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Behavioural and physiological effects of electrical stimulation in the nucleus accumbens: a review

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Summary

Electrical stimulation (ES) in the brain is becoming a new treatment option in patients with treatment-resistant obsessive-compulsive disorder (OCD). A possible brain target might be the nucleus accumbens (NACC). This review aims to summarise the behavioural and physiological effects of ES in the NACC in humans and in animals and to discuss these findings with regard to neuroanatomical, electrophysiological and behavioural insights. The results clearly demonstrate that ES in the NACC has an effect on reward, activity, fight-or-flight, exploratory behaviour and food intake, with evidence for only moderate physiological effects. Seizures were rarely observed. Finally, the results of ES studies in patients with treatment-resistant OCD and in animal models for OCD are promising.

Keywords: Neuromodulation; electrical stimulation; behaviour; nucleus accumbens; ventral striatum; review.

Abbreviations

5-HT serotonin; *6-OH-DA* 6-hydroxydopamine; *AMY* amygdala; *DA* dopamine; *DAergic* dopaminergic; *DOPAC* 3,4-dihydroxyphenylacetic acid; *DTγE* (Des-Tyr[1])-γ-endorphin; *ES* electrical stimulation; *FCV* fast cyclic voltammetry; *GABA* gamma-aminobutyric acid; *HC* hippocampus; *HVA* homovanillic acid; *ICSS* intracranial self-stimulation; *LH* lateral hypothalamus; *MD* mediodorsal thalamic nucleus; *MDMA* methylenedioxymethamphetamine; *MFB* medial forebrain bundle; *NA* noradrenaline; *NACC* nucleus accumbens; *SN* substantia nigra; *SNc* substantia nigra pars compacta; *SNr* substantia nigra pars reticulata; *VP* ventral pallidum; *VTA* ventral tegmental area.

Introduction

Some patients with obsessive-compulsive disorder (OCD) are treatment-refractory to conventional behavioural therapy and/or pharmacological treatment. Part of these patients may benefit from a neurosurgical lesion in a specific brain target [36, 46]. In one of those brain targets, the anterior limbs of the internal capsule [60, 67], we demonstrated that high frequency ES was also therapeutically effective [77]. In contrast to neurosurgical lesions, electrical brain stimulation is a reversible technique, which is a major advantage in case severe side effects occur. Moreover, in Parkinson's disease ES has a lower rate of side effects compared to lesioning with thermocoagulation [103].

Although the clinical outcome of ES in the anterior limbs of the internal capsule is satisfactory, high voltage levels are necessary. Hence, the battery lifetime is limited to 4–12 months requiring frequent exchange of the batteries under local anaesthetic, limiting the comfort of the patient. One of the strategies to surpass the high energy consumption is to search for other brain targets that yield the same or even better therapeutic results with a lower voltage.

A possible new target for ES in patients with treatment-refractory OCD might be the nucleus acccumbens (NACC) [1, 117], which participates as the antero-ventral part of the ventral striatum in the cortico-striato-pallido-thalamo-cortical circuitry. Functional brain imaging studies indicate that this circuitry is involved in OCD [100]. Additional evidence for the involvement of the NACC in OCD comes from stereotactic lesioning studies in the anterior limbs of the internal capsule. Lesioning of the ventro-caudal part of the internal capsule was imperative for successful treatment. It is likely that such a lesion also affects the NACC [67, 110]. The

current article reviews the reported behavioural and physiological effects of ES in the NACC of humans and different mammalian species.

Methods and results

We performed a computer-aided search of Pubmed using the keywords 'nucleus accumbens', 'ventral striatum' and 'ES' and selected articles dealing with the behavioural and physiological effects of ES in the NACC. In addition, we searched the reference lists of these selected relevant articles. Because we cannot read or comprehend Chinese language one article was rejected [53]. The results of our search are described in the following sections.

Anatomy of the NACC

Core and shell NACC

The NACC has been subdivided in a core and shell subregion based on cytoarchitectonic and neurotransmitter characteristics and differences in afferent and efferent connections [142]. The shell is situated in the medial

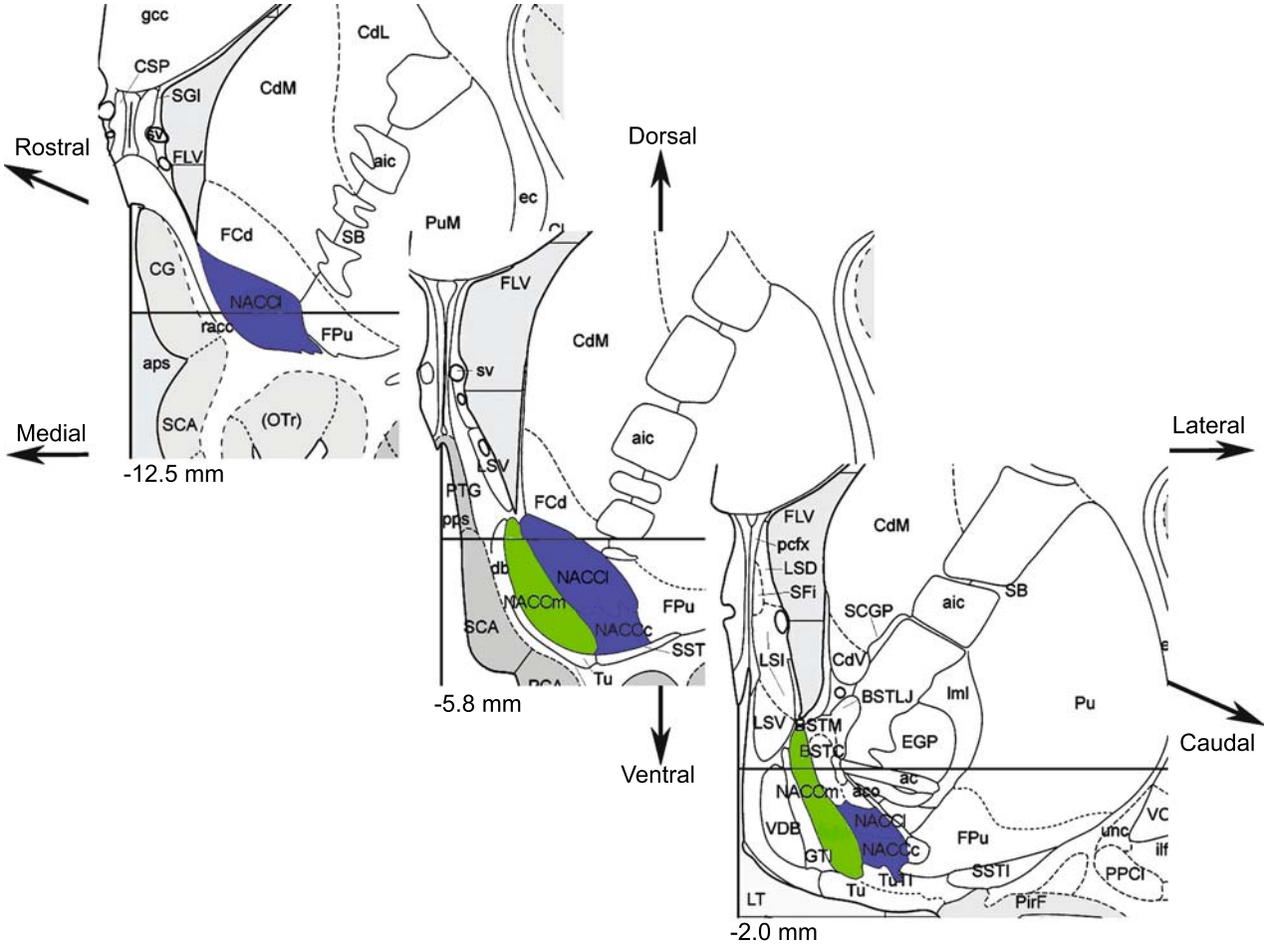

Fig. 1. NACC core and shell: Graphical representation of coronal sections through the human NACC core (blue) and shell (green) and its surrounding structures (modified from the atlas of Mai *et al.* 63). The distance from the midpoint of the anterior commissure at the midline is denoted below each coronal section. *ac* Anterior commissure; *aco* anterior commissure, olfactory limb; *aic* anterior limb of internal capsule; *aps* anterior parolfactory nucleus; *BSTC* bed nucleus of the stria terminalis, central division; *BSTLJ* bed nucleus of the stria terminalis, lateral division, juxtacapsular part; *BSTM* bed nucleus of the stria terminalis, medial division; *CdL* lateral caudate nucleus; *CdM* medial caudate nucleus; *CdV* ventral caudate nucleus; *CG* cingulate gyrus; *CSP* cavity of septum pellucidum; *db* diagonal band; *ec* external capsule; *EGP* external globus pallidus; *FCd* caudate fundus region; *FLV* frontal horn of the lateral ventricle; *FPu* putaminal fundus region; *gcc* genu of the corpus callosum; *GTI* great terminal island; *lml* external medullary lamina of the globus pallidus; *LSD* dorsolateral septal nucleus; *LSI* intermediolateral septal nucleus; *LSV* ventrolateral septal nucleus; *NACCc* acccumbens nucleus, central (subventricular) part (core); *NACCl* accumbens nucleus, lateral subventricular part (core); *NACCm* accumbens nucleus, medial (subventricular) part (shell); *OTr* olfactory trigone; *pcfx* precommissural fornix; *PirF* (pre-)piriform cortex, frontal area; *PPCI* (pre-) piriform claustrum; *pps* posterior parolfactory sulcus; *PTG* paraterminal gyrus; *PuM* medial putamen; *racc* radiation of corpus callosum; *SB* striatal cell bridges; *SCA* subcallosal area; *SCGP* supracapsular part of the globus pallidus; *SFi* septofimbrial nucleus; *SGI* substantia gliosa; *SSTI* substriatal terminal island; *sv* septal vein; *Tu* olfactory tubercle; *TuTl* tubercular terminal island(s); *unc* uncinate fasciculus; *VDB* vertical limb of the diagonal band

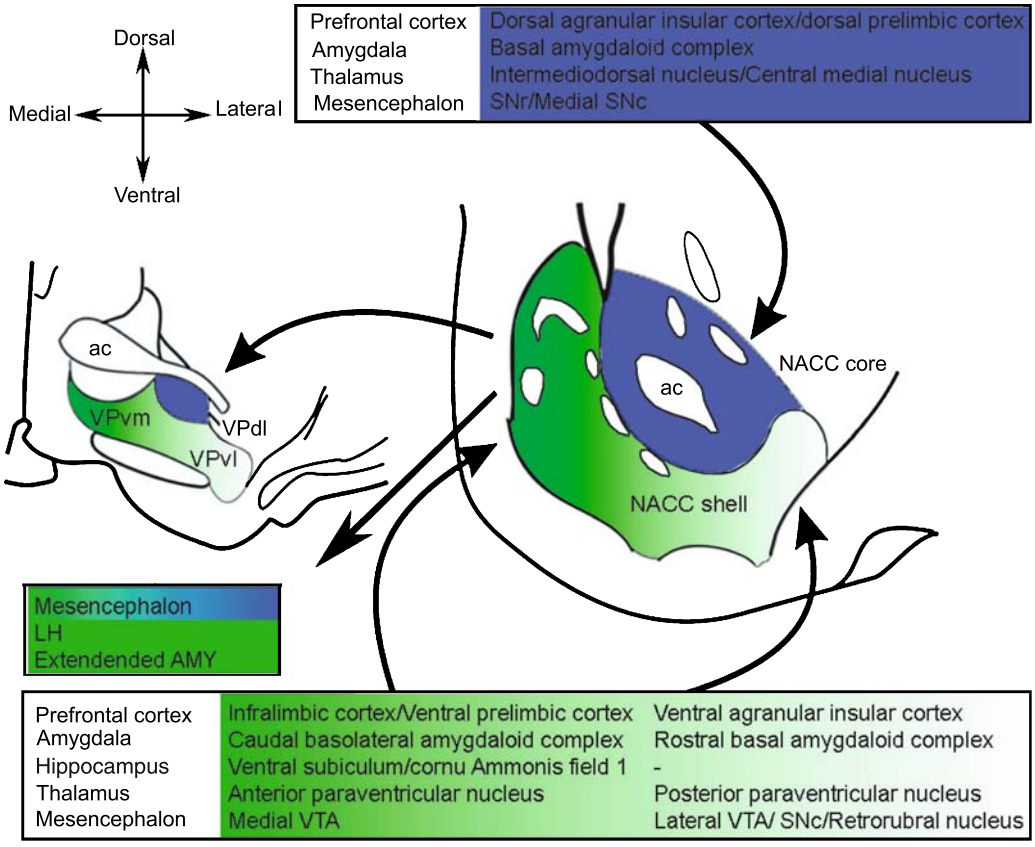

Fig. 2. Neuroanatomical connections of the NACC: The topographical organisation of the main afferents and the VP efferents of the NACC core and shell is represented in a transverse section through the NACC (right) and the VP (left) (modified from Ref 15). *ac* Anterior commissure; *NACC* nucleus accumbens; *VPdl* dorsolateral ventral pallidum; *VPvl* ventrolateral ventral pallidum; *VPvm* ventromedial ventral pallidum

and ventral part of the caudal two thirds of the NACC and encompasses the core, situated laterally in the NACC [19] (Fig. 1). The NACC core is connected to the extrapyramidal motor system and the NACC shell to limbic brain areas mediating emotional processes. In addition to the NACC shell and core, some authors have recognized a rostral pole [152].

Main afferent and efferent projections

We shortly summarize the main connections of the NACC (see Fig. 2) but refer to other reviews for in depth expositions of the NACC neuroanatomy in the rat [37] and nonhuman primates [39]. For a topographical organisation of the connections of the NACC core and the shell, we refer to the Fig. 2 (obtained with permission from 37).

The NACC receives mainly glutamatergic projections from the amygdala (AMY) [92], hippocampus (HC) [17, 61, 121, 135, 150], thalamus [6, 9] and prefrontal cortex (PFC) [11, 13, 23, 34, 71, 72, 105, 113] and a dopaminergic (DAergic) projection from the mesencephalon, i.e. ventral tegmental area (VTA) and substantia nigra (SN) [22, 85]. The major efferent projection from the NACC terminates in the ventral pallidum (VP) and is principally gamma-aminobutyric acid (GABA)ergic [14, 41, 137, 143]. The ventral pallidum, in turn, projects strongly to the substantia nigra pars compacta (mediolateral part) as well as to the limbic part of the subthalamic nucleus and its extensions into the local hypothalamus [38]. In addition, the NACC provides a recurrent projection to the VTA and SN in the mesencephalon [41]. An important difference between NACC core and shell is the efferent projection from the NACC shell to the lateral hypothalamus (LH) and the extended AMY, which does not exist in the NACC core [41].

Signal processing in the NACC

'Up' and 'down' membrane potential states

More than 90% of the projection neurons in the NACC are medium-sized neurons with spines on their dendrites [4, 12, 79]. These neurons show membrane

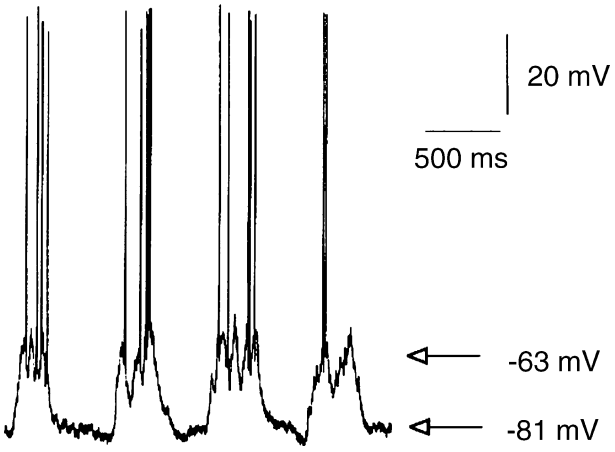

Fig. 3. Typical firing pattern of NACC neurons: Typical firing pattern of most NACC neurons exhibit 'up' and 'down' states in their membrane potential. Action potential firing is only observed during these 'up' events (reprinted from O'Donnell, 1999 [46])

potential shifts (±20 mV) from a negative 'down' state to a depolarized 'up' state [141] (Fig. 3), which are regulated by inputs from the HC [80] and the VTA [35]. The potential shifts bring the membrane potential during 100–1000 ms close to the firing threshold enabling other inputs (e.g. from the PFC) to evoke action potentials in the NACC (see Fig. 3). Hence, afferents from the HC and the VTA are able to gate other inputs. In accordance, slow frequency firing was recorded in the NACC during the 'up' state membrane transitions, taking place at a frequency less than 1 Hz [35].

Neuronal ensembles

The transitions in membrane potentials to the 'up' state occur synchronously in ensembles of NACC neurons, rather than in the global NACC or in single NACC neurons [81]. Many of the afferent projections from the abovementioned brain areas converge their input on single NACC neurons and their dendrites within these ensembles [18, 106]. Based on the topographical organisation of afferent connections to the NACC, each of these ensembles integrates different inputs. Likewise, the NACC ensembles relay the input to distinct output areas upon activation.

Presynaptic modulation of input

In addition to directly modulating the neuronal activity of NACC neurons, afferent projections also modulate the input of other afferents. For instance, VTA activation of D2 receptors on terminals of hippocampal afferents to the NACC, enhances the excitability of these neurons [136].

Behavioural effects of ES in the NACC

ES in the NACC has an effect on a wide range of behaviours, which will be discussed in the following sections. ES in the NACC has rewarding properties: animals with an electrode in the NACC will perform *self-stimulation (intracranial self-stimulation)* to apply electrical pulses in the NACC. In addition, ES in the NACC influences activity, fight-or-flight behaviour, exploratory behaviour and food intake. The effect of ES in the NACC on OCD symptoms in animal models and humans will be discussed in the following sections. Finally, the risk for seizures will be evaluated.

Reward – intracranial self stimulation (ICSS)

In 1954, Olds and Milner discovered that rats perform an operant task to apply trains of electrical pulses in the septal area and other regions of the brain [82]. This behaviour, called intracranial self-stimulation, has rewarding properties probably by activation of neural systems, which mediate natural rewards like food intake [126]. Therefore, ICSS has been used in models for depression to quantify the ability to experience pleasure. In these models, a decrease in ICSS rate or an increased threshold for ICSS is indicative for depression. The clinical effect of supposed new antidepressants was predicted in the animal models by evaluating the effect on ICSS rate or threshold. The NACC is one of the brain targets where it is possible to induce ICSS (for references, see below). In the NACC, ICSS is accompanied by a highly stereotypic backing away from the lever, sniffing, licking and digging [69].

Regional differences in ICSS rate within the NACC

The rate of ICSS in the NACC may be more than 20 per minute [95]. It depends on the NACC subregion where the electrode tip is located. In mice, differences in ICSS rates were noticed with rostro-caudal and dorso-ventral gradients. In the dorsal NACC, ICSS rates were very high rostrally but decreased more caudally. To the contrary, in the ventral NACC, ICSS rates were almost absent rostrally whereas good ICSS rates were observed caudally, with even higher values than in the dorsal NACC at this level. In regions intermediate between dorsal and ventral NACC, there was generally a good responding with higher ICSS rates caudally then rostrally [147]. In another study, a medio-lateral gradient was observed with higher ICSS rates in the medial NACC [89]. Only in one study,

in Rhesus monkeys, no ICSS was observed in the NACC [133].

ICSS in the NACC versus ICSS in other brain targets

There are also differences in ICSS rates between the NACC and other brain regions. ICSS rates in the NACC are lower than in the LH [123, 93], the medial forebrain bundle (MFB) [99, 144], the VTA [69, 123], the PFC [109] and the substantia nigra (SN) [8, 90, 144] but higher than in the caudatoputamen, the AMY and the olfactory tubercle [89]. One study found no difference in ICSS rate in the NACC versus the SN [21]. Except for the above-mentioned studies, no other comparisons in ICSS rate between NACC and other brain targets were reported. These differences in ICSS rates between brain areas, however, may depend on the duration of the test period. For instance, it was reported that rats self-stimulate at the same rate in the NACC like in the LH but that rats with an ICSS electrode in the NACC need more days to achieve these equal ICSS rates [47]. Differences in the number of days to acquire ICSS were also observed within the NACC itself. ICSS was faster acquired in dorsomedial anterior versus posterior NACC subregions [147].

Stimulation parameters

In the ICSS paradigm, animals work to obtain *trains of electrical pulses* (train duration: 0.1–1 s [99, 149] in a rewarding brain area. In the NACC, animals will respond with higher ICSS lever pressing rates if the *frequency* of these pulses in the train is increased, with a plateau at approximately 60 Hz [123]. Also changes in pulse parameters influence the ICSS rate. The ICSS rate increases as a function of *current intensity* [8, 47, 69, 109] until a plateau is reached [90]. In rats with a lesion in the VTA (and consequently with a destruction of DAergic input to the NACC), ICSS decreased at higher current intensities [21]. As far as we know, there are no studies in which the effects of different *pulse widths* were compared. In most of the studies, pulse widths between 0.2 and 0.3 ms were used [59, 148]. Typical pulse *waveforms* used to induce ICSS in the NACC were monophasic [90] and biphasic square [148] wave pulses, as well as sine wave pulses [89].

Influence of stress on ICSS in the NACC

The NACC is not only involved in processing reward but also in mediating stress responses [130] (see also below: Fight-or-flight). Exposure to acute stress results in an enhanced DA and serotonin (5-HT) release in the NACC [7]. There is evidence that stress decreases the ability to experience NACC mediated reward. Uncontrollable footshock specifically decreases the ICSS rate in the NACC immediately after and even 7 days after application of the stressor, however, without affecting ICSS rate in the SN [8]. Desmethylimipramine, a tricyclic antidepressant, reverses this footshock-induced decrease in ICSS rate in the NACC [146]. Similar findings were observed after immunological stress: injection with sheep red blood cells in mice, an antigen that induces a peak immune response at the fourth day after inoculation, reduced the response rate for ICSS in the NACC on the third, the fourth and the fifth day after inoculation. The dose of sheep red blood cells is known to influence DA activity in the NACC. Another stressor, food deprivation, had no effect on the response rate for ICSS in the NACC. This is quite remarkable since the NACC is known to be involved in food intake [54] (see also below: Food intake). In other brain areas, like the MFB [99], the LH and the substantia innominata [95] ICSS rate clearly increased after food deprivation. Finally, it was observed that the effect of stress on ICSS in the NACC depends on the mouse strain [148]. While there was a decrease in ICSS rate in DBA/2J mice after footshock stress, an increase in ICSS rate was observed in BALB/cByJ mice and no change in C57BL/6Jmice.

Effect of drugs or brain lesions on ICSS in the NACC

One way to study the mechanism of ICSS in the NACC is to administer pharmacological agents of different classes and to evaluate the effect on ICSS. For a summary of the findings of the literature we refer to Table 2.

CNS stimulants

Cocaine, amphetamine and methylenedioxymethamphetamine (MDMA) are three stimulants of the central nervous system (CNS), which all induce a significant increase in DA metabolism in the NACC (Table 1). After administration of these stimulants, rats will start ICSS in the NACC at lower stimulation frequencies and will press more and at higher rates [84, 90, 149]. Only for MDMA, a derivative of amphetamine commonly known as ecstasy, a decrease in the total number of presses was observed. MDMA affects the serotonergic system and

Table 1. *Drug effects on ICSS in the NACC*

Drug	Species	Admin. route	Dose	Effect	Ref.
CNS stimulants					
Cocaine – Mainly blocks the uptake of DA, 5-HT and NA at the neuronal plasma membrane transporters [116]; rewarding properties are mediated via simultaneous actions on DA, 5-HT and NA transporters [116]; 0.5 and 1 mg/kg systemic cocaine increases DA in the NACC shell [87]	Wistar rat	IP	5 mg/kg 15 mg/kg	↑ ICSS rate & maximal rate, ↓ stimulation frequency threshold	[59]
Amphetamine	Wistar rat	SC	100 µg	↑ ICSS rate	[118]
– release of monoamines (especially DA and NA) from nerve terminals; 0.5–3 mg/kg amphetamine increases DA in the NACC 7–25-fold [52, 88];	Wistar rat	IP	0.3 mg/kg 1 mg/kg	↑ ICSS rate; highest dose: ↑ maximal rate & ↓ stimulation threshold	[59]
1–3 mg/kg reduces 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the NACC with more than 50% [52]; no effect on 5-HT levels in the NACC, except at high dose (9 mg/kg)	Charles River rats	IP	1 mg/kg	↑ ICSS rate, also increase in function of time	[90]
	Wistar rat	IP	1 mg/kg	↑ ICSS rate	[84]
+ 6-OH-DA lesion	Wistar rat	LH	not applicable	lesions neutralized the effect of amphetamine	[84]
MDMA – binds to DA, 5-HT and NA transporters and reverses the action of these transporters, resulting in the release of DA, 5-HT and NA in the synapse; 1–3 mg/kg induces a 3 fold increase of DA and 5-HT in the NACC [52]; 1–3 mg/kg increases DOPAC in the NACC by 75–80% [52]; 3 mg/kg decreased the 5-HT metabolite 5-HIAA by 60% [52]	Wistar rat	IP	0.5 mg/kg 2 mg/kg 4 mg/kg	highest dose: ↓ ICSS total lever presses & stimulation threshold	[59]
+ Methysergide antagonist at 5-HT2 receptor and agonist at some 5-HT1 receptors [108]	Wistar rat	IP	5 mg/kg	reversal of MDMA induced decrease in ICSS rate & maximal rate	[59]
+ Ketanserin 5-HT2 receptor antagonist	Wistar rat	IP		no effect on MDMA induced decrease	[59]
Methysergide	Wistar rat	IP	5 mg/kg	no effect	[59]
D2-like DA antagonists					
Haloperidol	Wistar rat	SC	5 µg	↓ ICSS rate	[118]
– D2-like DA antagonist with α-adrenergic receptor affinity; 0.1–1 mg/kg increases DA release in the NACC by 50% [16, 58]	Rhesus monkey	IM	0.1–0.4 mg/kg (1^*/2d) during 3 wks	ICSS at 25–75% lower stimulation amplitudes. This is reversible.	[104]
	Wistar rat	IP	0.07 mg/kg 0.2 mg/kg 0.67 mg/kg	↓ ICSS rate	[76]
+ Hyoscine muscarinic acetylcholine receptor antagonist; 0.5 mg/kg increases DA in the NACC [45]	Wistar rat	IP	0.3 mg/kg 1.5 mg/kg	attenuation of haloperidol induced decrease in ICSS rate	
Spiroperidol – D2-like DA antagonist	Albino rat	NACC homo-lateral	1 µg	58%↓ ICSS rate (range 25–83%)	[69]
		NACC contra-lateral	1 µg	no effect	

(*continued*)

Table 1 (*continued*)

Drug	Species	Admin. route	Dose	Effect	Ref.
Opioids and endorphins					
Naltrexone – μ opioid receptor antagonist [122]; lower affinity for δ and κ receptors, able to reverse agonists at δ and κ sites [122]; 1 mg/kg systemic naltrexone had no effect on basal DA in the NACC but reverses ethanol or food intake induced DA release in the NACC [5, 112]	Long-Evans rat	IP	2.5 mg/kg 5 mg/kg 10 mg/kg 20 mg/kg	↓ ICSS rate & ↑ stimulation frequency necessary to obtain the same ICSS rate, not dose dependent	[123]
(Des-Tyr^1)-γ-endorphin – endogenous non-opioid peptide which probably acts on presynaptic mesolimbic dopamine receptors [120]; DTγE has no effect on basal DA release in the NACC in vitro but suppressed K+-induced DA release [102]	Wistar rat	SC	2.5 μg/kg 25 μg/kg	↓ ICSS rate, dose dependent	[118]
α-endorphin – endogenous opioid peptide; 10 and 20 μg intracerebral a-endorphin tended to decrease DA and DOPAC in the striatum and 20 μg decreased HVA [51]	Wistar rat	SC	2.5 μg/kg 25 μg/kg	no effect	[118]
Tricyclic antidepressant					
Desipramine – tricyclic antidepressant; inhibition of NA re-uptake; 5 mg/kg systemic desipramine has no effect on DA, DOPAC or HVA in the NACC [83]; in vitro has no effect on DA release in the NACC induced by electrical stimulation in the NACC [48]	CD-1 mice	IP	5 mg/kg	no effect on ICSS rate when given alone, reversal of the reduction in ICSS induced by uncontrollable footshocks	[145] [146]

Summary of drug effects on ICSS in the NACC, including drug dose and administration route. A decrease in ICSS threshold indicates that lower current intensities are needed to induce the same ICSS rate. *ICSS* Intracranial self-stimulation; *IM* intramuscular; *IP* intraperitoneal; *LH* lateral hypothalamus; *NACC* nucleus accumbens; *SC* subcutaneous

Table 2. *Lesion effects on ICSS in the NACC*

Lesion type	Species	Target	Effect	Reference
6-OH-DA lesion	Wistar rat	LH	↓ ICSS rate at 1–3 days after lesion, no effect during next 18 sessions	[84]
RF lesion		VTA	↑ ICSS rate	[109]
Blockade	?	GABAergic input to the mesolimbic DA neurons	↑ ICSS rates of the NACC	personal communication [139]

Summary of the effects of lesions in the brain on ICSS in the NACC, including the type and the target of the lesion. *6-OH-DA* 6-hydroxydopamine; *DA* dopamine; *GABA*: gamma-aminobutyric acid; *ICSS* intracranial self-stimulation; *LH* lateral hypothalamus; *NACC* nucleus accumbens; *RF* radiofrequency; *SC* subcutaneous; *VTA* ventral tegmental area

often induces motor deficits known as the '5-HT syndrome' [59]. The decrease in lever pressing is probably due to these motor deficits: concomitant administration of MDMA and methysergide, a 5-HT2 antagonist and 5-HT1 agonist which prevents these motor deficits, increased the total number of presses and ICSS rate [59]. Single methysergide administration and augmentation of MDMA with ketanserin, a drug related to methysergide but without 5-HT1 agonistic properties, had no effect. Therefore, it was concluded that the decrease in lever pressing with MDMA was due to 5-HT1 receptor mediated motor deficits.

D2-like DA antagonists

Acute administration of haloperidol and spiroperidol, two D2-like DA antagonists, decreases the ICSS rate in the NACC in rats [67, 76, 118]. Although haloperidol

may induce disturbances in motor performance [44], it is unlikely that motor deficits induced the decrease in ICSS rate. Indeed, injection of spiroperidol in the NACC only decreased the ICSS rate when it was on the same side of the ICSS electrode. The lack of effect on ICSS when injected contralateral to the ICSS electrode suggests that motor performance was intact [69]. The decrease in ICSS rate induced by haloperidol could be attenuated by administration of hyoscine (scopolamine), which is a muscarinic acetylcholine receptor antagonist [76]. Contrasting these results, one study reported that ICSS was facilitated after chronic haloperidol administration: monkeys started ICSS at lower stimulation amplitudes [104].

Opioids and endorphins

The effect of naltrexone, (Des-Tyr^1)-γ-endorphin (DTγE) and α-endorphin on ICSS in the NACC was verified. None of these agents influences basal DA release in the NACC but naltrexone and DTγE decrease evoked DA release in the NACC. It was observed that these two agents suppress ICSS in the NACC [118, 123]. In contrast, α-endorphin, has no effect on ICSS in the NACC.

Tricyclic antidepressant

Desipramine (desmethylimipramine) had no effect on ICSS in the NACC but could reverse the reduction in ICSS induced by uncontrollable footshocks [145, 146].

Brain lesions

The NACC receives a massive DAergic projection from the VTA, which is part of the mesolimbic projection. Interruption of this pathway with a 6-hydroxydopamine (6-OH-DA) lesion at the level of the LH, leads to a decrease in ICSS rate after three days [84]. After long-term recovery (21 days), however, this decrease in ICSS rate normalised and even tended to increase [84]. Indeed, Simon *et al.* demonstrated an increase in ICSS in rats with a radiofrequency lesion in the VTA after 17 days [109]. The discrepancy between the short- and long-term effects of a lesion in the afferent DAergic projection, might be attributed to increased sensitivity for DA in the NACC due to upregulation of postsynaptic DA receptors [31]. Probably therefore, no correlation was observed between the increase in ICSS rate and the decrease in DA concentration [109].

Dopamine

The studies on the effects of drugs and brain lesions on ICSS in the NACC, present evidence for the involvement of the DAergic system. Agents, which increase DA release in the NACC, are likely to increase the ICSS rate or lower its threshold and vice versa. Additional evidence comes from fast cyclic voltammetry (FCV) studies. DA is one of the neurotransmitters that oxidises after application of a voltage waveform. The resulting current flow can be measured and is proportional to the DA concentration at the microrecording electrode. With this technique, called FCV, an increase in extracellular fluid DA at a distance of 200–400 µm from the NACC stimulation electrode was measured *in vitro*. Local application of cocaine [125] facilitated DA release in the NACC induced by ES [10]. Other findings oppose the involvement of DA. Prado-Alcada and Wise mapped ICSS sites in different regions in the brain but discovered no close correspondence between the boundaries of the reward system and those of the DA terminal fields as revealed by DA fluorescence [89, 147]. However, ICSS in the medial and ventral NACC, corresponding to regions of DA and cholecystokinin (CCK) co-localization, was accompanied with significant elevations in motor activity [147].

Other behavioural effects of ES in the NACC

Activity

A significant increase in activity was reported following ES in the NACC in freely moving animals [32, 40] and in animals tested for ICSS [144], especially when stimulated in the medial NACC [147]. In addition, ES in the NACC influences changes in activity induced by the administration of different drugs. It enhanced the increase in activity after administration of amphetamine [56] and partly blocked the decrease in activity induced by a 5-HT1A agonist [117]. In contradiction to these increases in activity, stimulation in the NACC either had no effect [119] or even caused a decrease in activity in another study [93].

Fight-or-flight

Subjects facing threats dispose of a behavioural repertoire to handle the threat including opposing the threat (aggression or fighting) or flying away from it. The protagonists in the neurocircuitry involved in fight-or-flight behaviour are the AMY, the hypothalamus and the peri-

aqueductal gray [68]. The connectivity of the NACC with these brain areas suggests a role for the NACC as well in mediating these behavioural effects. Indeed, several experiments demonstrate that ES in the NACC can induce but also mitigate aggression and fighting behaviour, as well as fear.

Hano *et al.* observed violent running during NACC stimulation in rats, sometimes accompanied by backing, rearing on the hind paws, body shakes and increased muscular tone. Immediately after stimulation they noticed an increased excitement and aggression [40]. In accordance, ES in the NACC in male western fence lizards induced species-specific assertion display and challenge behaviour. In no case did stimulation elicit proper fighting in these lizards [114]. Two other reports, however, report the induction of aggression by ES in the LH and the decrease of this aggression by concomitant ES in the NACC [32, 33]. During ES in the LH, touching the region of the mouth elicits a biting reflex in cats. Stimulation at 6 or 60 Hz amplitude-dependently reduced the size of the region where these biting reflexes could be elicited. At the highest voltage level, the region for biting reflex was even completely abolished.

The effect of ES in the NACC on fear also varied considerably between studies. In one article, a decrease in fear responses was observed in cats during stimulation in the NACC [128], while in another an arrest reaction (sudden interruption of all movements) and escape behaviour were elicited at threshold and suprathreshold stimulation amplitudes, respectively [75]. In the latter study, the escape response consisted of movement of the cat to another place in the observation box, accompanied by crouching and flattening of the ears. It was suggested that the arrest-escape response was mediated via the efferent pathway to the VP, since a kainic lesion in this area increased the NACC stimulation threshold significantly (+51%). Finally, in fully conscious but restricted monkeys, no escape-like behaviour was observed [133].

Exploratory behaviour

An increase in sniffing was observed at 6Hz stimulation in the NACC in cats. Above threshold voltage, stimulation caused sniffing, searching head movements, and in-and-out tongue movements [32]. In rats, continuous ES in the NACC also increased sniffing [40] and ICSS in the NACC increased normal sniffing [47] as well as amphetamine-induced sniffing [21]. ES during 10 days preceding the amphetamine injection had, however, no effect on amphetamine-induced sniffing [56]. Remarkably, in patients with OCD bilateral as well as unilateral ES produced a transient smell sensation. These olfactory perceptions were described as ''something burning'', ''stale air'', ''an old bag'', ''some sort of glue'', ''something sweet'', or ''as in nature''. One patient also tended to sniff the air in search of the source of the smell [27].

Food intake

Several interventions locally in the NACC influence feeding behaviour [151]. Upon ES in the NACC, increases as well as decreases in food intake were reported. In a food-reinforced task, food pellets were retrieved faster during ES in the NACC [119]. Also, upon termination of ICSS in the NACC, food intake was increased in normal rats, but decreased after amphetamine injections [21]. The decrease in the latter condition was larger than during amphetamine administration alone. Finally, a sudden interruption of all movements was observed in cats, including goal directed movements as those observed when the animals advance toward a dish of food [75].

ES resulted in considerable weight gain in 5 of 11 patients suffering from treatment refractory OCD (increase of 26, 13, 12, 12 and 8 kg). The increase in body weight is probably not just a consequence of the relief of OCD symptoms in these patients, since it was not always proportionate to the improvement in symptoms. Neither is it possible to state whether the increase in body weight is due to a stimulation-induced change in the subjects metabolism or hunger drive. Although patients were not asked to keep food diaries, some of them report to eat more and to crave for sweet things. Others deny eating more, but gain weight nevertheless. During consecutive episodes without stimulation, patients sometimes lost some of the gained weight. These effects of ES in the NACC on food intake are probably mediated by the connections of the NACC, mainly the mediodorsal shell, to the LH.

Seizures

Upon termination of stimulation, seizure like behaviour characterised by extreme hyperactivity, loud meowing, urination, and profuse salivation was observed in one cat (stimulation parameters: monophasic pulses, 0.5 ms pulse duration and 60 Hz frequency) [32]. In the ICSS experiments of Jenkins *et al.*, all rats stimulated in the NACC showed involuntary motor effects gradually

increasing during 3 weeks, comprising at first wet-dog shakes, eventually developing in full clonic seizures, which increased in frequency and severity (variable train duration, biphasic pulses, 0.2 ms pulse duration, 250–400 μA, and 100 Hz frequency) [47]. In humans, no seizures were observed in the region of the anterior limbs of the internal capsule and the NACC, although stimulation was also performed with relative large pulse widths (0.06–0.45 ms) and at high frequency (100–130 Hz).

Effects of ES in the NACC on compulsive behaviour

Animal models of obsessive-compulsive disorder

To examine whether ES in the NACC shell might benefit patients with treatment-refractory OCD, we electrically stimulated in the T-maze and the schedule-induced polydipsia animal model [117]. Spontaneous alternation behaviour is the natural tendency of most species to successively explore both arms of a T-maze alternately, provided the two goal boxes are equally reinforced. Subcutaneous injection of the selective 5-HT 1A receptor agonist 8-hydroxy-2-(di-n-propylamino)-tetralin hydrobromide reduces this alternation behaviour. This behaviour models the compulsive and repetitive behaviour of patients suffering from OCD [134]. In our experiments, we found that a lesion and ES in the NACC had the same behavioural effects in this model. However, alternation behaviour further decreased, suggesting that ES in the NACC would not benefit patients with OCD [117].

In the schedule-induced polydipsia model, hungry rats that receive a food pellet every minute will drink water after each pellet delivery, what also models compulsive and repetitive behaviour of human patients [132]. The total amount of water intake during the test sessions is inappropriate and even toxic especially when considering that the animals are in a deprived state (80% of normal body weight). In contrast to earlier findings in the T-maze model, we observed a stimulation amplitude-dependent reduction of schedule-induced polydipsia at high frequency but not at low frequency stimulation (unpublished personal observations). Finally, high-frequency stimulation in the NACC core decreased quinpirole-induced compulsive checking behaviour in rats [129]. In this animal model, quinpirole-sensitised rats return more often to their home cage in an open field, that models compulsive checking behaviour in patients suffering from obsessive-compulsive disorder [111].

OCD patients

In 1999, we implanted electrodes in the anterior limbs of the internal capsule of 4 treatment-resistant OCD patients with the most ventral contact (contact 0) being located near to or in the NACC. In three of them, marked beneficial effects could be demonstrated during acute test sessions [77]. In a subsequent blinded crossover design with randomly chronic stimulation on and off, a significant decrease on the Yale-Brown Obsessive Compulsive Scale and Clinical Global Severity scores was observed in 4 of 6 patients [78]. These stimulation-induced effects could be maintained for at least 21 months. Sturm *et al.* also demonstrated a favourable outcome of ES in the NACC in OCD and other anxiety disorders [100, 115]. Unipolar stimulation (90 μs, 130 Hz, 2–6.5 V) in the right NACC resulted in a significant reduction of the symptoms in 3 of 4 patients. Bipolar stimulation was tried in one patient without additional improvement of the symptoms. In the fourth patient, a displacement of the electrode resulted in missing of the target area that might explain the negative outcome in this patient. In accordance, Lippitz *et al.* [60] showed that capsulotomies in the right hemisphere were decisive for a favourable therapeutic outcome.

Physiological effects of ES in the NACC

Physiological parameters are likely to change in concert with behaviour. Nevertheless, we describe them in a separate section, since they were in some studies analysed under a general anaesthetic. Usually, ES in the NACC has only limited or inconsistent effects on physiological parameters.

Cardiovascular effects

ES in the NACC in freely-moving rats with parameters which induced ICSS, decreased the heart rate (-8.42 ± 14.21 beats/min; mean $\pm$ SD) and increased the mean arterial pressure (9.5 ± 7.7 mmHg) [96]. Usually, the changes in mean arterial pressure preceded the changes in heart rate. During fear experiments, however, either no or inconsistent changes in heart rate were observed [128]. The cardiac responses upon ES in anaesthetized rats were also very limited. Ross and Malmo [96] found no changes in heart rate and a decrease of the mean arterial pressure in rats.

Respiratory effects

In a fear conditioning paradigm, ES in the NACC had little or no effect on respiration in awake cats except in

one of the three subjects in which an increase in respiration rate and a decrease in respiration amplitude were found [128]. In anaesthetized monkeys, there was no respiratory depression and no change in respiratory pattern or galvanic skin response [133]. In 6 of 8 patients with treatment-resistant OCD, switching the stimulator 'on' and 'off' induced a deep sigh. In addition, acute hyperventilation was observed in 4 of these patients when stimulated with particular contact combinations [27].

Hormonal changes

Koikegami *et al.* [55] found that ovulation can be induced in the unanaesthetised rabbit (a reflex-ovulating species) following a one-hour period of NACC stimulation. Also, oxytocin is released upon ES in the NACC [2]. In contrast, in female Wistar rats, ES in the NACC during 15 minutes had no significant effect on the concentration of plasma luteinising hormone although a slight elevation was present after 30 minutes [98]. Plasma cortisol and growth hormone levels were non-significantly increased in anaesthetised rhesus monkeys [25, 26, 133].

Autonomic changes

ES induced no autonomic effects like pupillary dilatation and salivation in one study [32] but increased alertness and induced pupillary dilatation and mild piloerection in another [75]. During ES in OCD patients, paresthesias or a warm feeling in certain body parts or over the whole body with transpiration and flushing were observed in all of them. Brusque abolition of stimulation frequently caused a transient hot feeling, transpiration and flushing as well [27].

Mechanisms of ES in the NACC

ES is a rather new treatment option for patients with psychiatric disorders and is subject to improvement. Insight in the underlying mechanisms of ES may contribute to adaptations in the treatment. We already mentioned that FCV experiments indicate an increase in extracellular DA 200–400 µm from the stimulation electrode in the NACC. Hence, stimulation in the NACC is likely to propagate DA release from DAergic afferents from the VTA and the SN. It is known that DA in the NACC is able to suppress spontaneous or glutamate-evoked firing of NACC neurons [124, 131, 140]. Other evidence for the mechanism of NACC ES comes from electrophysiological experiments in which the effect of ES in the NACC on cellular activity in other brain targets was evaluated with microrecording. Neurons in brain targets lying downstream from the NACC may respond with excitation, inhibition, or a combination of both (early excitation followed by a period of inhibition and vice versa). Most neurons in the VP [20, 49, 64], the VTA [62, 138, 139] and the SN [101] were inhibited when single electrical pulses were given in the NACC, although excitation was also frequently observed in some studies [20, 57, 62]. The major part of the neurons in the AMY [66, 99] and the LH were excited with single pulse ES in the NACC [99]. Neurons in the tuberoinfundibular hypothalamus were equally excited and inhibited [98] and the effect of stimulation in the NACC on neurons in the supraoptic nucleus depended on the cell type (excitation in vasopressin cells, inhibition in oxytocin cells) [107]. Finally, also neurons in the orbitofrontal cortex [94] and mediodorsal thalamic nucleus (MD) [70] responded orthodromically upon ES in the NACC. In addition to orthodromic activation, several authors reported antidromic neuronal activation in brain areas with afferents to the NACC like the prelimbic and orbitofrontal cortex [71, 94], agranular cortex [71], entorhinal cortex [24], HC [24, 136], AMY [66], MD [70], VTA [15, 29, 62, 69], SN [69, 101] and the VP [138]. It is clear from these studies that single pulse ES influences activity in several brain areas lying afferent and efferent to the NACC. Whereas low frequency stimulation may exert effects similar to single pulse stimulation, the effect of high frequency stimulation is likely to differ.

Discussion

High variability of behavioural effects

The current overview of the behavioural changes demonstrates that ES in the NACC evokes a range of diverse effects. Depending on the publication even opposite observations were reported: ES in the NACC increased but also decreased aggressive behaviour, exploratory behaviour, food intake and compulsions in a model for OCD. In the next sections, we will discuss which factors might attribute to these contrasting results.

Motivational context

The effect of ES in the NACC may depend on the behavioural paradigm in which the animal was tested. Functionally, the NACC has been regarded as an inter-

face between motivation and action. Depending on the context and the motivational status of the subject, the response might differ. The NACC is anatomically well placed to accomplish this function. This nucleus receives its major afferents from the PFC (involved in higher functions like planning), the HC (memory and previous experiences) and the AMY (emotions), areas which belong to the limbic system, and projects towards the VP, the mesencephalon, both involved in motor behaviour, and the LH (e.g. food intake, ICSS, hormone regulation). Several of the afferents are able to gate information from other afferents by depolarising (or not) the membrane potential to an 'up' state (see Signal processing in the NACC).

NACC subregional differences

Histological staining and connectivity studies demonstrate that the NACC may be divided into a core and shell subregion (see: General features of the NACC). Connectivity patterns with other brain areas differ between and even within these subregions. Hence, depending on the electrode contact location, the behavioural and physiological effects may differ considerably. For instance, rostro-caudal, dorso-ventral and medio-lateral differences were observed between ICSS rates in the NACC [89, 147]. In these reports, high ICSS rates were observed in the ventral, caudal and medial NACC. It is likely that this subregion of the NACC with high rewarding properties is the most promising target for symptom relief with ES in humans suffering from psychiatric disorders in which depression is involved (like major depression disorder and obsessive-compulsive disorder with co-morbid depression). However, it is also possible that other structures, like the projections from the internal capsule or the nearby MFB mediate the good clinical effects of ES. The latter structure has higher rewarding properties (see above).

Stimulation parameters

The *amplitude* directly affects the extent of the stimulated region and the intensity of stimulation in nearby neurons.

The behavioural effects of *high versus low frequency* stimulation are often different and may be even opposite to each other. For instance, in Parkinson's disease, bradykinesia [73], tremor and the onset of myoclonic jerks [91] worsen at 5 Hz stimulation compared to stimulation with a frequency higher than 60 Hz, which leads to symptom relief. In the NACC ICSS studies, response rates depended on the stimulation frequency (see above). There is neurophysiological evidence for the differential effects of high versus low frequency stimulation in the NACC. When recording single cell activities in the LH upon trains of electrical pulses at 50 Hz in the NACC, 16 neurons were excited and 8 neurons were inhibited (of the 31 LH neurons tested in total). Of the 8 inhibited neurons, 4 were also inhibited by single pulse stimulation whereas the other 4 and the 16 neurons, which were excited by stimulus trains, responded with excitation followed by inhibition [99]. The pulse width, on the other hand, directly influences the neuronal target element that is stimulated. Cell bodies and dendrites are optimally stimulated with a pulse width in the 1–10 ms range, small axons in the 200–700 μs range and large myelinated axons in the 30–200 μs range [43]. It is not clear whether behavioural differences in this review could be attributed to different pulse widths.

Side effects

Approximately, half of the OCD patients experienced weight gain during ES in the region of the NACC. This weight gain is probably not only due to symptom relief but also to a change in metabolism or an increase in hunger drive. From the ES experiments in animals, there is only limited evidence for physiological side effects. An increased blood pressure was observed in awake animals [96], which may increase the risk for cardiovascular diseases when it is sustained for a long period of time. However, the duration of this acute experiment was too short to take definite conclusions on increased blood pressure. Moreover, the raise in blood pressure may be related to behavioural changes induced by the ES. Seizures were observed in two animal studies in which large pulse widths and high stimulation frequency were used [32, 47]. Since stimulation in OCD patients is performed with similar stimulation parameters, the clinician has to be aware not to induce seizures when stimulating electrically in the NACC. The respiratory and hormonal changes were only of minor significance.

Finally, application of an electrical current in the brain may lead to an electrolytic lesion around the electrode tip, which depends on the electrical current and on electrode properties. First, the magnitude of the *charge density* around the electrode tip determines the susceptibility to induce a lesion. *Charge density* is the ratio of the energy per pulse over the free contact area of the electrode [65]. Second, biphasic stimulation is less det-

rimental than monophasic since every pulse is followed by a second pulse of the opposite polarity [97]. Third, platinum-iridium electrodes diminish the risk to induce an electrolytic lesion tenfold versus stainless steel electrodes [74]. For clinical applications, platinum-iridium electrodes are used. Post-mortem studies in chronically stimulated patients with intractable pain or movement disorders did not reveal electrolytic lesions around the electrode tip (e.g. Ref [3]). In most studies, there was limited gliosis around the foreign implanted material without any further implications. In one study, there was a limited lesion in a patient with Parkinson's disease probably due to migration of the electrode [42]. In this patient, the migration of the electrode was without side effects but the good clinical outcome of stimulation disappeared. In these post-mortem studies, none of the deaths was related to ES.

ES in the NACC for OCD

In the T-maze model and the schedule-induced polydipsia model, opposite findings were observed. In the former model, there was an increase in compulsive behaviour while there was a decrease in the latter. In humans, there is evidence from a limited number of patients that ES has a beneficial effect on the OCD symptoms. This puts the validity of the T-maze model into question. A good model for a psychiatric disorder has a highly predictive face, construct and discriminant validity [127]. The primary application of predictive validity is to assess the effects of potential therapeutic treatments: the model has *predictive validity* if it successfully discriminates between effective and ineffective treatments. *Face validity* concerns the degree to what extent a model resembles the condition being modelled. *Construct validity* means that the procedure in the model is based on a sound theoretical rationale. Finally, a model for OCD has *discriminant validity* when the evidence points to OCD as the disorder being modelled as distinct from a different or a non-specific psychiatric disorder [30]. In our experiments [117], the T-maze model incorrectly predicts that ES in the NACC would worsen the symptoms of OCD in humans. The face and construct validity of both models were not studied in our experiments but are discussed elsewhere [86].

ES in the NACC for other psychiatric disorders

In patients with treatment-resistant OCD, electrical stimulation in the region of the NACC significantly decreases scores on the Hamilton Depression Scale (stimulation off: 26.7, stimulation on: 13.3) [27]. Therefore, a trial with electrical stimulation in the region of NACC was recently initiated in patients suffering from treatment-resistant major depression in our laboratory. Preliminary results are promising (own observations). Finally, electrical stimulation in the NACC may also be a potential new treatment in humans suffering from severe treatment-resistant addiction. The release of dopamine in the nucleus accumbens in humans is required in reward (e.g. drug high) and for the initiation of addiction [50]. Electrical stimulation in the NACC elicits DA release and is rewarding as well [125]. It is conceivable that certain stimulation parameters suppress or override addictive behavior. As far as we know the effect of ES in the NACC on addictive behavior has not been investigated in patients. However, a stereotactic lesion in the NACC reduced the relapse rate in patients suffering from addiction [28].

Conclusion

ICSS experiments suggest that stimulation in the NACC has rewarding properties. Pharmacological studies point to the involvement of the DAergic system in mediating these rewarding effects. In addition, ES in the NACC affects general activity, fight-and-flight behaviour, exploration and food intake, although contrasting effects were often observed. In parallel with ES experiments in animal models for compulsions in OCD, a good clinical outcome was observed in patients with OCD during stimulation in the NACC.

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