with Sullivan[1] the following: whomever is wrong between the two of us on this subject should write a Letter to Molecular Psychiatry in 2020, titled *Mea Culpa on DISC1*.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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Deep brain stimulation of the nucleus accumbens and its usefulness in severe opioid addiction

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Deep brain stimulation (DBS) of the nucleus accumbens (NAcc) has been recently reported to modulate substance-induced dysfunction and to promote an alteration of addictive behavior.[1–4] Here, we describe DBS-induced sustained heroin abstinence in two therapy-resistant opioid addicted patients treated during the piloting phase to our clinical trial NCT01245075. Inclusion was based on (1) longtime heroin addiction according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (2) at least one detoxification (here: up to 20 detoxifications) without a prolonged phase of abstinence and (3) longtime opiate replacement therapy with a constant dose of levomethadone (Ethics approval has been obtained for both pilot testing and clinical trial.)

Both patients were yet consuming other psychotropic substances (Pat.1: alcohol and amphetamines, Pat.2: amphetamines and benzodiazepines). Stereotactic implantation of NAcc electrodes (Model 3389, Medtronic Inc., Minneapolis, MN, USA), as well as empirical testing of the optimal stimulation parameters (patient 1 bilateral: -0,-1, + case; 140 Hz; 120 μs; 5,0 V and patient 2 bilateral: -0,-1,-2, + case; 130 Hz; 90 μs; 4,5 V) was carried out in analogy to previous reports.[1–3] Patient 2, who has had epileptic seizures before, experienced an epileptic seizure 2 days after surgery; no further peri- or postoperative side effects have been observed.

A 10- point visual analog scale (VAS), ranging from 1 (no craving) to 10 (intense craving) was used to estimate the patients' subjective level of craving.[5] Levomethadone (patient-blinded administration) was gradually reduced if VAS <5 until tapered off completely (Figure 1), without resulting in increased craving for levomethadone or heroin, respectively (Figure 1). Although previous replacement treatments were not able to lastingly prevent heroin abuse, both patients, except for one singular incident of heroin consumption a few weeks after surgery, remained lastingly off heroin and levomethadone. Patients reported that this singular consumption was solely motivated by mere curiosity and that the psychotropic effect was perceived as clearly alleviated and did not reinstate chronic heroin abuse, as was confirmed by urine analyses.

In line with previous findings from DBS in depression[6] accumbal stimulation led to an amelioration of the patients' depressive and anxious symptoms, as well as an increase of the subjectively perceived quality of life (Figure 1). Both patients still reported the occasional consumption of other psychotropic substances arising out of boredom or coexisting private and occupational strains with at the same time lacking alternative behavioral patterns and compensatory social skills.

Recent findings from animal studies indicate that psychotropic substances (for example, cocaine) promote rather immediate changes of synaptic plasticity in D1- expressing accumbal neurons, which can be reversed by inhibitory optogenetic stimulation of

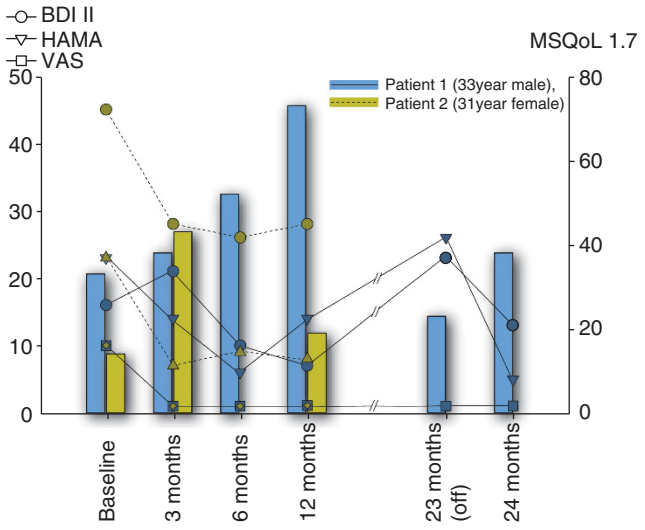

Figure 1. Graphical display of ratings of general quality of life (Modular System for the assessment of Quality of Life subscale 1.7[10]) (bars), mood (Beck Depression Inventory (BDI)), anxiety (Hamilton Anxiety Scale (HAMA)) and craving (VAS) (dashed and solid line) over a 2 and 1 year period of stimulation for patient 1 and 2, respectively. (Shortly before his 2 years follow-up examination, patient 1 reported a significant increase of alcohol and amphetamine consumption, accompanied by an increase of BDI and HAMA values, and an abatement of quality of life. However, an exchange of the battery was followed by a recovery of his psychiatric symptoms. We speculate that unchanged craving might be related to persisting synaptic plasticity[2]). (Funded by DFG (German Research Foundation) KFO 219, Else Kröner-Fresenius-Stiftung and BMBF (German Federal Ministry of Education and Research (01KN1106)).

limbic afferents.[7] Furthermore, experiences of DBS in man also suggest a persisting modulation of synaptic plasticity,[2] as indicated by a lasting abstinence- sustaining effect of NAcc DBS even after explantation of the stimulation device. On the basis of these findings, we hypothesize that NAcc DBS facilitates heroin and methadone abstinence by promoting neuroplastic changes in dopaminergic neurons.

It remains unclear whether the observed beneficial effects allow a generalization to other forms of substance addictions. However, the fact that the patients' comorbid drug consumption did not decline challenges this view. The interpretation of this circumstance in terms of a cross addiction, developing because heroin is no longer available, is also unlikely as the patients did not report increased craving for other psychotropic substances.

From a socio behavioral perspective, the application of DBS could have initially led to a heightened motivation to abstain from drugs. However, the disappointing awareness of persisting private and occupational strains in combination with lacking alternative problem solving strategies might account for the ongoing comorbid drug consume. Patient 2 for example, reported to consume amphetamines mainly to keep her weight in balance. Remaining psychosocial difficulties might likewise explain the renewed decrease of self-perceived quality of life (Modular System for Quality of Life (MSQoL) in patient 2, thereby underlining the importance of psychotherapy accompanying DBS in mental disorders to foster the acquisition of alternative behavioral strategies.[8]

Although the achieved abstinence from heroin in our patients is highly promising, clinical studies with larger samples (as the clinical trial that is to follow) are needed to further support our hypothesis, and to evaluate accumbal DBS as a cost effective treatment option[9] for otherwise treatment resistant drug addiction. Herein, emphasis must be placed on the patients' pattern of comorbid drug consumption.

CONFLICT OF INTEREST

Möller M, Treppmann JF, Bartsch C, Gruendler TOJ, Brosig A, Barnikol UB and Klosterkötter J declare no conflict of interest. Kuhn J has occasionally received honoraria from AstraZeneca, Lilly, Lundbeck and Otsuka Pharma for lecturing at conferences and financial support to travel. Kuhn J received financial support for IIT-DBS studies (not the present investigation) from Medtronic GmbH (Meerbusch, Germany). Lenartz D reports having received financial assistance for travel to congresses from Medtronic AG. Maarouf M has occasionally received honoraria from Medtronic for lecturing at conferences and consulting. Strum V 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 a co-holder of patents on desynchronized brain stimulation and shareholder of ANM-GmbH Jülich, a company that intends to develop new stimulators.

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Microbiota is essential for social development in the mouse

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The microbiota–gut–brain axis is an emerging concept in modern medicine informed by the ability of gut microbiota to alter brain and behaviour.[1] Although some clinical studies have revealed altered gut microbiota composition in patients with neurodevelopmental disorders such as autism,[2,3] the specific

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