NEURAL CORRELATES OF IMPULSE CONTROL IN PARKINSON'S DISEASE

By

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To Peter and Patricia Rossi

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TABLE OF CONTENTS

page

ACKNOWLEDGMENTS 4

LIST OF FIGURES 7

LIST OF ABBREVIATIONS 9

ABSTRACT 10

CHAPTER

1 THE STN AND GPI DIFFERENTIALLY ENCODE VALENCE 12

Introduction 12
Materials and Methods 16
Patients 16
Behavioral Task 17
Localization of Recording Sites 18
Data Acquisition 18
Recording Protocol 19
Behavioral Data Analysis 19
Electrophysiological Analysis 20
Recording Site Mapping 22
Behavioral Results 23
Reaction Time 23
Response Accuracy 23
Electrophysiological Results: Valence Processing in the STN 24
Responses to Reward Opportunity and Threat of Loss 24
Responses to Reward and Loss Avoidance 25
Movement-related Activity 26
Error-related Activity 27
Exclusive Correct Neurons 28
Neuronal Mapping 28
Electrophysiological Results: Valence Processing in the GPi 28
Responses to Reward Opportunity and Threat of Loss 29
Responses to Reward and Loss Avoidance 29
Movement-related Activity 30
Error-related Activity 31
Neuronal Mapping 32
Discussion: Comparing STN and GPi 32
Behavioral Data 33
Electrophysiological Data 35
Neuronal Mapping 37
Conclusion 40

2 IMPULSIVITY AND DIFFERENCES IN STN NEURON BEHAVIOR 57

Introduction 57
Materials and Methods 59
Patients 59
Assessment of Impulse Control Disorders 60
Results 61
Patient Characteristics 61
Subthalamic Nucleus 61
Globus Pallidus internus 62
Discussion: Comparing STN and GPi 63

3 DEEP BRAIN STIMULATION MODIFIES IMPULSE CONTROL 69

Introduction 69
Materials and Methods 70
Patients 70
Assessment of Impulse Control Disorders 71
Statistical Analysis 72
Results 72
ICD Prevalence 72
Rate of Change in ICD Status Post-DBS 73
Qualitative Changes in Impulse Control Post-DBS 74
Changes in ICD Status and Dopaminergic Medication 74
Other Psychological Changes 76
Discussion 76

LIST OF REFERENCES 86

BIOGRAPHICAL SKETCH 96

LIST OF FIGURES

Figure		page
1-1	Behavioral task	41
1-2	Task performance	42
1-3	Neuronal and waveform characterization	43
1-4	Valence responsiveness in STN neurons	44
1-5	Excitation and inhibition at stimulus presentation in STN neurons	45
1-6	Excitation and inhibition at feedback presentation in STN neurons	46
1-7	STN movement-related activity	47
1-8	Error sensitive neurons in the STN	48
1-9	Positions of recorded STN neurons	49
1-10	Anatomical coordinates of responsive populations	50
1-11	Valence responsiveness in GPi neurons	51
1-12	Excitation and inhibition at stimulus presentation in GPi neurons	52
1-13	Excitation and inhibition at feedback presentation in GPi neurons	53
1-14	GPi movement-related activity	54
1-15	Error sensitive neurons in the GPi	55
1-16	Positions of recorded GPi neurons	56
2-1	ICD status impacts reward and loss sensitivity in STN but not GPi neurons	67
2-2	ICD status impacts response specificty in STN but not GPi neurons	68
3-1	Comparison of pre-DBS and post-DBS prevalence of ICDs	80
3-2	ICD changes after STN and GPi DBS surgery	81
3-3	Post-DBS ICD changes are not dependent on dopamine therapy	82
3-4	Comparison of impulsive and non-impulsive patients	83

3-5 Changes in impulsivity following GPi and STN DBS..... 84

3-6 Changes in ICD status in bilateral versus unilateral DBS..... 85

LIST OF ABBREVIATIONS

AC	Anterior commissure
BG	Basal ganglia
D2	Dopamine receptor D2
D3	Dopamine receptor D3
DAA	Dopamine agonist
DDS	Dopamine dysregulation syndrome
GPe	Globus pallidus externus
GPi	Globus pallidus internus
ICD	Impulse control disorder
LEDD	Levodopa equivalent daily dosage
LFP	Local field potential
LHb	Lateral habenula
MRI	Magnetic resonance imaging
PC	Posterior commissure
PD	Parkinson’s disease
PETH	Peri-event time histogram
QUIP	Questionnaire for impulsivity in Parkinson’s disease
SD	Standard deviation
SEM	Standard error of the mean
STN	Subthalamic nucleus

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A significant portion of Parkinson's disease (PD) patients suffers from impulse control disorders (ICDs). A hallmark feature of ICDs is the repetitive pursuit of rewarding behaviors despite negative consequences. The pathophysiology of ICDs is not well understood. Recent evidence suggests that alterations in reward/punishment (i.e. valence) processing in two subcortical brain regions—the subthalamic nucleus (STN) and the globus pallidus internus (GPi)—may contribute to this disorder. The objective of this research was to prospectively study the effect of STN and GPi DBS on impulse control, investigate the role of the human STN and GPi in valence processing, and determine if ICDs are associated with aberrations in valence processing in these structures.

PD patients (12 with an ICD and 31 without) undergoing DBS electrode placement were studied. Patients performed a behavioral task in which their action choices were motivated by the potential for a reward or a loss. The activity of individual STN or GPi neurons was simultaneously recorded. Neuronal activity was analyzed to determine firing rate modulation in response to task conditions. Patients were also

evaluated pre- and post- operatively using clinical measures to determine the effects of DBS on impulse control.

We found that STN and GPi neurons encode valence-related information during action control, but the proportion of valence-responsive neurons was greater in the STN compared to the GPi. In the STN, reward-related stimuli mobilized a greater proportion of neurons than loss-related stimuli. We also found surprising limbic overlap with the sensorimotor regions in both the STN and GPi. ICDs were associated with significantly greater proportions of reward responsive neurons and significantly lower proportions of loss responsive neurons in the STN, but not in the GPi. Of the ICDs present at baseline, 60% resolved post-operatively; 20% of patients experienced new onset ICDs. Change in ICD status was not associated with change in dopamine agonist medication. These findings support the idea that STN and GPi DBS can directly alter impulse control. Changes in the STN—possibly via functional conversion of neurons in the limbic circuit—may underlie impulsive behavior in the PD population.

CHAPTER 1
THE STN AND GPI DIFFERENTIALLY ENCODE VALENCE

Introduction

The common requirement for animals to perform goal-directed behaviors for survival suggests that phylogenetically older (i.e. sub-cortical) brain regions have retained fundamental mechanisms for reward-seeking and loss-avoidant behavior[1]. The study of subcortical involvement in the reward system has been largely focused on the striatum, the nucleus accumbens, and the ventral pallidum[2]; however, roles for the subthalamic nucleus (STN) and, to a lesser degree, the globus pallidus (GP) have only recently been recognized[1]. The observation that lesions or high frequency stimulation of the STN or the globus pallidus internus (GPi) in some human patients were associated with changes in affective or goal-directed behavior, including depression, suicidal ideation, apathy, mania, and impulsivity[3], motivated much of the exploration of the potential involvement of these structures in the reward system.

Substantial evidence from animal studies over the past decade indicates a role for the STN in processing reward[3]. It has been shown that a large subset of STN neurons in the rat encodes the prospect of reward, reward receipt, the magnitude of different possible reward outcomes, and reward prediction error[4–6]. Darbaky and colleagues showed that neurons in the monkey STN were modulated during movement, just before reward delivery, and during reward delivery[7]. More recently, Espinosa-Parrilla and colleagues demonstrated that monkey STN neurons modulated in response to reward during task performance as well as to the expectation of reward delivery when the reward was delayed in time[8]. Interestingly, they also showed that movement-related modulations were commonly combined with reward delivery modulations, suggesting a

convergence of signals related to the animal's movement and its outcome in the same neurons[8,9].

Until recently, it was widely believed that the STN could be divided into three distinct functional zones: an anteromedial limbic zone, a posterior sensorimotor zone, and an overlapping associative zone between the two[10–12]. The evidence for this so-called tripartite hypothesis derived mainly from tracer studies[13–14], although limited electrophysiological findings supported this model as well[15,16]. However, the notion of a tripartite division has recently been called into question[17]. Comprehensive reviews of the extant evidence suggest that substantial overlap exists between the putative functional zones and that the tripartite model may thus require revision[13,17,18].

Less is known about the putative limbic function of the GPi, as it has been most intensively studied as a purely motor nucleus. However, a few critical animal studies suggest it has a role in reward processing. The dorsal pallidum—the region corresponding to the globus pallidus externus (GPe) and GPi collectively—has been shown to encode reward signals[1]. Hikosaka and colleagues identified a subpopulation of GPi neurons in the monkey that project to the lateral habenula (LHb) which strongly encode reward prediction signals[19,20]. Arkadir and colleagues studied single neuron activity in the GPe in monkeys while they performed reward-motivated arm movements[21]. Although they identified only a small percentage of neurons (3%) that responded exclusively to reward, they found that 41% of neurons co-modulated activity in response to both reward and movement. Another single unit studies in monkeys examining reward-motivated movement specifically in the GPi found 15% (12/82) of neurons modulated with reward delivery[22]. Recently, functional neuroimaging in humans

has shown that the pallidum exhibits greater neural activation in response to visual cues predicting potential gains compared to predictors of neutral outcomes and to actual financial gains compared neutral outcomes[23]. Regarding the existence of a “limbic” zone in GPi, immunohistochemical studies in humans implicates the anterior GPi as a recipient of limbic afferents, although, importantly, the boundaries between putative limbic and motor territories were not sharp but rather were consistent with overlap[24]. Further evidence of a limbic hot spot in the anterior GPi comes from clinical observations, particularly that DBS of the anterior GPi has been shown to relieve obsessive compulsive symptoms in Tourette syndrome[25] and self-mutilation behavior in Lesch-Nyan syndrome[26].

The construct of “reward” is best understood within the broader construct of valence, which is defined as the intrinsic attractiveness or aversiveness of a given stimulus. Stimuli that are rewarding are considered to be positively valenced, while stimuli that are undesirable or aversive are considered to be negatively valenced[27]. Valence and action control are intimately intertwined in that organisms tend to act or inhibit action to obtain positively valenced outcomes (rewards) and avoid negatively valenced outcomes (punishments or loss). Moreover, a well-documented feature of the effect of valence on action control is the so-called Pavlovian bias in which many organisms (including humans) tend to learn better to act to obtain reward (as opposed to avoid punishment) and to inhibit action to avoid punishment (as opposed to obtain reward)[28–30]. While such interactions between action and valence are behaviorally apparent, their neurobiological substrates are not well understood. For example, the observation that the same GPe neurons can convey information regarding both

movement and gain from that movement (predicted or attained)[21] raises the question of whether such co-modulation occurs in other BG structures implicated in both movement and reward (i.e. STN and GPi). Moreover, it is unclear if such co-modulation might apply to negatively valenced motivations as well. Elucidating the neurobiological bases for these interactions could have implications for treating certain neuropsychiatric disorders, such as impulsivity, where valence perception and action control are believed to be dysfunctional[3].

The successful pursuit of goal-directed motor behavior is also dependent on the detection of errors and the adaptive learning required to avoid future errors[31]. Error detection involves the perception that one has failed to obtain an expected, positively valenced outcome or has obtained an unexpected negatively valenced outcome. Error detection is thus another concept in which action and valence are intimately intertwined. The error monitoring system is complex, and it is believed to involve both cortical and subcortical structures. The observation of abnormal cortical error-related activity in patients with diseases of the basal ganglia (PD, Huntington's disease, Tourette syndrome, or focal BG lesions) implicates the BG in error monitoring and error-associated motor adaptation[31]. Studies of single-cell neural activity in the rodent STN[2,6,32] and monkey dorsal pallidum[1,21] show distinct error-related changes in firing rate. With the exception of a single local field potential (LFP) study in parkinsonian humans showing error-related changes in theta-band oscillations in GPi[31], little is known about error-responsiveness in the human STN and GPi.

We are thus interested in investigating the neural encoding of valence in human STN and GPi neurons and assessing potential neural integration of valence and action

selection signals within these structures. To this end, we assessed the behavior of individual neurons in the STN or GPi of Parkinsonian humans undergoing DBS lead placement surgery while they performed a cognitive task that orthogonalizes valence and action requirements such that four conditions are tested: act to obtain reward, act to avoid punishment, inhibit action to obtain reward, and inhibit action to avoid punishment (see design pioneered by Guitart-Masip et al.[29,33] and modified by van Wouwe et al.[34]).

Our working hypothesis was that both STN and GPi neurons would modulate activity in response to 1) predictors of positively and negatively valenced outcomes (opportunity for reward and threat of punishment), 2) movement and inhibition, 3) reward receipt and loss avoidance, and 4) failure to obtain reward/ loss (error feedback). Given the ongoing debate about the location of "limbic zones" within these structures, we also sought to document the topographical positions of any valence-responsive neurons identified. Based on the extant data discussed above, we hypothesized that valence-responsive neurons would be concentrated toward the anterior portion of the GPi and the anteromedial portion of the STN.

Materials and Methods

Patients

Patients with Parkinson's disease undergoing unilateral de novo STN or GPi DBS electrode placement surgery were studied. All patients fulfilled the Movement Disorder Society clinical diagnostic criteria for PD[35]. All participants were non-demented, hearing, and sighted. A total of 53 patients participated and had a mean age of 65.69 years (SD=7.85). The Institutional Review Board approved the study and all patients provided their informed consent before entering the study.

Behavioral Task

All stimuli were presented on a 15-inch screen positioned at eye level approximately one meter from the patient. Responses were made with the thumb contralateral to the brain hemisphere being recorded using a handheld, single-button joystick. In the pre-operative clinic approximately 24 hours prior to surgery, subjects completed practice sessions (2 blocks) of the action-valence learning task to associate combinations of action (action, inaction) and valence (reward acquisition, loss avoidance) to a specific stimulus color. The same action-valence learning task was then presented to the subject intra-operatively during the microelectrode-recording (MER) phase of the DBS operation.

The details of the action-valence task are as follows (Fig. 1-1). Subjects were instructed that they had 1000 milliseconds (ms) to either act (i.e. make a button press) or to withhold action after being presented with a color patch. Button press or expiration of the 1000 ms window was followed by a 250 ms delay period (to facilitate separation of movement and feedback neuronal signals). Because delayed outcome of a choice is known to reduce the subjective value of the reward, the shortest possible delay duration was chosen while still permitting accurate signal separation. After this delay, feedback was displayed for 500 ms in the center of the color patch indicating that the action decision had led to monetary reward (+$100), monetary loss (-$100) or no monetary outcome ($0). Monetary rewards were accompanied by a “positive contingency” audio feedback simulating the jingle of coins. Monetary losses were accompanied by a “negative contingency” audio feedback simulating an aversive buzzer sound. The feedback and color patch were then extinguished, and an inter-trial interval followed for 500ms after which the next trial began. A running total of earnings was presented in the

upper center of the screen throughout the task. The four color patches appeared in pseudorandom order and with equal probability across the 120 trials per block. Thus, each color appeared 30 times within a block of trials. Unbeknownst to the subject, two of the color patches provided outcomes that were either rewarded (+$100) or unrewarded ($0), and the other two colors provided outcomes that were either punished (-$100) or unpunished ($0)[34]. Two colors were thus associated with reward learning and the two other colors were associated with loss avoidance learning. Also unknown to the subject, one color from each set produced the optimal outcome (either gain of reward or avoidance of loss) when the button was pressed (action), but the other color from each set produced the optimal outcome by not pressing the button (withholding action)[34].

Localization of Recording Sites

A proprietary stereotaxic surgical software system was used to visualize MRI images, estimate anatomical locations of the STN and GPi, define target location, predict trajectories for microelectrode penetrations, and map results of microelectrode recordings[36]. To avoid sampling bias, cells were selected strictly on the basis of signal integrity rather than the presence or absence of sensorimotor activity[37]. Anti-Parkinsonian medications were withheld 24 hours before neural recording, and no sedatives were given prior to or during recordings[37].

Data Acquisition

Extracellular spiking activity of subthalamic and pallidal neurons was recorded using platinum/iridium-tipped microelectrodes (FHC, Inc., Bowdoin, ME) with impedances of 0.5–1 MΩ mounted in a motorized, hydraulic microdrive (FHC, Inc., Bowdoin, ME). The behavioral task was administered by a Dell Optiplex 9020 computer using BCI2000 software[38]. Neuronal activity was band-pass filtered between 300 Hz-6

kHz and sampled at 48 KHz (16 bit resolution; Tucker Davis Technologies, Alachua, FL). The neuronal recording was monitored via computer display and audio speakers.

Recording Protocol

All recordings were performed using an array of three microelectrodes, separated by 2 mm in an L-shaped configuration, lowered transdurally into the STN or GPi. For recordings of the STN, the microelectrode array was configured with a central contact, a second co-axial contact positioned 2 mm laterally, and a third positioned 2 mm anteriorly. For recordings of the GPi, the microelectrode array was configured with a central contact, a second co-axial contact positioned 2 mm laterally, and a third positioned 2 mm posteriorly. Electrophysiological determination of STN and GPi borders was based on electrode depth along the planned trajectory, spontaneous firing rate and pattern, and kinesthetic responses[39]. When one (or, less frequently two) neuronal units were isolated by at least two of the recording electrodes in the array and the recording was determined to be stable, the cognitive task was initiated. Neuronal data, electrode location, and task performance data were then collected following a standard protocol of 120 stimulus presentations (30 of each of the 4 conditions) in pseudorandom order to ensure an equal number of trials of each condition. Data collection was stopped only if signal quality deteriorated. Upon completion of the task, the microelectrode was advanced so that other units could be evaluated until the microelectrode array was determined to no longer be in the region of interest.

Behavioral Data Analysis

Performance on the behavioral task was assessed via methods used previously by Wagenbreth and colleagues[40]. Accuracy was defined by the percentage of trials in which the patient selected the optimal response[34]. In brief, mean accuracy on the

behavioral task was analyzed utilizing two-way repeated measures ANOVA, followed by post-hoc Tukey test for multiple comparisons to compare individual conditions. Mean reaction times for correct responses during the Go conditions were compared using an unpaired student's t-test; *p* values <.05 were considered significant.

Electrophysiological Analysis

Amplitude thresholds for neural spike data were selected, and candidate action potentials were sorted into clusters in principal components space (Spike2, Cambridge Electronic Design, Cambridge, UK). Neurons were considered acceptable for further analysis only if their action potentials were of a consistent shape, had a clear refractory period of at least 2 ms, and could be reliably distinguished from the waveforms of other units and from background noise[41]. Additionally, analyzed neurons had to be associated with a complete set of task-related data (i.e. 120 stimuli trials). Peri-event time histograms (PETHs) were then constructed from the correct trials of each of the 4 conditions, and for the additional conditions where "incorrect" responses occurred.

Stimulus-related changes, movement-related changes, and outcome-related changes in firing rate were defined as a significant deviation from the baseline inter-trial interval. Baseline activity was defined as activity occurring in the 500 ms period that preceded cue presentation in each trial. Event-related activity was determined in the 500 ms that followed the onset of the visual stimulus (stimulus related), the 500 ms centered on the button press (movement related), the 500 ms centered on trial expiration (inhibition related), and the 500 ms that followed feedback delivery (outcome related).

Analyses were based on binned peri-event firing rates (50 ms bins). For each event of the task, we generated a PETH centered on that event using Matlab

(Mathworks, Cambridge, MA)[32]. For all trial types, the neuronal responses to stimulus presentation, button press, trial expiration, and feedback delivery were analyzed separately. The responses to the stimulus presentation, button press, and feedback were analyzed separately for correct and incorrect trials.

To minimize the contamination of signals by activity related to a previous event, the neural response to each event was analyzed across the 500 ms event-based epoch and was compared with the activity over the 500 ms inter-trial interval preceding the onset of that trial. The 500 ms baseline interval was chosen to maximize sampling while also preventing event-related activity from colliding by using the period between two consecutive events (the feedback delivery from a prior trial and the presentation the stimulus in the subsequent trial).

Analyses were performed according to the analysis of Teagarden and Rebec (2007)[4] and Breysse et al (2015)[2]. Briefly, the mean firing rate for each perievent bin was expressed as a z-score (z_i) based on the following formula:

$$z_i = \frac{Fq_i - \mu_{baseline}}{SEM_{baseline}} \quad (1\text{-}1)$$

with Fq_i as the mean firing rate (in hertz) of the bin (i) and $\mu_{baseline}$ the mean firing rate of the intertrial baseline period preceding each event, and $SEM_{baseline}$ indicating the standard error of the mean of the baseline. Three or more consecutive bins (≥150 ms) with z-scores ≥1.64 (95% confidence interval) were considered to be significant activation or inhibition.

Finally, for each event, neurons were classified as either “similar” and “specific”)[32]. The firing rate of neurons that responded to an event was compared for each outcome with a t-test on the normalized data. Thus, neurons were similar if they

responded to one event in a similar manner for both rewards (t-test, $p > 0.05$)[32]. Neurons were specific if they responded to one event for both rewards with a significantly higher response to one reward than the other or if they responded exclusively to one outcome[32].

The proportions of neuronal subpopulations (e.g., “Go/Reward selective” vs “Go/Loss selective”) expressed in percentages were compared using a χ^2-test. The average of the z-scores of the population PETH were illustrated by separating the specificity of neurons for either each reward or correct versus incorrect trials, based on the criteria defined above (three consecutive bins with z-scores ≥1.64). The neurons were also analyzed based on their response type (activation or inhibition), and the z-scores have been calculated. The percentage of variation for activated and inhibited neuronal populations was calculated by comparing the mean firing rate during baseline period and during the event-related period.

Recording Site Mapping

We defined the spatial location of the recording sites in STN and GPi in relation to the structure’s borders, as defined by the surgical planning software. We then transposed these positions onto the appropriate anatomical slices of the Schaltenbrand and Bailey atlas[42] via a method previously described by Plaha and colleagues[43]. Briefly, this method involves defining the recording position’s intra-structural vertical location by measuring its distance from the structure’s dorsal boundary. Anterior-posterior and medial-lateral positions are defined as a proportion of the lengths of the structure along the appropriate axis, and this spatial location was transposed onto the Schaltenbrand and Bailey atlas by proportional measurements[43]. Finally, anatomical coordinates were

derived for each recording position based on electrode trajectory and recording depth utilizing the surgical planning software.

Behavioral Results

Reaction Time

Figure 1-2 shows the differences in reaction times across the conditions. During the training phase, reaction time for Go to Win was .72s (±.02 SEM) for game 1 and .69s (±.01) for game 2. Mean reaction time for the Go to Avoid Loss was .73s (±.02) for game 1 and .73s (±.02) for game 2. During the intraoperative period, average reaction time for the GO trials decreased. Reaction times for the go-to-win condition were .51s (±.02), .49s (±.01), and .48s (±.01) for games 1, 2, and 3, respectively. Mean reaction times for the go-to-avoid loss condition were .55s (±.02), .54s (±.02), .52s (±.01) for games 1, 2, and 3, respectively. Mean reaction times were significantly shorter for the go-to-win condition during games 2 and 3, (unpaired student's t-test, p=0.038 and p=0.041, respectively, Fig 1-2B).

Response Accuracy

Response accuracy for the four conditions differed considerably in the training period. The two-way repeated measures ANOVA with the factors action (go/no go) and valence (win/avoid loss) revealed no significant main effects for the factors action ($F(1,228)=.49$; $p=.49$) or valence ($F(1,228)=.38$; $p=.54$) but did reveal a significant valence x action interaction ($F(1,228)=17.00$); $p<.0001$). Thus, for PD patients the choice of action was modulated by the anticipation of the outcome. The post-hoc Tukey test for multiple comparisons (alpha=0.05) revealed significant differences between the Go-Avoid Loss and No Go-Avoid Loss conditions and between both No Go conditions (Fig 1-2C).

Response accuracy for the four conditions differed considerably in the intraoperative period. The two-way repeated-measures ANOVA with the factors action (Go/No Go) and valence (win/avoid loss) revealed a significant main effect for the factors action ($F(1,380)=16.57$; $p<.0001$) and a significant valence x action interaction ($F(1,380)=17.54$); $p<.0001$). Thus, the patients performed better in Go trials than in No Go trials, and the choice of action was modulated by the anticipation of the outcome[40]. The post-hoc Tukey test for multiple comparisons revealed significant differences between the Go-Win and No Go to Win conditions, between the Go to Avoid Loss and No Go to Win conditions, and between the No Go to Win and No Go to Avoid Loss conditions (Fig 1-2D).

Electrophysiological Results: Valence Processing in the STN

A total of 100 STN cells from 20 patients and 100 GPi cells from 30 patients met signal quality criteria. The mean duration of recordings for these neurons was 224s (range: 204s - 232s). STN neurons exhibited an average firing rate of 36±22 Hz (mean±SD), a finding consistent with the results of other studies[44] (Hutchison et al. reported a rate of 37±17 Hz for 248 cells in eight patients[45], and Bejjani et al. reported a rate of 38.9±24 Hz for approximately 530 cells in 12 patients[46]). The waveforms of the action potentials were biphasic (Fig 1-3A). Most neurons recorded where single units, although several multi-unit recordings occurred (Fig 1-3A).

Responses to Reward Opportunity and Threat of Loss

Of the STN neurons recorded, 57% (57/100) responded to stimulus presentation. The proportion of neurons responding to reward opportunity was significantly greater than the proportion responding to the threat of loss for both the Go [38% vs. 25%, $\chi^2=3.916$, $p=0.0478$, Fig. 1-4E] and No Go conditions [25% vs. 12%, $\chi^2=5.604$,

p=0.0179, Fig. 1-4F). These results highlight that STN activity was more responsive to a potential reward than a potential loss, and that this reward sensitivity occurred independent of the action context in which the stimulus was presented.

The majority of STN neurons that responded to stimulus presentation were valence specific (i.e. they responded exclusively to either reward opportunity or threat of loss). The degree of specificity was independent of the action condition. For example, we observed that 80.7% were specific during the Go condition and 85.7% were specific during the No Go condition (Fig 1-4A,B).

Interestingly, when the response to reward opportunity was an excitation, there was a 42% increased amplitude of the excitation in the Go condition (Fig 1-5), while it reached only a 21% increase in the No Go condition (42% vs. 21%, χ^2=10.22, *p*=.0014).

Responses to Reward and Loss Avoidance

We observed that 66% of STN neurons recorded (66/100) responded to feedback presentation during correct trials. The proportion of neurons responding to obtained reward was significantly greater than the proportion responding to loss avoidance for both the Go [48% vs. 32%, χ^2=5.33, *p*=.02, Fig. 1-4G] and No Go conditions [27% vs. 15%, χ^2=4.34, *p*=.03, Fig. 1-4H). These results highlight that STN activity was more responsive to reward than an avoided loss, and that this reward sensitivity occurred independent of the action context in which the stimulus was presented.

A majority of feedback responsive neurons were also valence specific (69.9% for the Go condition, 80.6% for No Go condition), and the ratios were similar to those observed following stimulus presentation. A breakdown of the relative proportions of neuron specificity during feedback is shown in Figure 1-4C,D. The relative changes in

firing rate amplitude for excitations and inhibitions following feedback are shown in Figure 1-6.

Movement-related Activity

Of the neurons recorded, 69% (69/100) responded to button press during correct trials. Proportions of neurons responding in the “obtain reward” and “avoid loss” conditions were similar [52% (52/100) and 47% (47/100), respectively (Fig. 1-7A,B)]. Responsive populations for both conditions were also similar in terms of the proportions of activated and inhibited neurons (29 activated neurons/ 23 inhibited for the “obtain reward” condition; 32 activated neurons/ 15 inhibited for the “avoid loss” condition). Amplitude changes in responsive neurons were also similar, with respect to both activations (+35% for “obtain reward”, +32% for “avoid loss”) and inhibitions (-20% for “obtain reward” and -23% for “avoid loss”). Interestingly, however, we observed evidence contrary to our hypothesis that movement-related modulation would occur independent of the movement’s motivational context. Specifically, a majority of neurons (55%, 38/69) responded to movement for just one of the motivational contexts (obtaining reward or avoiding loss), and just 45% of neurons were “similar,” responding to movement whether movement was motivated by reward seeking or loss avoidance (Fig. 1-7C). Specifically, 26.1% (18/69) of neurons responded to movement exclusively during the obtain reward scenario while 29% (20/69) responded to movement exclusively during the avoid loss scenario. This finding suggests that a sizeable sub-population of movement-responsive neurons exists in the STN whose firing rate is affected by the motivational context of action. Also interestingly, neurons that responded to movement for both motivational contexts were significantly more likely to be “movement only neurons”

Error-related Activity

Neurons responding to feedback during both correct and incorrect trials (which resulted in either an unexpected monetary loss or a failure to receive an expected reward) were recorded. Consistent with the findings in rats previously described by Lardeaux[6,32] and Breysse[2], we observed a trend toward higher mean baseline firing rate in correct as compared to incorrect trials (37.97±2.5 vs. 25.64±4.6 Hz, mean±SEM, respectively), although this difference did not reach statistical significance (student's t test, $p>.05$). Changes in firing rate for both activating and inhibiting neurons are given in Figure 1-8A.

To accurately determine the proportion of neurons responsive to feedback during incorrect trials, we examined only neurons that were recorded during blocks of the task with at least 20% incorrect responses in one of the conditions (i.e. a premature button press during No Go trials or failure to press the button during Go trials)—a total of 52 neurons. Of these neurons, 34.6% (18/52) responded to negative feedback during incorrect trials. This was somewhat higher than the proportion of error-responsive neurons observed in the human STN by Bastin et al.[47] As shown in Figure 1-8B, most of these neurons (77.7%, 14/18) were exclusively responsive to error, whether monetary loss (50%, 7/14) or failure to obtain reward (50%. 7/14). No neurons were observed to be responsive to both. A small portion of error responsive neurons (22.3%, 4/18) responded to incorrect feedback and some other condition of the task (including stimulus, movement, or correct feedback). This suggests that error sensitive neurons specially encode responses related to the type of negative feedback experienced.

Exclusive Correct Neurons

In contrast to the neurons exclusively responsive to error, we identified a small subset of neurons that responded exclusively to positive feedback during correct trials (8/100, 8%), which we call “exclusive correct neurons.” This proportion of exclusive correct neurons is close to that observed by Breysse and colleagues in the rat STN (11.7%)[2]. The majority of these neurons (87.5, 7/8) were specific, with a slight majority for reward receipt as compared to loss avoidance (57% vs. 43%); interestingly, this corresponds closely to the ratio Breysse and colleagues documented when rats experienced both positive and negatively valenced outcomes (32% sucrose solution vs. quinine, respectively)[2]. Also interestingly, exclusive correct neurons were responsive to feedback for the most part only during the Go condition (87.5%, 7/8), suggesting that goal-directed action (rather than passive or inhibition-related feedback) evokes positive-reinforcement feedback responses in this subpopulation of STN neurons.

Neuronal Mapping

The mean position of the recording sites in STN were 10.69 ± 1.2 mm (mean ± SD) lateral to the AC–PC line in the mid-sagittal plane, 1.34 ± 1.39 mm posterior to the inter-commissural point and 3.8 ± 1.25 mm below the AC–PC plane (Fig. 1-9). For the mean position of sub-populations of responsive neurons, see Figure 1-10.

Electrophysiological Results: Valence Processing in the GPi

A total 100 GPi cells from 30 patients met signal quality criteria. The mean frequency of GPi neurons was 66.2±3.4 Hz (mean±SE), similar to the mean human GPi frequency of 77.2±6.6 found by Lee and colleagues[48] and 72±2.9 by Levy and colleagues[49], although mean discharge rates as high as 91.7±3.0 have been reported[50].

The waveforms of the action potentials were biphasic (Fig. 1-2A). Most neurons recorded where single units, although several multi-unit recordings occurred (Fig. 1-2A).

Responses to Reward Opportunity and Threat of Loss

We observed that 46% of GPi neurons recorded (46/100) responded to stimulus presentation. In contrast to the STN, the proportion of GPi neurons responding to reward opportunity was similar to the proportion responding to the threat of loss for both the Go [18% (18/100) vs. 14%, respectively; χ^2=.5952, p=0.4404, Fig. 1-11E] and No Go conditions [13%, vs. 16%, respectively; χ^2=.363, p=0.5469, Fig. 1-11F]. The majority of GPi neurons that responded to stimulus presentation were also valence specific. Similar to the STN, the degree of specificity was independent of the action condition. We observed that 76.5% were specific during the Go condition and 81.4% were specific during the No Go condition. A breakdown of the relative proportions of neuron specificity is shown in Figure 1-11A,B. The relative changes in firing rate amplitude for excitations and inhibitions following feedback are shown in Figure 1-12. These results suggest that the GPi is equally responsiveness to potential reward and potential loss.

Responses to Reward and Loss Avoidance

We observed that 38% of GPi neurons recorded (38/100) responded to feedback presentation during correct trials. In contrast to the STN, the proportion of GPi neurons responding to reward receipt was similar to the proportion responding to loss avoidance for both the Go [26% vs. 25% χ^2=.0263, p=0.8711, Fig. 1-11G] and No Go conditions (19% vs. 16%, respectively; χ^2=.312, p=0.5766, Fig. 1-11H). The relative changes in firing rate amplitude for excitations and inhibitions following feedback are shown in Figure 1-13.

A majority of feedback responsive neurons were also valence specific (69.9% for the Go condition, 80.6% for No Go condition), and the ratios were similar to those observed following stimulus presentation. A breakdown of the relative proportions of neuron specificity is shown in Figure 1-11C,D.

Movement-related Activity

Of the GPI neurons recorded, 49% (49/100) responded to button press during correct trials. Proportions of movement-responsive neurons responding in the “obtain reward” and “avoid loss” conditions were similar, with 34% (34/100) during “obtain reward” and 32% (32/100) during “avoid loss.” Action-responsive populations for both valence conditions were similar in terms of the ratios of activated to inhibited neurons (21 activated neurons/13 inhibited for the “obtain reward” condition; 16 activated neurons/ 16 inhibited for the “avoid loss” condition; χ^2=.9623, p=.3358).

Amplitude changes in responsive neurons were also similar, with respect to both activations (+23.69% for “obtain reward”, +19.52% for “avoid loss”; Fig. 1-14) and inhibitions (-14.6% for “obtain reward” and -15.24% for “avoid loss”; Fig. 1-14). Here again, we observed evidence contrary to our hypothesis that movement-related modulation would occur independent of the movement’s motivational context. Specifically, a majority of neurons (65.3%, 32/49) responded to movement for just one of the motivational contexts—obtaining reward [34.7% (17/49)] or avoiding loss [30.6% (15/49)], and just 34.7% (17/49) of neurons were “similar,” responding to movement whether movement was motivated by reward seeking or loss avoidance (Fig. 1-14C). This finding suggests that a sizeable sub-population of movement-responsive neurons exists in the GPi whose firing rate is affected by the motivational context of action.

Error-related Activity

GPi neurons responding to feedback during both correct and incorrect trials (which resulted in either an unexpected monetary loss or a failure to receive an expected reward) were recorded. In contrast to the STN, we observed a trend toward lower mean baseline firing rate in correct as compared to incorrect trials (64±3.57 vs. 71.85±9.2 Hz, mean±SEM, respectively), although this difference also did not reach statistical significance (student's t test, $p>.05$). Also in comparison to the STN, average amplitude changes in the GPi were not significantly different between neurons responsive to correct and incorrect feedback. When the response to error feedback was an excitation, there was on average a +25.5±3.11% change in amplitude and when the response was an inhibition the average amplitude change was -23±4.22% (Fig. 1-15A).

To accurately determine the proportion of neurons responsive to feedback during incorrect trials, we examined only neurons that were recorded during blocks of the task with at least 20% incorrect responses in one of the conditions (i.e. a premature button press during No Go trials or failure to press the button during Go trials)—a total of 59 neurons. We observed that 42.4% (25/59) of this population responded to feedback presentation during incorrect trials. As shown in Figure 1-15B, the vast majority of these neurons (92%, 23/25) were specific—exclusively responsive to either monetary loss (44%, 11/25) or failure to obtain reward (48%, 12/25). Just 8% (2/25) of these neurons were responsive to both feedback conditions.

Just 24% (6/25) of these neurons responded to incorrect feedback and some other condition of the task (including stimulus, movement, or correct feedback). Thus, the majority of error sensitive neurons (19/25) were condition-specific. These results are

consistent with the findings of Ruiz et al. regarding involvement of the human GPi in error monitoring[31].

Neuronal Mapping

The mean position of the recording sites in GPi were 22.22 ± 1.65 mm lateral to the AC–PC line in the mid-sagittal plane, 2.08 ± 2.55 mm posterior to the inter-commissural point and 1.06 ± 1.94 mm below the AC–PC plane (Fig. 1-16). For the mean position of sub-populations of responsive neurons, see Figure 1-10.

Discussion: Comparing STN and GPi

The present study shows that STN and GPi neurons in PD patients can encode multiple valence conditions, including the opportunity for reward, the threat of loss, reward receipt, and the successful avoidance of an aversive outcome.

In accordance with the findings of previous animal studies[2,6,32], STN neurons are mostly specific to one of the two optimal outcomes, based on the responses observed at both stimulus presentation and feedback delivery. Here we also show a clear tendency for STN neurons to encode the positively valenced optimal outcome (reward) versus the neutrally valenced optimal outcome (loss avoidance). It has been theorized that the proportion of mobilized neurons may encode the relative value of one outcome compared to another, with a greater proportion of neurons responding to the so-called preferred outcome[2]. Assuming rewarded outcomes are preferred to neutral outcomes where losses are avoided (which seems reasonable given the observation of lower mean reaction times for Go-to-Win vs. Go-to-avoid losing and higher mean accuracy for Go-to-win vs. Go-to-avoid losing), our findings appear to corroborate this theory.

Since the STN and GPi are well known to be involved in motor behavior, it may be argued that responses at stimulus presentation might not be strictly valence-related[2].

Our experimental design holding motor behavior constant while valence is modified (and conducting this test in both movement and non-movement scenarios) should in theory permit dissociation between valence-related and motor-related activity. The observation that movement-centered and stimulus-centered activity can co-occur in the same neuron raises the possibility that valence- and motor-related signaling in these neurons temporally converge; that is, it is not clear precisely when valence-related and movement-related activity begin and end and where overlap might occur (if at all). Experimental designs that implement a gating approach to motor response, i.e. intervals between stimulus presentation and the time when a successful motor response can be registered, may permit clearer dissociation between valence and motor activity, but they introduce an artificial component into the evaluation of action control and may obscure the character and temporal dynamics of action-valence interactions in their natural state. A change in activity after stimulus presentation might thus be associated partly with motor preparation, but the signal is modulated by the motivational context associated with a specific stimulus (clearly shown by our results when motor condition is constant but valence is varied)[2]. Finally, the possibility of overlap between movement- and valence- related activity in the feedback epoch is greatly diminished by the delay period between completion of action selection (button press or expiration of the decision interval) and feedback delivery.

Behavioral Data

Wagenbreth and colleagues previously studied the performance of Parkinson's patients on a very similar version of this task[40]. The only difference was a directional component (the stimulus cue instructed subjects to press either a left or right button), which was not feasible in our experiment given our goal of simultaneously studying the

neuronal responses in contralateral brain regions. Their objective was to compare the performance of 16 PD patients in the task in the STN-DBS ON vs. OFF states. They observed that PD patients OFF DBS performed equally well in the NO GO conditions (~100% accuracy) and equally poorly (~80% accuracy) in the GO conditions. These findings varied considerably from our results. We consistently had patients perform poorly in the No Go condition. Importantly, Wagenbreth's experimental design consisted of many more trials than we were able to implement (320 vs. 120 per session, respectively), due to the constraints of the operating room environment. Also, the appropriate response for each condition was made explicit to patients during their training period. Furthermore, Wagenbreth did not report performance change over time across the 320 trials; it is therefore possible that subject fatigue could be an important factor explaining the observed differences. Also the subjects in the Wagenbreth study were ON medication and the subjects in the present study were OFF medication.

Interestingly, the relative performance of PD patients in their natural OFF medication state tended to correspond to the performance biases observed in this task (with the directional component) in healthy control populations[30,29]. Among healthy controls, No Go-to-Avoid Loss performance exceeded No Go-to-Win performance, and Go-to-Win performance exceeded Go to Avoid Loss performance. Our results thus indicate that the typical Pavlovian action-valence performance biases are maintained in the PD population.

It is important to note that during the training phase, patients remained on their supplementary dopaminergic medication, while for the intraoperative trials dopaminergic medications had been withdrawn 24 hours prior. Therefore, it is difficult to directly

compare performance between these epochs, especially given that motor performance during the intraoperative period could be confounded by the emergence of motor deficits in the OFF medication state. Thus, it is conceivable that motor performance (accuracy and response time) was underestimated in the intraoperative period. Nonetheless, we observed significant improvements in task performance from the second training epoch to the first intraoperative epoch performed approximately 24 hours later. This suggests firstly that the memory of the action-valence associations was quite strong across subjects and secondly that any motor deficits in the OFF medication state did not significantly impact the subjects' ability to invigorate the relatively simple button press movement the task required.

Electrophysiological Data

This is the first study to record the responses of human STN neurons to stimuli indicating an opportunity for reward or a threat of loss, in both action and inhibition contexts. We show that distinct neuronal populations responded for each motivational context. Interestingly, the population responding to reward opportunity was larger than that responding to threat of loss. As discussed above, if obtaining reward is the preferred outcome (as evidenced by behavioral results), then the STN seems to encode more strongly the preferred outcome. This finding is in line with previous studies by Lardeaux and colleagues[6] who identified preferential encoding in the rat STN.

The internal and external globus pallidus corresponds in most animal studies to the dorsal pallidum[1], with the ventral pallidum occupying a distinct region strongly associated with representing reward information[1,51,52]. Although less well studied, the dorsal pallidum has been shown to encode reward signals[1]. Specifically, Hikosaka and colleagues identified a subpopulation of GPi neurons in the monkey that project to the

LHb which strongly encode reward prediction signals[19,20]. Our results corroborate the notion that the GPi participates in reward signaling, both in terms of the expectation of reward and reward-related feedback/reinforcement. Moreover, GPi neurons also encoded the prospect of loss (stimulus) and successful loss avoidance (feedback), suggesting that the GPi can encode other valenced stimuli beyond pure “reward.” Finally, our finding that a large proportion of pallidal neurons were comodulated by both valence and action corresponded to the finding of Arkadir’s study in the monkey GPe (41% comodulated by reward expectation and movement)[21].

Our study provides critical evidence from the individual neuron level that the human GPi plays a role in error monitoring. A few studies of individual pallidal neuron behavior in animals have supported this view[19,21], but to date human evidence has been sparse. The most relevant human study was performed by Ruiz and colleagues; studying LFPs in the GPi, they demonstrated modulation of pallidal activity prior to erroneous responses and at the time of erroneous response onset[31]. They furthermore observed that the error-related signal was enhanced in the ipsilateral GPi. Our demonstration of a substantial population of neurons that are responsive to error feedback in the GPi corroborates the notion of a role for the GPi in error monitoring. Furthermore, the fact that the majority of error-responsive neurons responded exclusively to error suggests a dedicated error-monitoring role for some GPi neurons. The notion of parallel processing of error-related signals in the motor and limbic loops of the cortical-BG-thalamocortical circuitry is not new[31] and is supported by the finding that certain GPi neurons in monkeys project to the LHb and encode error signals[19].

The present study shows that STN neurons also respond to error and that the majority of these are error-specific, a finding consistent with rodent studies reporting that a majority of error-responsive STN neurons are also error specific[2]. The observation that error-responsive STN neurons can respond either to overt loss or reward omission, in similar proportions but specifically, suggests that in encoding error STN neurons also encode information about the relative value of the error's outcome.

Neuronal Mapping

The prevailing view of the functional topography of the STN is division into three zones: an anteromedial limbic zone, a posterior sensorimotor zone, and an overlapping associative zone located between the two[10–12]. Initially, Lambert and colleagues put forth data consistent with a model of distinct limbic and motor zones with an associative zone representing a transition between the two[14]. Alkemade and others interpreted this, but Lambert and colleagues later cautioned that their methods would not be able to accurately model graduated architectural features and instead artificially provide "anatomically distinct" boundaries. Thus, we postulated the existence of a graduated region and expected to find a subtle transition across the anterior and medial axes where limbic-processing neurons would become more rare toward the STN's lateral and posterior boundaries. Interestingly, we did not observe such a transition but rather identified limbic processing neurons distributed throughout the structure. Moreover, we observed significant overlap of limbic processing with motor responsive neurons.

The findings of our study contribute some valuable evidence to the ongoing controversy about the parcellation of the STN into functional zones[14,18]. Specifically, we show significant overlap between neurons responding to limbic/affective cues, and, importantly, these neurons were not confined to the anteromedial portion of the STN,

the region widely held to be the zone of limbic involvement. It is important to note that our study was unable to sample a significant number of neurons in the anteromedial STN, due to the inherent limitations of recording neurons encountered exclusively along pre-defined trajectories for therapeutic DBS lead placement. Thus, our findings do not preclude the possibility that the anteromedial portion of the STN is more heavily involved in limbic processing (either by proportion of sampled neurons or magnitude of modulation). However, our results do suggest that limbic overlap with the sensorimotor region is greater than has been previously reported.

Similarly for the GPi, our findings did not corroborate the prevailing notion of a limbic GPi limited to the anterior portion of the nucleus. Instead, we found a wide distribution of neurons that were responsive to valence. Here again, our results do not necessarily preclude a higher concentration of valence-responsive neurons in anterior GPi given that pre-defined electrode trajectories did not permit significant sampling from this region; however, we conclude that valence-responsive neurons are more widely distributed in the GPi than has been acknowledged elsewhere.

Part of the motivation to map valence-responsive neurons in these structures is to explain the occurrence of cognitive and behavioral decline following DBS utilizing either target but with the susceptibility to decline apparently greater following STN DBS[53–59]. It is important to note key anatomical differences between the two structures. The human STN is approximately 140 cubic mm[60] and consists of approximately 250,000 neurons[61], while the human GPi is approximately 460 cubic mm[62] and the pallidum comprises approximately 700,000 neurons[63]. In light of 1) this size and neuron density difference, 2) the apparently wide distribution of valence-responsive neurons in

both structures, and 3) the higher concentration of valence-responsive neurons in the STN, one plausible explanation for the observed clinical differences is that the effective DBS electrical field targeting STN would incorporate (and thereby manipulate) more valence-responsive neurons than would a comparable field targeting the GPi. Moreover, since it is generally accepted that the volume of a target structure positively influences stereotactic lead placement[64], the likelihood of misplaced leads increases in STN targets, which in turn creates the requirement of a spatially larger field to achieve therapeutic effect, providing yet another reason why STN DBS might incorporate more valence neurons despite wide distribution across the nucleus.

Finally, we note that individual neuron recording in vivo—despite its decreasing popularity in favor of techniques offering broader spatial resolution such as local field potentials—may provide a greater degree of subtlety in elucidating graduated changes across the structure and provide more accurate estimates of overlaps and transitions in topographic organization. In such cases, the use of larger arrays could be beneficial[65]. Also, the proposed intentional targeting of perceived “limbic zones” in these structures to treat psychiatric and behavioral disorders[25,66,67] could enable greater sampling of the regions not possible in this cohort of patients being treated for motor symptoms. Indeed, combining single unit neuronal recordings with advanced imaging techniques (eg. 7T MRI[68] and tractography) could be of even greater value, as it must be recognized that our method of identifying recorded neuron locations, no matter how rigorous, is subject to inherent limitations, including the resolution of imaging used for surgical targeting (3T MRI)[68] and the need to superimpose these images onto a two-dimensional brain atlas

with known inconsistencies[36,69,70]. The implications of these limitations for mapping neurons in a structure as small as the STN could be significant.

Conclusion

In conclusion, we report here that STN and GPi neurons encode valence-related information during action control, with valence-responsive neurons comprising a greater proportion of neurons in the STN compared to the anatomically larger GPi. Valence-responsive STN and GPi neurons appear to be evenly distributed throughout both structures. In the STN, reward-related stimuli mobilize a greater proportion of neurons than loss-related stimuli. These attributes of the STN and GPi suggest that both structures occupy critical positions in decision-making circuitry, and they help to explain the numerous behavioral complications that have been associated with high-frequency electrical stimulation of these structures, as well as the higher incidence of these complications following manipulation of the anatomically more compact STN. Future work elaborating on valence processing and action-valence interactions in STN and GPi in broader contexts will be important to the refinement of DBS surgery techniques and the further development of neuromodulatory therapies targeted at psychiatric disorders.

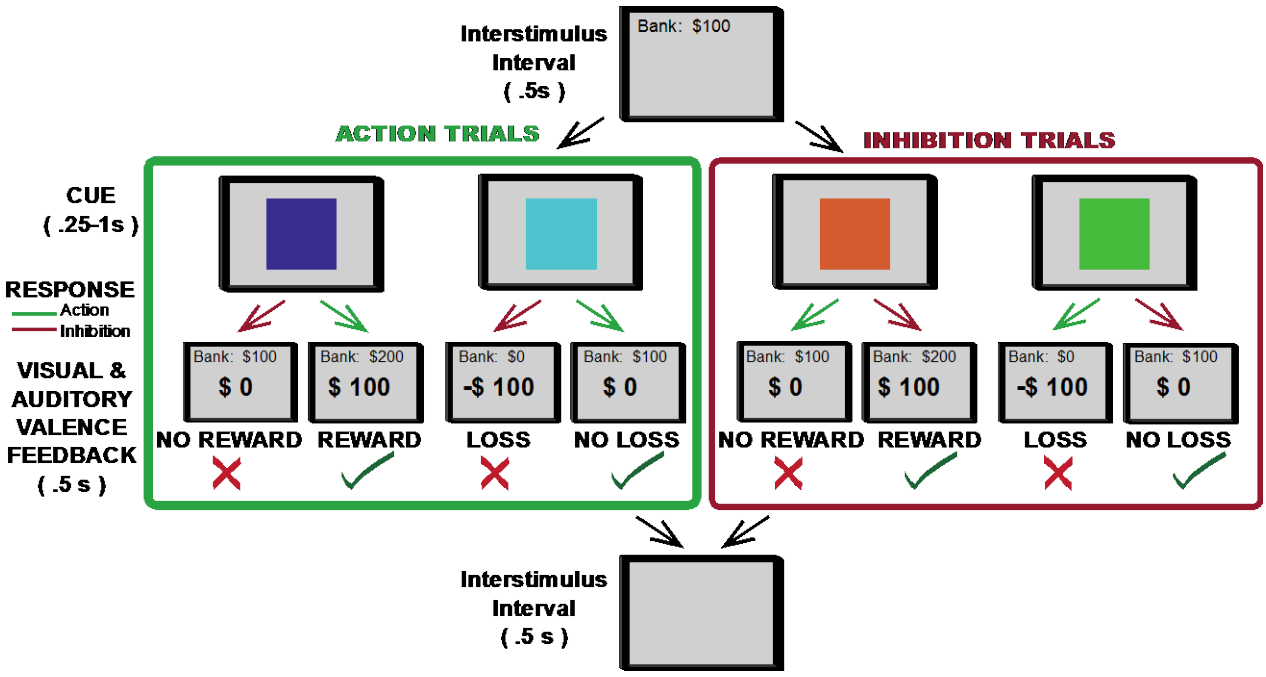

Figure 1-1. Behavioral Task. On each trial, one of four possible color patches indicated the combination of required action (making or withholding button press) and outcome valence (win or loss). An action decision was required following presentation of the color patch. After a brief delay, the outcome was presented: '+$100' in green indicated a reward, a red '-$100' indicated a loss, and a black '$0' indicated the absence of a win or a loss. In go to win trials (purple cue), button press was rewarded; in go to avoid losing trials (blue cue), button press avoided punishment; in no-go to win trials (orange cue) withholding button press was rewarded, and in no-go to avoid losing trials (green cue) withholding button press avoided punishment. A running total score was presented at the top of the screen throughout the task. Each trial was preceded by an interstimulus interval in which a blank screen was presented. Stimuli were presented in pseudorandom order for a total of 120 trials (30 trials of each color/condition).

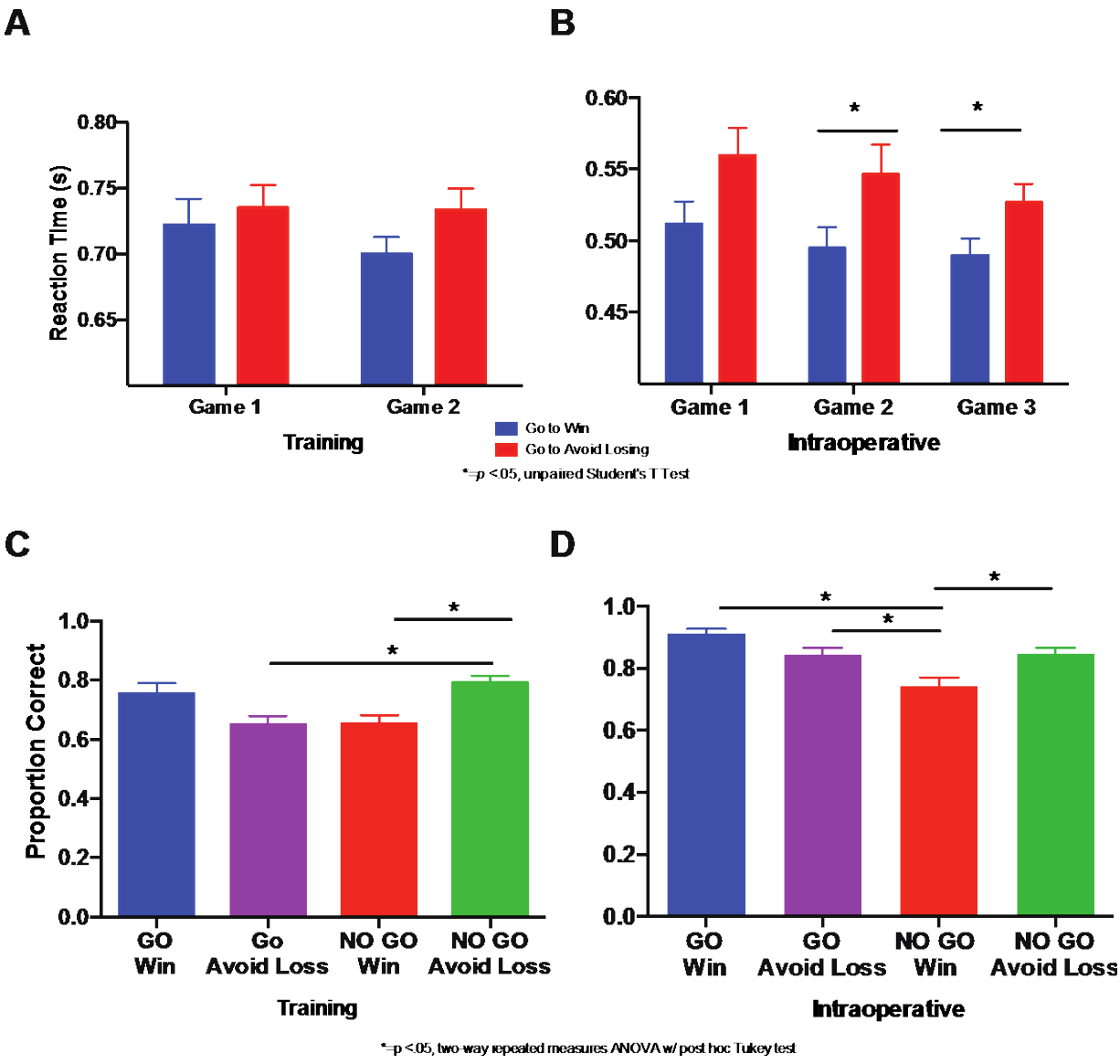

Figure 1-2. Task Performance. A-B) Mean reaction times for all training A) and intraoperative B) "Go" trials, by consecutive game. Results for Go to Win trials are depicted on the left in blue; Go to Avoid Losing trials are depicted on the right in red. Error bars indicate SEM. *=p<.05, unpaired student's T test. Intraoperative games occurred approximately 24 hours after training session. C-D) Mean task accuracy for all training C) and intraoperative D) trials, by consecutive game. Error bars indicate SEM. *=p<.05, two-way repeated measures ANOVA with post-hoc Tukey test for multiple comparisons.

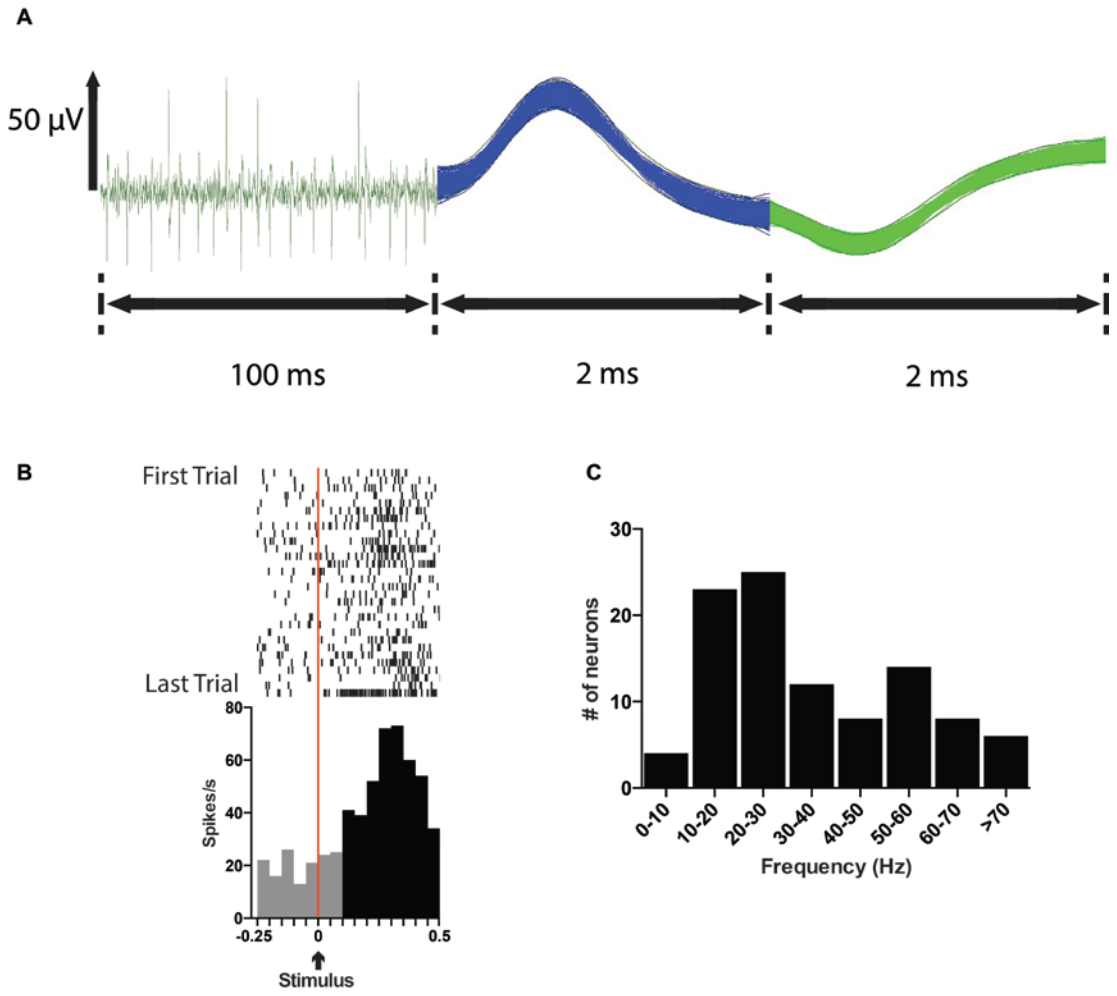

Figure 1-3. Neuronal and waveform characterization. A) Example of different waveforms of some representative neurons recorded in the STN showing spikes (left) and biphasic waveforms (middle and right) from two distinct neurons recorded simultaneously from the same electrode. B) Example of the firing pattern of one STN neuron classified as reward opportunity specific, showing increased activity to the color patch stimulus signifying Go for Reward. Rasters are centered on the occurrence of the stimulus presentation (time = 0). The stimulus is indicated with a black arrow. The area to the left of the vertical red lines represents the baseline period (intertrial interval) on which the bins were analyzed [0:500 ms]. The black bins represent the bins significantly different from the baseline ([−500:0 ms]), with a Z-score >1.64. Light grey bins represent the bins not significantly different from baseline, with a Z score <1.64. This neuron was determined to respond with significant neuronal activation due to the occurrence of 3 or more consecutive bins with Z scores >1.64. Top, raster plot of spike firing on each trial (each row illustrates one trial), with the top row of dots corresponding to the first trial. Bottom, peri-event time histogram showing mean firing rate across all trials, with a bin size of 50 ms. C) Distribution of the 100 STN neurons according to their mean firing rate (Hz).

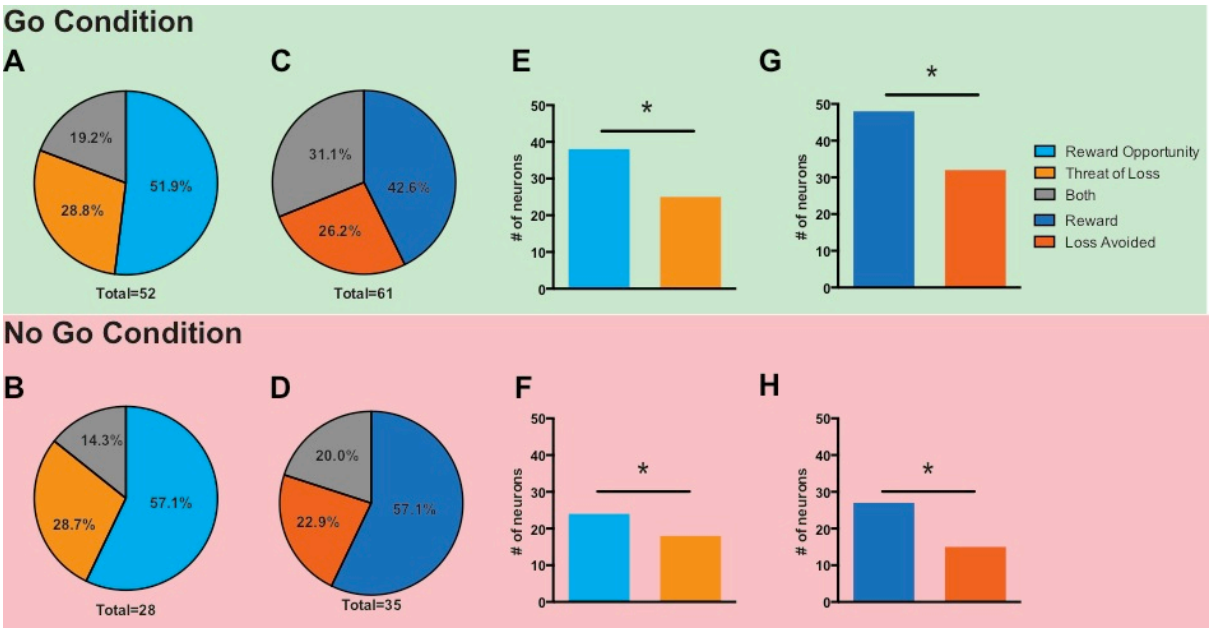

Figure 1-4. Valence Responsiveness in STN Neurons. Proportions of the neuronal population responding in the post-stimulus period to reward opportunity, threat of loss, and both conditions during A) Go trials and B) No Go trials. Proportions of the neuronal population responding in the post-feedback period to reward, loss avoidance, and both conditions during C) Go trials and D) No Go trials [reward receipt (dark blue), loss avoidance (dark orange), and both (grey)]. Total number = total number of responding neurons out of 100 neurons analyzed. Comparison of neurons responding to reward opportunity and neurons responding to threat of loss for the E) Go and F) No Go conditions. Comparison of neurons responding to reward obtained and loss avoided for the G) Go and H) No Go conditions. (* = $p<0.05$, χ^2-test).

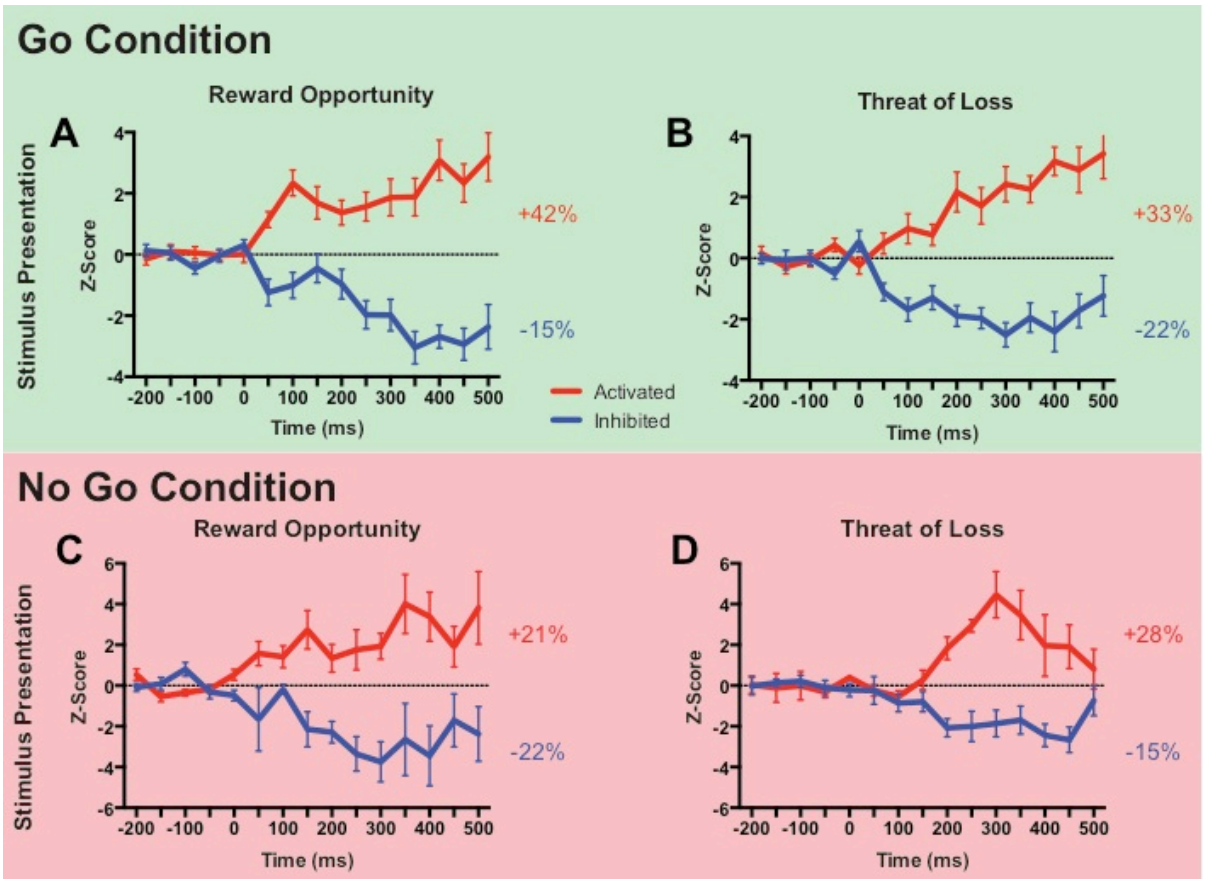

Figure 1-5. Excitation and Inhibition at Stimulus Presentation in STN Neurons. Average z-scores (mean ± SEM) of the firing activity for STN neurons responding by an activation (red line) or an inhibition (blue line) to the visual stimulus (time= 0 ms) in Go-to-Win A), Go-to-Avoid Loss B), No Go-to-Win D), and No Go-to-Avoid Loss E) conditions. The percentages represent the mean variation of activity after each event for activated (red) and inhibited (blue) neuronal population. The z-scores are represented for the period on which the time bins were analyzed (-250:500ms).

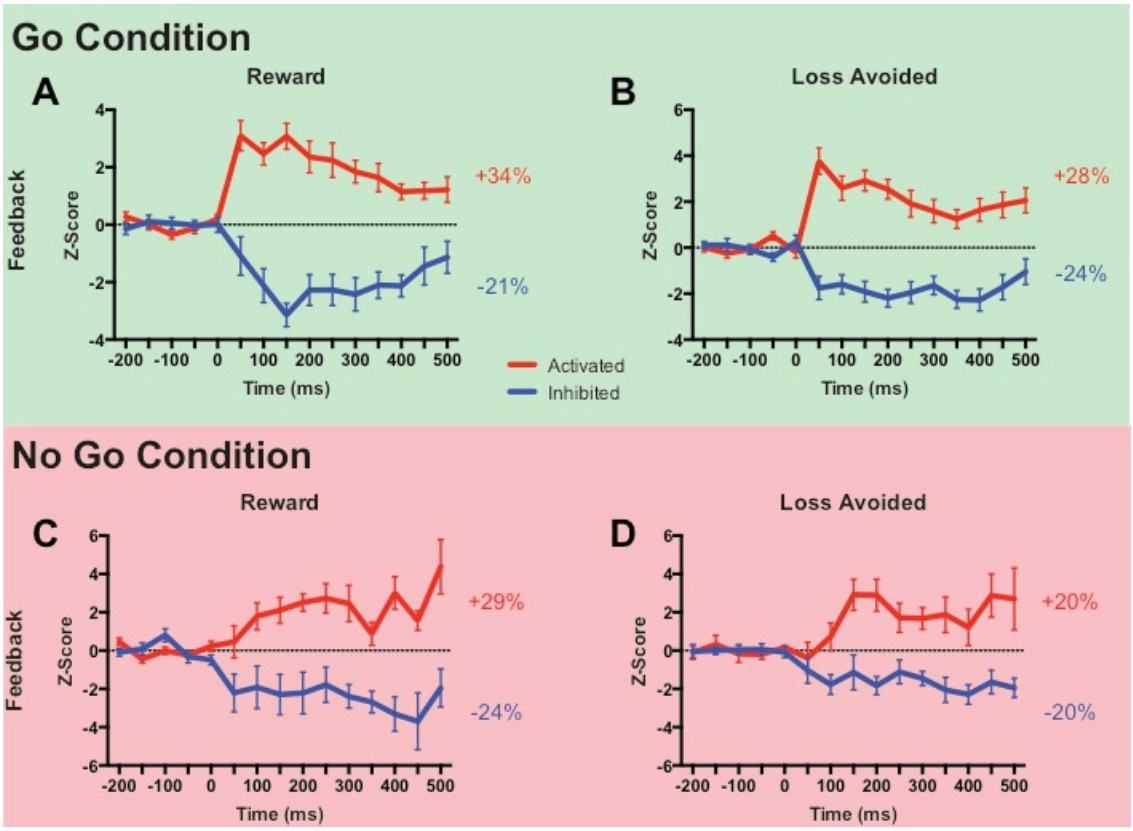

Figure 1-6. Excitation and Inhibition at Feedback Presentation in STN Neurons. Average z-scores (mean ± SEM) of the firing activity for STN neurons responding by an activation (red line) or an inhibition (blue line) to the visual stimulus (time= 0 ms) in Go-to-Win A), Go to Avoid Losing B), No Go to Win D), and No Go to Avoid Losing E) conditions. The percentages represent the mean variation of activity after each event for activated (red) and inhibited (blue) neuronal population. The z-scores are represented for the period on which the time bins were analyzed (final 250 ms of baseline from the intertrial interval and 500ms after stimulus presentation).

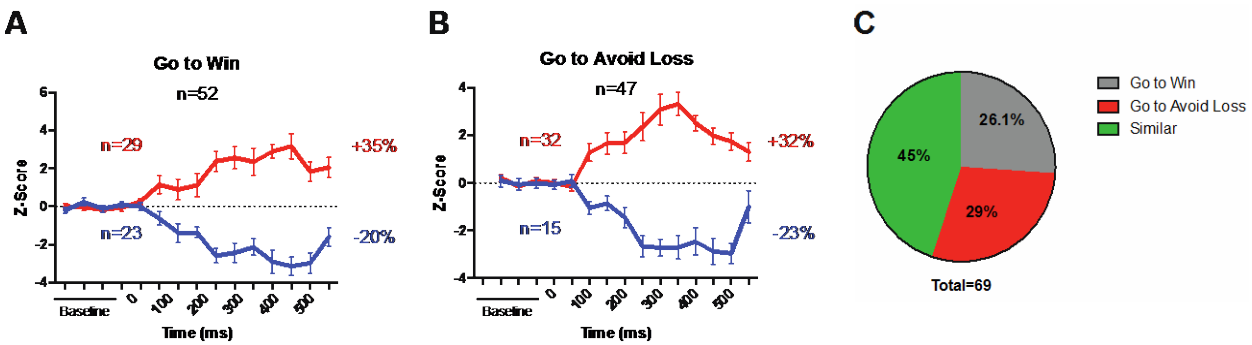

Figure 1-7. STN Movement-related Activity. A-B) Excitation and inhibition at button press. Average z-scores (mean ± SEM) of the firing activity for STN neurons responding by an activation (red line) or an inhibition (blue line) at button press (time= 0 ms) in Go-to-Win A) and Go to Avoid Losing B) conditions. The total number of neurons responding (black), total number of neurons responding by excitation (red), and total number of neurons responding by inhibition (blue) are given with n. The percentages represent the mean variation of activity after each event for activated (red) and inhibited (blue) neuronal population. The z-scores are represented for the period on which the time bins were analyzed (final 250 ms of baseline from the intertrial interval, and (0:500ms). The far right panel C) shows the proportion of the neuronal population [Go-to-Win (grey), Go-to-Avoid Loss (red), and similar (green)] responding to movement. Total number = total number of responding neurons out of 100.

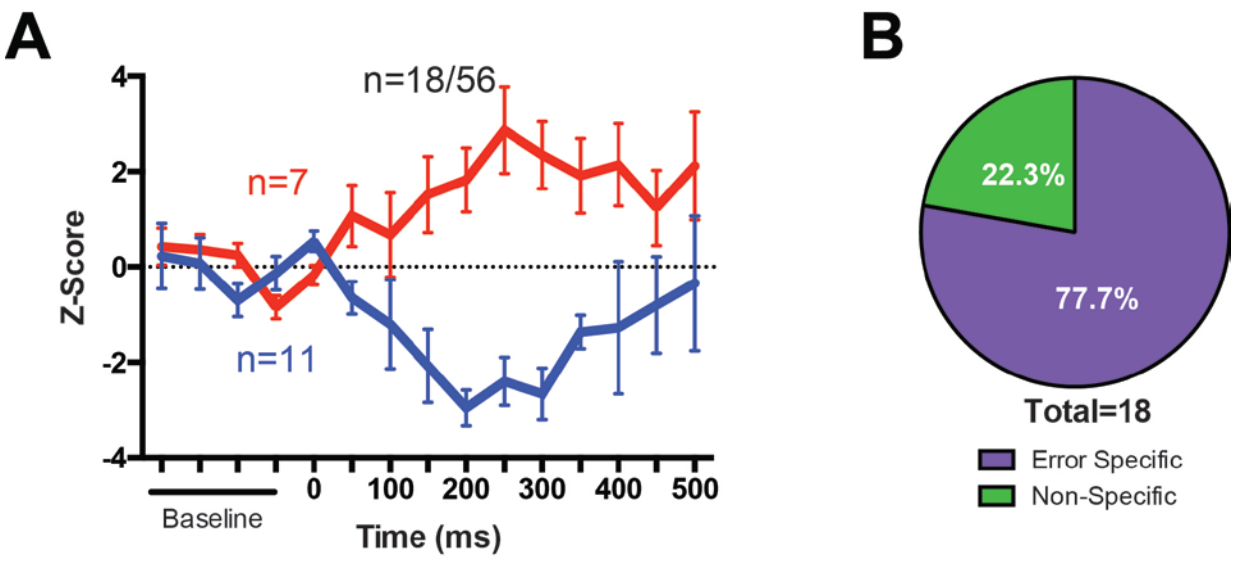

Figure 1-8. Error Sensitive Neurons in the STN. A) Excitation and inhibition at feedback presentation for incorrect trials. Average z-scores (mean ± SEM) of the firing activity for STN neurons responding by an activation (red line) or an inhibition (blue line) to error feedback (time= 0 ms) across all conditions. The total number of neurons responding (black), total number of neurons responding by excitation (red), and total number of neurons responding by inhibition (blue) are given with n. The percentages represent the mean variation of activity after each event for activated (red) and inhibited (blue) neuronal population. The z-scores are represented for the period on which the time bins were analyzed (final 250 ms of baseline from the intertrial interval and (0:500ms). B) Proportions of error-responsive neurons that were specific for error (purple) and responsive to error and some other stimulus (green).

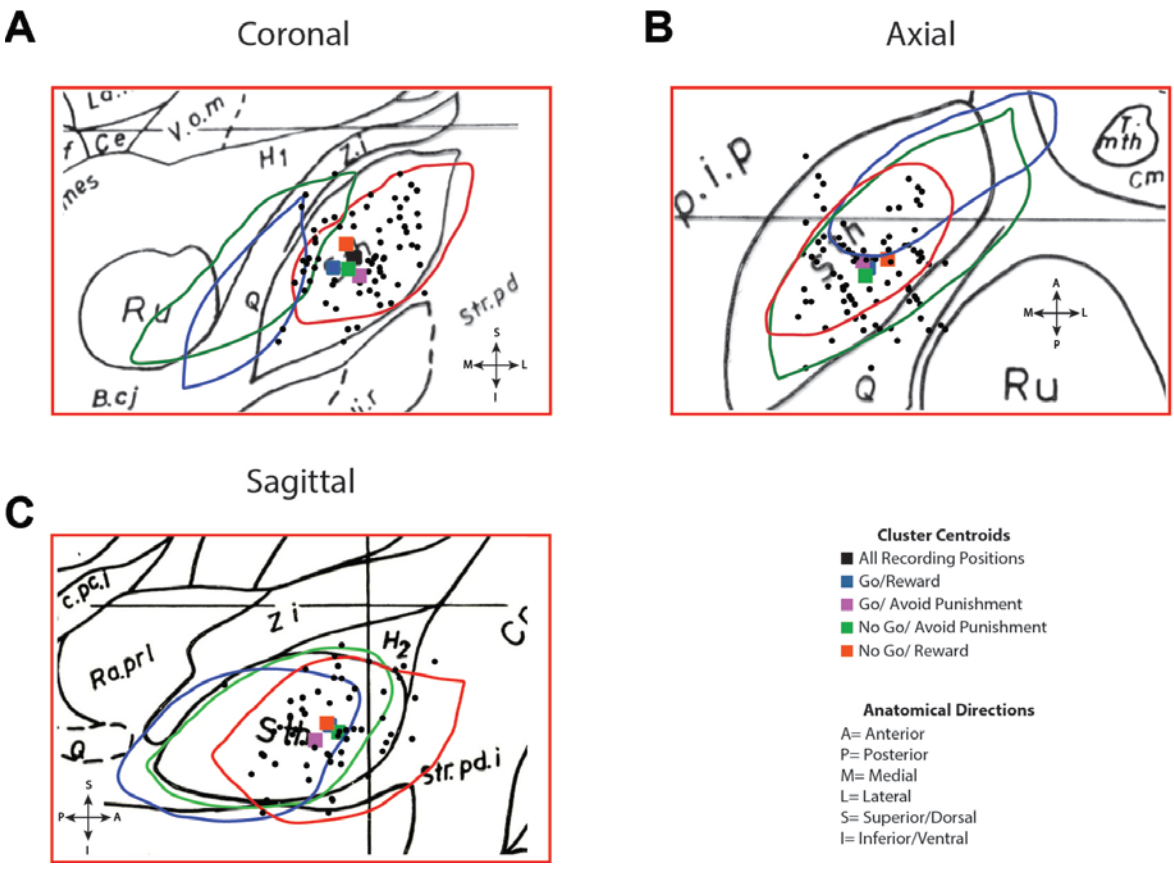

Figure 1-9. Positions of Recorded STN Neurons. The spatial location of the microelectrode recording sites in STN as transposed onto the Schaltenbrand-Bailey atlas. A) The STN from coronal slices F.p 4.0 (drawn in red), F.p 1.5 (drawn in green), and F.a 2.0 (drawn in blue) are superimposed on F.p 3.0 (drawn in black). B) The STN from axial slices H.v -1.5, (drawn in red) H.v -3.5, (drawn in green) and H.v -6.0 (drawn in blue) are superimposed on H.v -4.5 (drawn in black). The portion of each slice shown is 10mm by 15 mm. Black dots represent recording positions. C) The STN from sagittal slices S.l 10 (drawn in red), S.l 13.5 (drawn in green), and S.1 15 (drawn in blue) are superimposed on S.1 11 (in black). Colored squares represent the centroid of clusters of neurons responsive to feedback in each of the conditions.

Table 1

	STN			GPi		
	Anatomical Coordinates					
	Lateral Mean±SD	Posterior Mean±SD	Inferior Mean±SD	Lateral Mean±SD	Posterior Mean±SD	Inferior Mean±SD
All Recorded Neurons	10.69 ± 1.20	1.34 ± 1.39	3.8 ± 1.25	22.22 ± 1.65	2.08 ± 2.55	1.06 ± 1.94
Stimulus						
Go/Win	9.53 ± 1.70	1.827 ± 1.33	3.69 ± 1.59	21.64 ± 1.74	2.44 ± 1.61	1.40 ± 2.28
Go/Avoid Loss	9.55 ± 1.21	1.483 ± 1.27	3.07 ± 1.75	21.96 ± 2.14	1.95 ± 1.67	1.90 ± 1.95
No Go/ Avoid Loss	8.97 ± 1.60	1.322 ± 1.56	4.20 ± 0.94	22.77 ± 1.38	2.95 ± 1.99	1.91 ± 1.75
No Go/Reward	9.35 ± 1.40	1.243 ± 1.27	3.42 ± 1.69	21.50 ± 1.35	2.64 ± 1.25	2.06 ± 1.96
Feedback						
Go/Win	10.08 ± 1.09	0.90 ± 1.73	4.12 ± 1.02	22.01 ± 1.84	2.39 ± 2.14	1.77 ± 1.85
Go/Avoid Loss	10.87 ± 1.13	1.57 ± 1.11	4.36 ± 1.06	22.45 ± 1.77	2.92 ± 1.84	1.28 ± 2.44
No Go/ Avoid Loss	10.53 ± 1.10	0.88 ± 1.46	4.17 ± 0.97	22.27 ± 1.94	1.89 ± 1.73	2.02 ± 1.83
No Go/Reward	10.48 ± 1.20	1.13 ± 1.35	3.41 ± 1.25	22.43 ± 2.37	2.01 ± 2.56	1.90 ± 1.59

Figure 1-10. Anatomical Coordinates of Responsive Populations. The mean anatomical coordinates are given in mm. Lateral coordinates are given in mm lateral to the AC–PC line in the mid-sagittal plane, posterior coordinates are given in mm posterior to the inter-commissural point and inferior points are given in mm below the AC–PC plane. SD= standard deviation

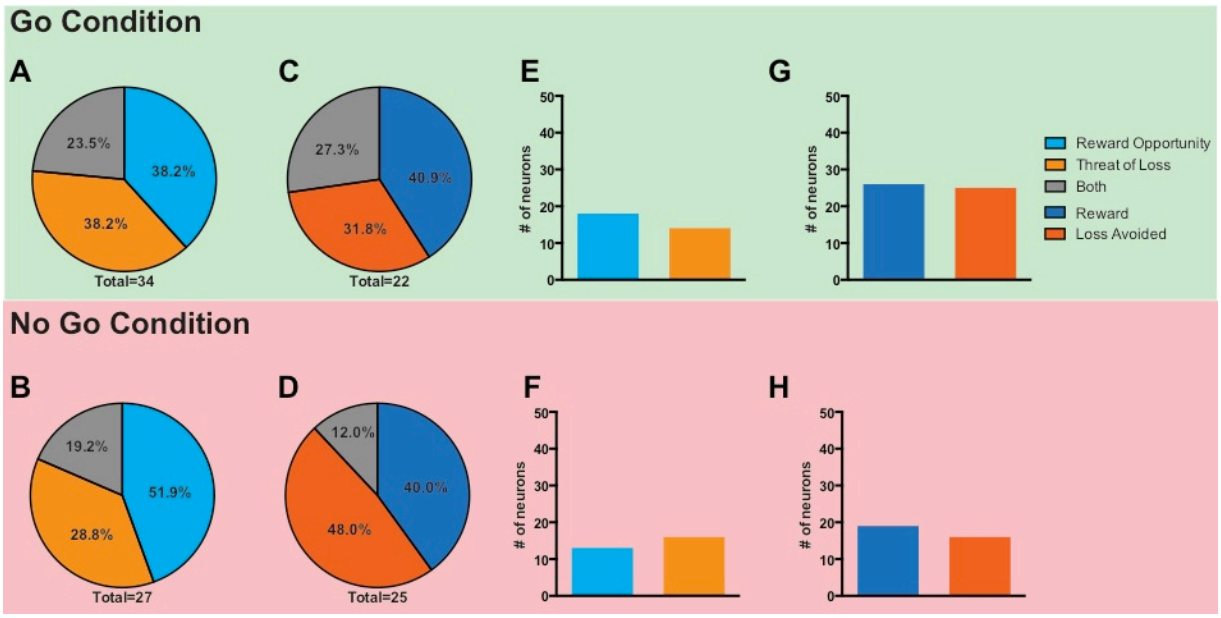

Figure 1-11. Valence Responsiveness in GPi Neurons. Proportions of the neuronal population responding in the post-stimulus period to reward opportunity, threat of loss, and both conditions during A) Go trials and B) No Go trials. Proportions of the neuronal population responding in the post-feedback period to reward, loss avoidance, and both conditions during C) Go trials and D) No Go trials [reward receipt (dark blue), loss avoidance (dark orange), and both (grey)]. Total number = total number of responding neurons out of 100 neurons analyzed. Comparison of neurons responding to reward opportunity and neurons responding to threat of loss for the E) Go and F) No Go conditions. Comparison of neurons responding to reward obtained and loss avoided for the G) Go and H) No Go conditions. (*= $p<0.05$, χ^2-test).

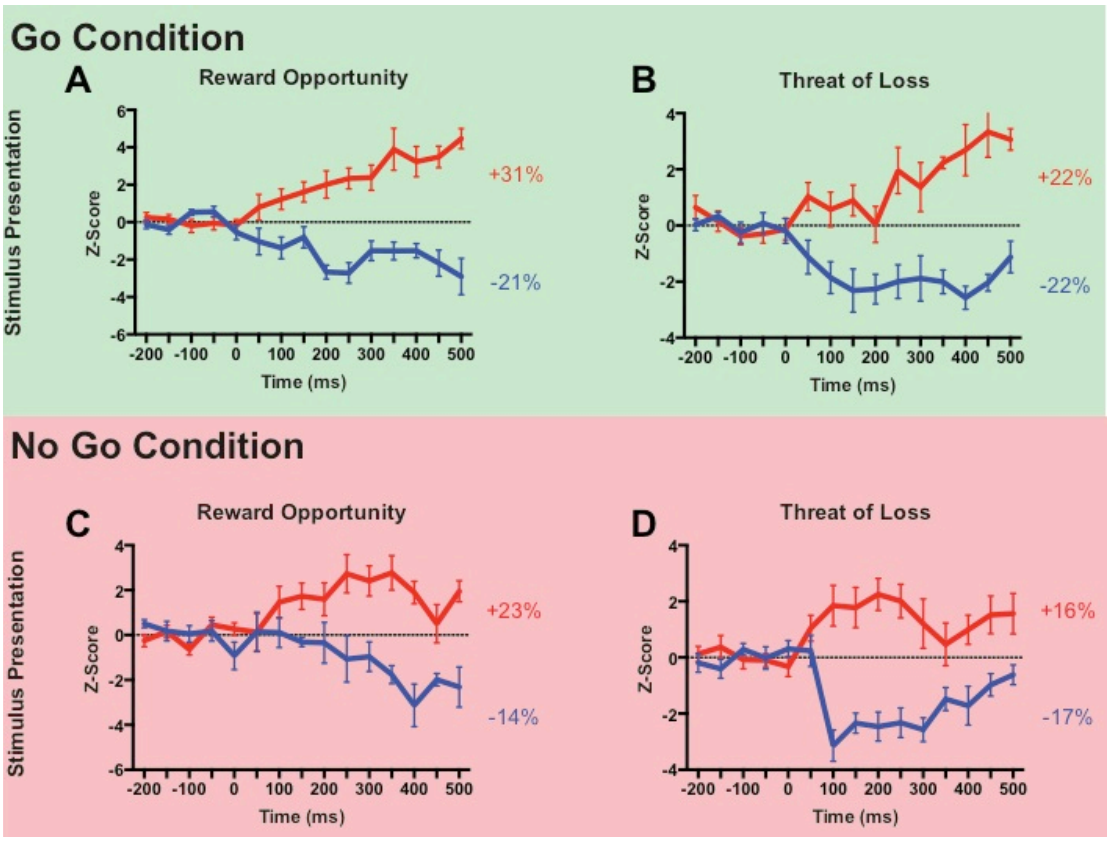

Figure 1-12. Excitation and Inhibition at Stimulus Presentation in GPi Neurons. Average z-scores (mean ± SEM) of the firing activity for GPi neurons responding by an activation (red line) or an inhibition (blue line) to the visual stimulus (time= 0 ms) in A) Go-to-Win, B) Go to Avoid Losing, C) No Go to Win, and D) No Go to Avoid Losing conditions. The percentages represent the mean variation of activity after each event for activated (red) and inhibited (blue) neuronal population. The z-scores are represented for the period on which the time bins were analyzed (final 250 ms of baseline from the intertrial interval, and (0:500ms).

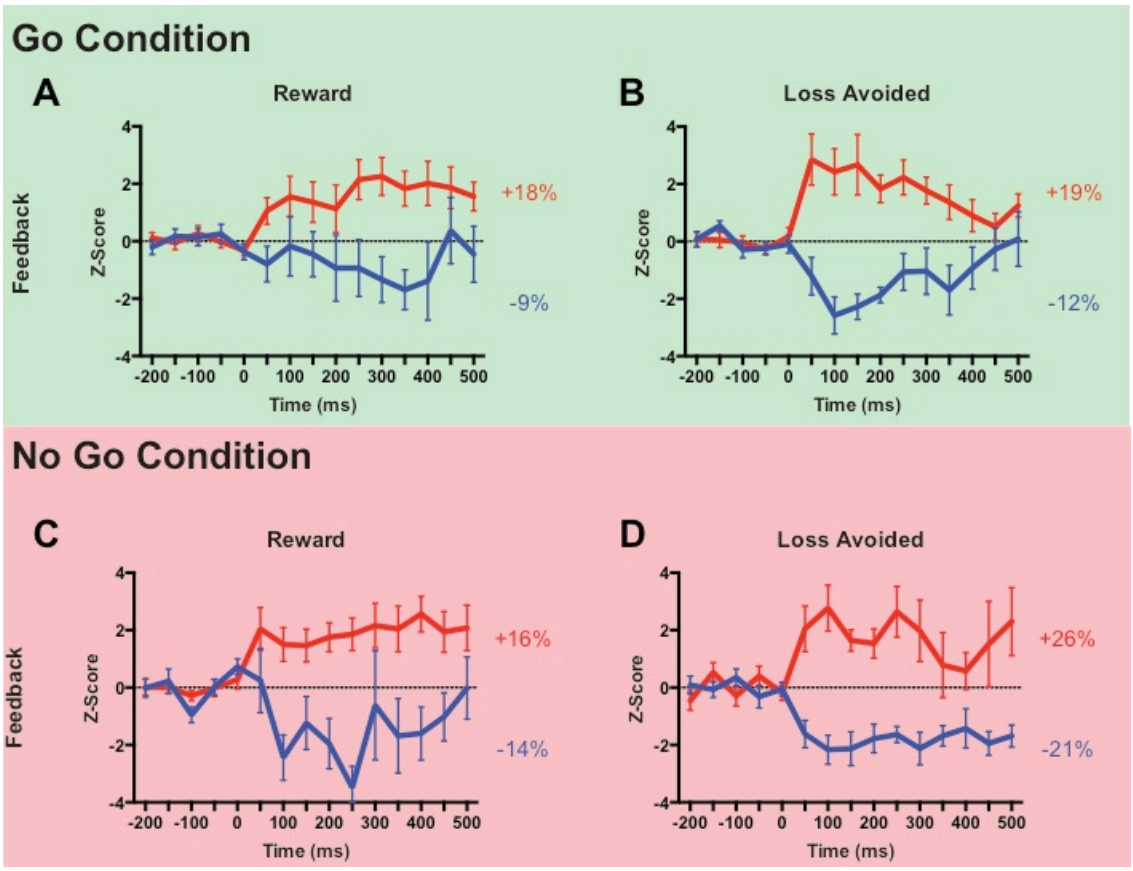

Figure 1-13. Excitation and Inhibition at Feedback Presentation in GPi Neurons. Average z-scores (mean ± SEM) of the firing activity for all GPi neurons responding by an activation (red line) or an inhibition (blue line) to the visual stimulus (time= 0 ms) in A) Go-to-Win, B) Go to Avoid Losing, C) No Go to Win, and D) No Go to Avoid Losing conditions. The percentages represent the mean variation of activity after each event for activated (red) and inhibited (blue) neuronal population. The z-scores are represented for the period on which the time bins were analyzed (final 250 ms of baseline from the intertrial interval, and (0:500ms).

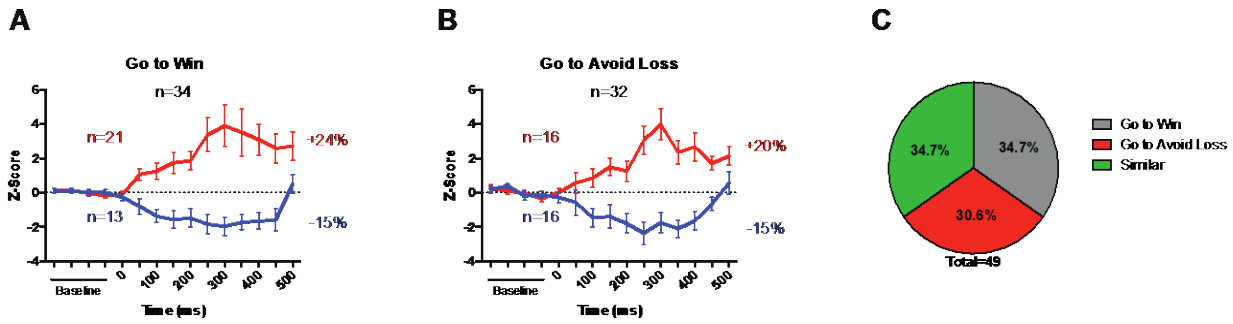

Figure 1-14. GPi Movement-related Activity. A-B) Excitation and inhibition at button press. Average z-scores (mean ± SEM) of the firing activity for STN neurons responding by an activation (red line) or an inhibition (blue line) at button press (time= 0 ms) in Go-to-Win A) and Go to Avoid Losing B) conditions. The total number of neurons responding (black), total number of neurons responding by excitation (red), and total number of neurons responding by inhibition (blue) are given with n. The percentages represent the mean variation of activity after each event for activated (red) and inhibited (blue) neuronal population. The z-scores are represented for the period on which the time bins were analyzed (final 250 ms of baseline from the intertrial interval,and (0:500ms). The far right panel C) shows the proportion of the neuronal population [Go-to-Win (grey), Go-to-Avoid Loss (red), and similar (green)] responding to movement. Total number = total number of responding neurons out of 100.

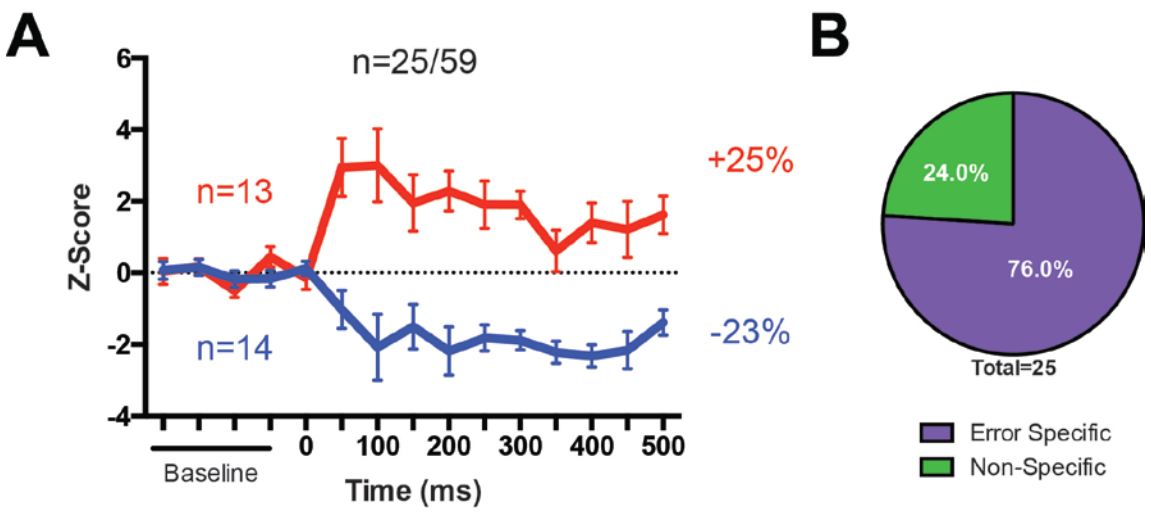

Figure 1-15. Error Sensitive Neurons in the GPi. A) Excitation and inhibition at feedback presentation for incorrect trials. Average z-scores (mean ± SEM) of the firing activity for GPi neurons responding by an activation (red line) or an inhibition (blue line) to error feedback (time= 0 ms) across all conditions. The total number of neurons responding (black), total number of neurons responding by excitation (red), and total number of neurons responding by inhibition (blue) are given with n. The percentages represent the mean variation of activity after each event for activated (red) and inhibited (blue) neuronal population. The z-scores are represented for the periods on which the time bins were analyzed (final 250 ms of baseline from the intertrial interval, and 0:500ms). B) Proportions of error-responsive neurons that were specific for error (purple) and responsive to error and some other stimulus (green).

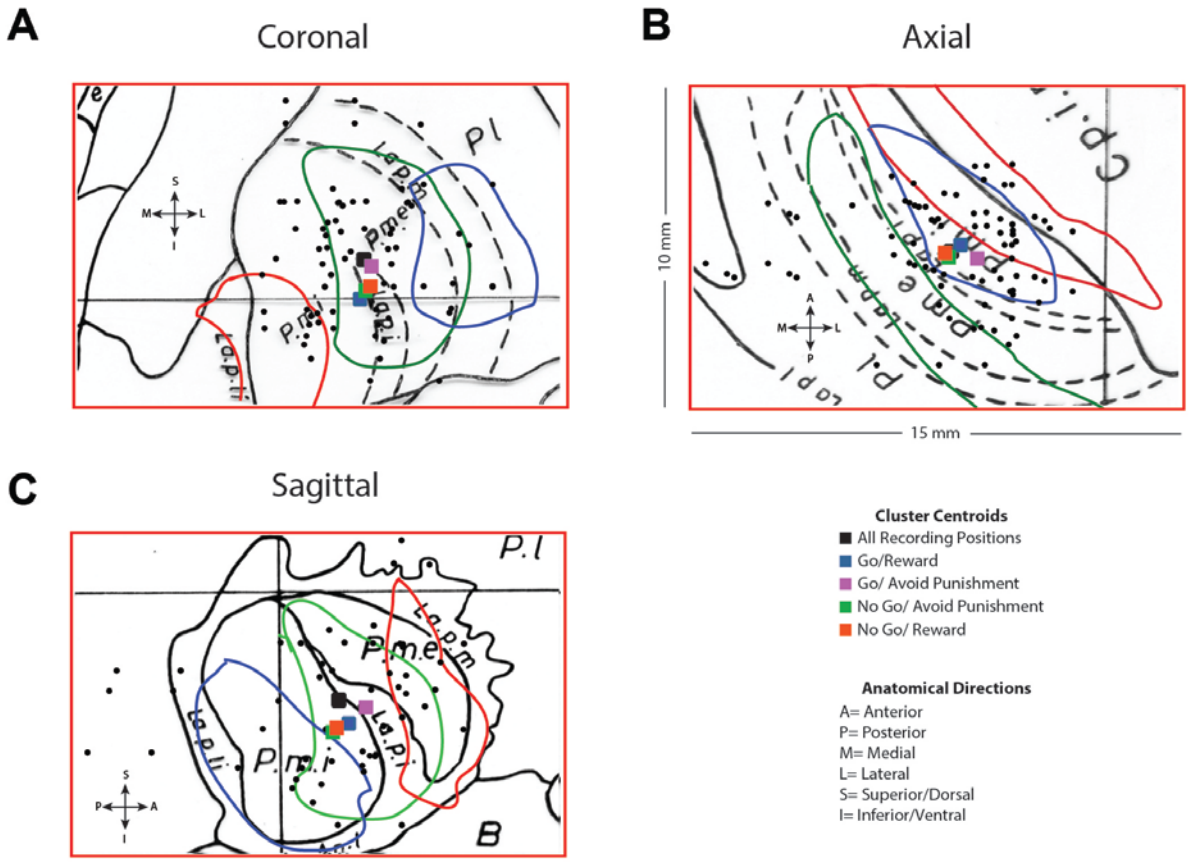

Figure 1-16. Positions of Recorded GPi Neurons. The spatial location of the microelectrode recording sites in GPi as transposed onto the Schaltenbrand-Bailey atlas. A) The GPi from coronal slices F.a 7.5 (drawn in red), F.a 3.0 (drawn in green), and F.a 2.0 (drawn in blue) are superimposed on F.p 5.0 (drawn in black). B) The GPi from axial slices H.v -1.5 (drawn in red), H.v -3.5 (drawn in green), and H.v -6.0 (drawn in blue) are superimposed on H.v -4.5 (drawn in black). C) The GPi from sagittal slices S.l 16 (drawn in red), S.l 18.5 (drawn in green), and S.l 21.5 (drawn in blue) are superimposed on S.l 20 (drawn in black). The portion of each slice shown is 10mm by 15 mm. Black dots represent recording positions. Colored squares represent the centroid of clusters of neurons responsive to feedback in each of the conditions.

CHAPTER 2
IMPULSIVITY AND DIFFERENCES IN STN NEURON BEHAVIOR

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by motor dysfunction, but PD patients can also suffer from behavioral and cognitive deficits. Impulse control disorders (ICDs) encompass a spectrum of behavioral disorders in PD characterized by an inability to resist an inappropriate drive, often of a hedonistic nature and this issue results in repetitive behaviors, that often have harmful consequences[71]. ICDs can take the form of pathological gambling, compulsive buying, compulsive or altered sexuality, binge eating[72], or the compulsive pursuit of hobbies or other manual activities. ICDs occur in approximately 15% of the PD population and can negatively impact quality of life for both patients[72,73] and caregivers[74,75,76]. Despite growing interest in ICDs and robust clinical research over the past decade, the underlying pathophysiology of ICDs is not well understood.

Deep brain stimulation (DBS) therapy of the STN and GPi has been associated with increases in ICD symptoms, though it should be noted that resolution of ICDs has also been reported[77]. Animal studies corroborate the notion that manipulation of these structures can alter impulse control. STN DBS has been shown to both increase[78] and decrease[79] premature responding in rats, and both lesions[80,81,5] and electrical stimulation[82] of the STN can alter rat motivation to obtain rewards, while electrical stimulation of the GPi has been shown to increase impulsivity in rodents[83]. Deep brain stimulation (DBS) of the STN in human patients has been associated with increased automatic response activation and susceptibility to impulsive responses[84].

Studies of individual neuron behavior in rodents and non-human primates suggest that the subthalamic nucleus (STN)[3] and (GPi)[1] mediate the processing of information related to reward and punishment. Large subsets of STN neurons in the rat have been shown to encode the prospect of reward[2,32,85] and loss[2], and similar signaling has been demonstrated in the STN of non-human primates[7–9]. Hikosaka and colleagues documented reward signaling in the primate GPi[19,86,87], and a recent study of single neurons in the human GPi demonstrated responsiveness to the prospect of reward and punishment[88].

Numerous behavioral studies have established a link between impulsive behavior and aberrant processing of reward and punishment[89-92]. Importantly, PD patients with an ICD have been shown to exhibit exaggerated sensitivity to reward[93] and diminished sensitivity to punishment[94,95].

We hypothesized that in PD patients with an ICD, neurons in the STN and GPi would be more responsive to reward-related stimuli and less responsive to loss-related stimuli. Specifically, we expected to observe these differences both in the proportion of responsive neurons and in the magnitude of response (i.e. firing rate).

To test this hypothesis, we studied a cohort of 43 PD patients (32 males, 11 females; 12 with an ICD and 31 without) undergoing DBS electrode placement surgery. ICD diagnosis was established using the Questionnaire for Impulsivity in Parkinson's disease (QUIP) and semi-structured clinical interview. Patients performed a behavioral task in which their action choices were motivated by the potential for either a monetary reward or a monetary loss. During task performance, single unit activity was recorded in either the STN or GPi [100 STN neurons (35 from ICD+ patients and 65 from ICD-

patients) and 100 GPi neurons (36 from ICD+ patients and 64 from ICD- patients)]. Neuronal activity was spike sorted and analyzed to determine responsiveness (i.e. significant change in firing rate from baseline in response to a stimulus), and proportions of responsive neurons were compared using chi square statistics and firing rate changes were compared using two-way repeated measures ANOVA and chi square statistics.

ICDs were associated with significantly greater responsiveness to reward opportunity and this was evidenced in the proportion of responsive neurons ($p<.01$) and in the significantly diminished responsiveness to the threat of loss ($p<.05$) in the STN but not the GPi neurons. Importantly, ICD status was not associated with any differences in firing rate among responsive neurons in either structure. These findings suggest that changes in the STN—possibly via functional conversion of neurons in the limbic circuit—may underlie impulsive behavior in the PD population.

Materials and Methods

Patients

Consecutive patients with Parkinson's disease undergoing de novo STN or GPi DBS electrode placement surgery were studied. All patients fulfilled the UK Brain Bank criteria for PD. All participants were English-speaking, non-demented, not hearing impaired, and sighted. We enrolled 43 patients in the study, with a mean age of 64.8 years (SD=8.9). The Institutional Review Board approved the study and all patients provided informed consent before entering the study.

We recorded complete details of anti-parkinsonian medication therapy for each patient. The recorded medications were those being taken at the time of assessment. Due to the strong association of dopaminergic agonists with the development of ICDs[96],

we compared ICD+ and ICD- groups in the use of dopaminergic agonists (pramipexole, ropinirole, pergolide, rotigotine, apomorphine, or bromocriptine).

Assessment of Impulse Control Disorders

Assessment of impulse control disorders involved modified version of the method employed by Papay and colleagues[97]. Participants completed the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP), a self-reported and self-completed validated measure of impulsivity in PD[98]. Participants were instructed to answer questions based on behaviors that occurred in the previous six months that lasted at least four consecutive weeks[99]. The full version of the QUIP includes five questions for each of the four ICDs most commonly reported in PD (compulsive gambling, buying, sexual behavior, and eating) and three questions about any other activity or hobby. Based on the results of the validation of the QUIP, the following thresholds were used to represent a positive screen for the patient-completed instrument: compulsive gambling (any 2 of the 5 items); compulsive sexual behavior (any 1 of the 5 items); compulsive buying (any 1 of the 5 items); compulsive eating (any 2 of the 5 items); other behavior (punding and hobbyism) (any 2 of the 3 items)[99,100].

The QUIP is designed as a screening instrument and as such is sensitive for the detection of ICD but is not highly specific[101]. To avoid over-identifying ICDs, after patients completed the QUIP, a medically trained investigator administered a semi-structured, diagnostic interview that was based upon published proposed criteria for ICDs in PD[102] and utilized the same time frame as in the QUIP. The interviewer was blinded to the patient's QUIP responses; however, patients occasionally verbalized their responses contrary to instructions. Self-identified primary caregivers who accompanied patients were given the opportunity to contribute during the interview, given the well-

documented phenomenon that patients suffering from ICDs tend to underreport symptoms either due to embarrassment or because they lack objective insight into negative behavior[99]. Primary caregivers were present and contributed in all but three of the interviews.

Participants performed the same behavioral task previously described. Data acquisition, recording protocol, and electrophysiological data analysis were identical.

Results

Patient Characteristics

The mean preoperative QUIP score for ICD+ patients was 7.4±.98 (SEM) and ICD- patients was .45±.21 (SEM). Dopamine agonist use was 29% for ICD- patients and 67% for ICD+ patients (p=.02, χ^2 test). ICDs diagnosed included pathological gambling (n=4), hypersexuality (n=10), pathological buying (n=6), binge eating (n=4), and hobbyism (n=3). Other impulsive activities observed in this cohort included illegal drag racing and shoplifting.

Subthalamic Nucleus

A total of 35 STN cells were recorded from five ICD+ patients, and a total of 65 STN cells were recorded from 14 ICD- patients. Overall, we observed that impulsivity was associated with discernible differences in the proportions of responsive STN neurons. ICD patients exhibited heightened sensitivity to reward opportunity. The proportion of STN neurons responding to the opportunity to earn a reward was significantly higher in ICD+ patients compared to ICD- patients (68.6% vs. 41.5%, χ^2 test, p=.009, Fig 2-1A). ICDs were also associated with significantly higher proportions of reward exclusive neurons—neurons responding only to reward opportunity (63% vs. 31.9%, χ^2 test, p=.009, Fig 2-2A). ICD patients exhibited diminished sensitivity to threat

of loss. The proportion of STN neurons responding to the threat of loss was significantly lower in ICD+ patients compared to ICD- patients (28.6% vs. 49.2%, χ^2 test, p=.045, Fig 2-1A). ICDs were also associated with significantly lower proportions of loss exclusive neurons—neurons responding only to threat of loss (11.1% vs. 42.6%, χ^2 test, p=.005, Figure 2-2A). Finally, ICD+ and ICD- patients exhibit similar firing rates in responsive STN neurons. The mean percent change in firing rate for responsive neurons was not significantly different between ICD+ and ICD- groups for activating or inhibiting neurons, either in reward or loss scenarios (T-test with *post-hoc* Holm-Sidak correction for multiple comparisons, Figure 2-1C). Investigation of the effect of ICD status on post-stimulus changes in firing rate using two-way repeated measures ANOVA also revealed no significant effect of ICD status on firing rate for any of the conditions.

Globus Pallidus internus

A total of 36 GPi cells were recorded from 7 ICD+ patients, and a total of 64 GPi cells were recorded from 17 ICD- patients. ICD+ and ICD- patients exhibited similar GPi responsiveness to reward opportunity. The proportion of GPi neurons responding to the opportunity to earn a reward was not significantly different in ICD+ patients compared to ICD- patients (27% vs. 34.9%, χ^2 test, p=.413, Figure 2-1B). ICDs were not associated with differences in the proportions of reward exclusive neurons (35.7% vs. 38.5%, χ^2 test, p=.856, Figure 2-2B). ICD+ and ICD- patients exhibited similar GPi responsiveness to threat of loss. The proportion of GPi neurons responding to the threat of loss was not significantly different in ICD+ patients compared to ICD- patients (24.3% vs. 39.7, χ^2 test, p=.117, Figure 2-1B). ICDs were not associated with differences in the proportions of loss exclusive neurons (28.6% vs. 41%, χ^2 test, p=.410, Figure 2-2B). Finally, ICD+ and ICD- patients exhibited similar firing rates in responsive GPi neurons. The mean

percent change in firing rate for responsive neurons was not significantly different between ICD+ and ICD- groups for either activating neurons (increased firing rate) or inhibiting neurons (decreased firing rate) (t test with *post-hoc* Holm-Sidak correction for multiple comparisons, Figure 2-1D). Investigation of the effect of ICD status on post-stimulus changes in firing rate using two-way repeated measures ANOVA also revealed no significant effect of ICD status on firing rate for any of the conditions.

Discussion: Comparing STN and GPi

The roles of the STN and GPi in human motor function are well-accepted principles of basal ganglia physiology. The roles of these structures in non-motor functions, however, continue to be intensely studied. Compelling animal evidence suggests that neurons from this region play a role in processing reward and punishment, and clinical evidence has shown that their manipulation via lesions or electrical stimulation may result in behavioral changes likely related to changed perceptions of reward and loss. The present study offers strong evidence suggesting that human subthalamic neuron activity is different in PD patients with an impulse control disorder as compared to PD patients without an impulse control disorder. Specifically, in PD patients with an ICD, the proportions of STN neurons that responded to reward were significantly greater and the proportions of STN neurons that responded to loss were significantly lower. In contrast, no such differences were observed with respect to GPi neurons.

The finding of heightened reward sensitivity and diminished loss sensitivity makes sense in light of the behavioral findings that PD patients with ICD exaggerate their response to rewards and attenuate their response to punishment[94]. What is intriguing about our findings is that these differences in reward/punishment sensitivity

are attributable to differences in the relative proportions of responsive neurons rather than to differences in the magnitude of firing rate changes. Indeed, we observed no significant differences in the ICD+ and ICD- groups in terms of the magnitude of firing rate changes following reward- or loss- related stimuli. In addition, our finding that the relative size of the responsive STN neuron population was stable across ICD- and ICD+ groups (with similar populations of neurons responsive to both reward and loss but different populations of reward exclusive and loss exclusive neurons) could possibly be interpreted as ICD+ patients converting STN loss neurons into reward neurons though this point cannot be concluded based on the available data.

An important remaining question is whether (and how) the observed differences in subthalamic function can be attributed to the use of dopaminergic agonist medications. There is a known association between the use of dopamine agonist drugs and the development of ICDs. A large multi-center study recently showed that up to 39% of patients being treated with non-ergot derived dopamine agonists (pramipexole, ropinirole, or rotigotine) developed ICDs[103]. It was therefore not surprising in or data that the use of dopaminergic agonists was significantly higher among ICD+ patients. Dopamine agonists have high affinities for the dopamine D2 and D3 receptors[96]. Intra-STN administration of the D2-like receptor agonist quinpirole does not alter firing rate patterns of STN neurons in Parkinsonian monkeys[104], and administration of the D1 and D2 agonist apomorphine has been shown to not affect overall STN neuron firing rates in humans[49]. However, the effects of acute administration of D2 agonists on the proportions of neurons responsive to limbic cues are not known. Given that subjects in the present study were withdrawn from dopamine agonist medications 24 hours prior to

study, it is unlikely that the functional differences observed could be due to the direct effects of medication. Rather, we speculate that chronic use of dopamine agonist medications may (directly or indirectly) induce persistent functional changes in STN neurons. ICD symptoms often resolve following discontinuation of dopamine agonist medications, but the timeline in the resolution of symptoms is not well understood. Still, a plausible alternative explanation might be that pre-existing functional differences (possibly disease-induced) predispose certain patients to the development of ICDs following DA exposure and that the observed differences in STN physiology are related to such pre-existing differences. Certainly, the present study raises a number of questions that warrant further investigation.

There are a few limitations to our study that must be acknowledged. First, patients performed the task during an on-going operation, which may raise stress levels and potentially cause a relative devaluation of the outcome stimuli[88]. Performing this task in a more relaxed environment may soon be possible with emerging technology that is enabling chronic post-operative physiological recordings. However, even this technology would permit only recordings of populations of neurons via local field potentials, not the behavior of single neurons. Also, while all patients were withdrawn from dopamine medication 24 hours prior to surgery, the withdrawal might have differentially affected subjects. Finally, it was only possible to sample neurons along the pre-planned trajectory for the DBS electrode. Thus, neuronal sampling from putative limbic regions of the STN and GPi (which are deliberately avoided by neurosurgeons) may have been insufficient. Our use of a triple array microelectrode system was intended to partially mitigate this bias. In addition, it should be noted that the idea of

distinct “limbic” regions in the STN has been recently questioned[14,18] and the existing evidence for such a region in the GPi is limited. Despite these limitations, our approach was required and facilitated an analysis at the level of individual human neurons.

In conclusion, we present findings from human single neurons suggesting that differences in subthalamic nucleus functioning may underlie ICDs in PD. We found that PD patients with ICD exhibited increased proportions of subthalamic neurons responsive to prospective reward and decreased proportions of subthalamic neurons responsive to prospective loss, compared to PD controls without ICD. No such differences were observed in globus pallidus internus neurons. Future work will be needed to assess long-term changes in STN physiology in light of post-stimulation changes in impulsive behavior. A deeper understanding of the pathophysiology of impulse control disorder in this population could potentially lead to improvements in patient and target selection for DBS surgery.

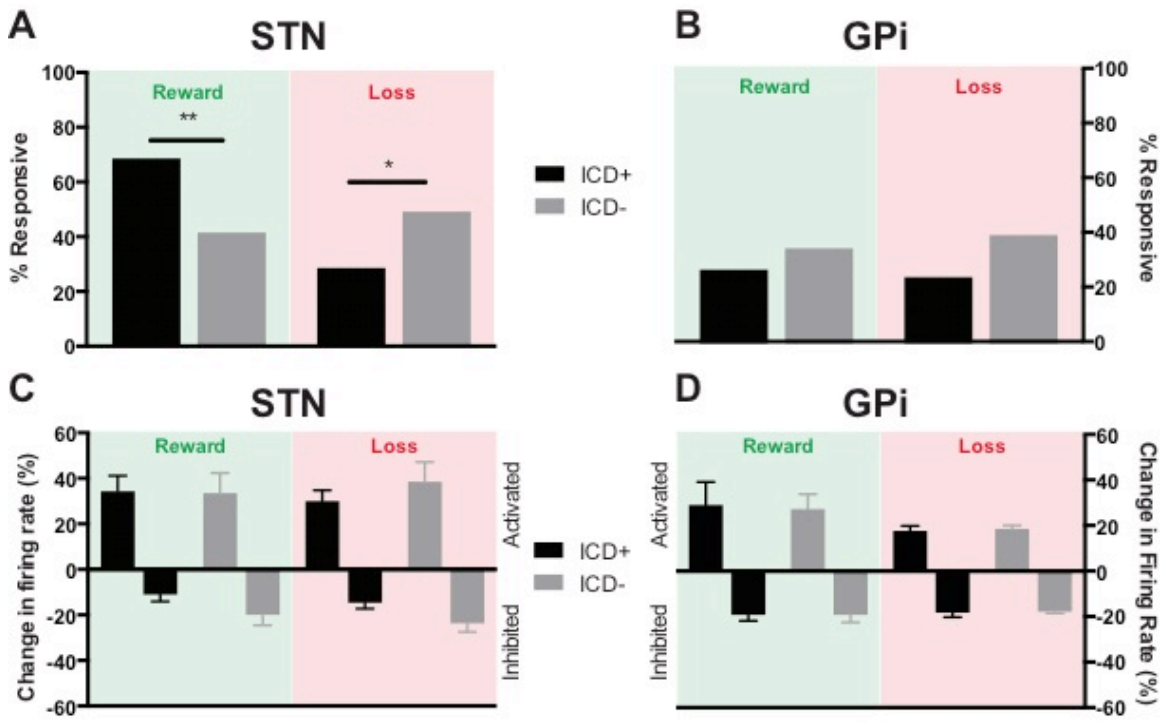

Figure 2-1. ICD status impacts reward and loss sensitivity in subthalamic neurons but not internal pallidal neurons. Comparison of responsive neuron populations in ICD+ and ICD- patients for A) STN and B) GPi; neurons responsive to stimuli indicating the opportunity for reward (left, green) and neurons responsive to stimuli indicating the threat of loss (right, red). Comparison of firing rate changes in ICD+ and ICD- patients for stimulus-responsive C) STN and D) GPi neurons. * indicates $p<.05$, ** indicates $p<.01$, χ^2 test. Activated indicates neurons that exhibited significant increases in firing rate following stimulus presentation. Inhibited indicates neurons that exhibited significant decreases in firing rate following stimulus presentation. Error bars indicate SEM. ICD+ indicates patients diagnosed with an impulse control disorder; ICD- indicates patients not diagnosed with an impulse control disorder; STN= subthalamic nucleus; GPi= globus pallidus internus.

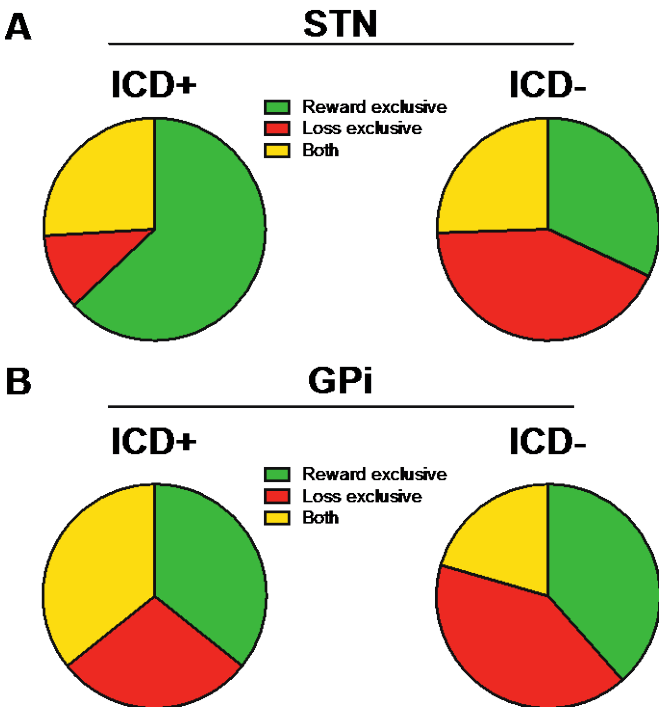

Figure 2-2. ICD status impacts proportions of loss and reward “exclusive” neurons in STN but not GPi. Stimulus response exclusivity and co-modulation proportions for ICD+ (left) and ICD- (right) patients in the A) STN and B) GPi. Reward exclusive neurons indicate neurons that exhibited significant changes in firing rate only in response to reward stimuli; loss exclusive neurons indicate neurons that exhibited significant changes in firing rate only in response to loss stimuli; “both” neurons indicate neurons that exhibited significant changes in firing rate in response to both reward and loss stimuli.

CHAPTER 3
DEEP BRAIN STIMULATION MODIFIES IMPULSE CONTROL

Introduction

A large portion of Parkinson's disease (PD) patients (~15%) suffers from impulse control disorders (ICDs)[105]. ICDs are characterized by an inability to resist an inappropriate drive which is frequently of a hedonistic nature[71]. Patients pursue certain behaviors repetitively, excessively, and compulsively to the point of interference in major areas of life functioning[106]. Common ICDs include pathological gambling, compulsive buying, hypersexuality, binge eating, or hobbyism.

Dopamine agonist (DAA) therapy is a major risk factor for the development of ICDs, and withdrawal or reduction of DAA has been shown to improve symptoms[107]. It has been argued by several expert groups that deep brain stimulation (DBS) could be used to treat ICDs, given that motor symptom control via DBS could enable therapeutic DAA reduction[108,109].

Studies comparing ICD symptoms before and after DBS have had conflicting results and suggest a more complicated picture—one in which DBS could potentially exert direct effects on impulse control. STN DBS coupled with a large reduction in dopaminergic medication has been shown to reduce pre-existing impulsive behavior[110], but onset of new ICDs and worsening of existing ICDs in the post-operative period despite reduction in dopaminergic medications have also been documented[77,111].

The results of retrospective case series and reports have revealed conflicting effects of DBS on impulse control, including improvement/resolution, worsening/new onset, and lack of change. Previous studies have been mostly retrospective[111–114] or cross-sectional[115] in design and have had small cohorts[116], while the few prospective

studies to date have not investigated the effects of DBS on both STN and GPi targets[108,110]. In addition, these studies, with one exception[77], have focused on the effects of bilateral STN DBS. Finally, it remains unclear from the available evidence whether changes in ICD status in these studies were due to changes in DAA or due to changes elicited by electrical stimulation.

We present the first prospective study in PD examining the effects of DBS on impulse control in both STN and GPi. Consecutive patients (GPi, n=30; STN, n=20) undergoing DBS surgery were evaluated for the presence of an ICD using the Questionnaire for Impulsivity in Parkinson's Disease (QUIP) and using a structured clinical interview. Patients were assessed for changes between 6 and 12 months post-operatively. Complete details of anti-Parkinsonian medication for pre- and post-operative periods were recorded and compared between brain targets.

Materials and Methods

Patients

Consecutive patients with Parkinson's disease undergoing de novo STN or GPi DBS electrode placement surgery were studied. The cohort was non-randomized; brain targets were selected by an interdisciplinary team following individual evaluations (neurology, neurosurgery, neuropsychology, physical therapy, occupational therapy, speech therapy). All patients fulfilled the UK Brain Bank criteria for PD. There were 53 patients enrolled in the study, with a mean age of 64.8 years (SD=8.9). The University of Florida Institutional Review Board approved the study and all patients provided informed consent before entering the study.

We recorded complete details of anti-parkinsonian medication therapy for each patient. The recorded medications were those being taken at the time of pre-operative

and post-operative assessment. Due to the strong association of dopaminergic agonists with the development of ICDs, we compared ICD+ and ICD- groups in the use of dopaminergic agonists (pramipexole, ropinirole, pergolide, rotigotine, apomorphine, or bromocriptine) as well as levodopa equivalent daily dosage (LEDD).

We intended to perform re-administration of QUIP and clinical interview between 6 and 12 months following DBS implantation. However, follow-up for some patients occurred between 5 and 14 months. Mean follow-up time for all patients was 9.8 months post-surgery. We separated patients into those with unilateral DBS and those with bilateral DBS and performed a sub-analysis comparing these groups.

Assessment of Impulse Control Disorders

Participants completed the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease Rating Scale (QUIP), a self-reported and self-completed validated measure of impulsivity in PD[98]. Participants were instructed to answer questions based on behaviors that occurred in the previous 6 months that lasted at least four consecutive weeks[99]. The QUIP includes 5 questions for each of the 4 ICDs most commonly reported in PD and 3 questions about any other activity or hobby. We utilized established thresholds to represent a positive screen for the patient-completed instrument: compulsive gambling (any 2 of the 5 items); compulsive sexual behavior (any 1 of the 5 items); compulsive buying (any 1 of the 5 items); compulsive eating (any 2 of the 5 items); other behavior (punding and hobbyism) (any 1 of the 3 items)[99].

The QUIP is designed as a screening instrument and as such is sensitive for detecting ICDs but is not highly specific[101]. To avoid over-identifying ICDs, after patients completed the QUIP, a medically trained investigator administered a semi-structured, diagnostic interview based on published proposed criteria for ICDs in PD[102] and utilized

the same time frame as in the QUIP[99]. The interviewer was blinded to the patient's QUIP responses; however, patients occasionally verbalized their responses contrary to instructions. Self-identified primary caregivers who accompanied patients were given the opportunity to contribute during the interview, given the well-documented phenomenon that patients suffering from ICDs tend to underreport symptoms either due to embarrassment or because they lack objective insight into negative behavior[99]. Primary caregivers were present and contributed in all but 3 of the interviews.

Statistical Analysis

Categorical variables were compared using χ^2 statistics. For continuous variables, Shapiro-Wilk tests for normality were performed. Provided that the data were normally distributed, continuous variables were then compared using unpaired *t* tests for comparisons by brain target and ICD status and using paired t tests for comparisons of pre-DBS and post-DBS outcomes. Statistical significance was based on an alpha of .05.

Results

Post-operative follow-up was obtained for 50 patients (30 GPi, 20 STN). Of the patients enrolled pre-operatively, 3 were lost to follow-up. These were not included in the final analysis. Of the 50 patients analyzed, 37 underwent unilateral DBS placement (23 GPi, 14 STN) and13 underwent bilateral DBS placement (7 GPi, 6 STN).

ICD Prevalence

Of the 50 patients studied, 20 patients (40%) had an ICD at pre-operative baseline (Fig 3-1). The mean pre-operative QUIP score for ICD+ patients was 6.41±1.0 (SEM); the mean post-operative QUIP score for ICD+ patients was 3.3±0.9 (SEM). There were no significant differences in the prevalence of ICDs or any ICD sub-type in the post-operative period compared to baseline for either GPi or STN (Fig 3-1). The

prevalence of ICDs and all ICD subtypes in the pre- and post-DBS periods for both STN and GPi are shown in Figure 3-2.

Clinical interviews provided valuable subjective insight into the impulsive-compulsive behaviors reported in the QUIP. For example, common manifestations of hypersexual behavior in this cohort included inappropriate touching of others, increased masturbation, exhibitionism, and pornography use. Hobbyism and other impulsive activities included model boat-building, drag-racing, hedge clipping and gardening, vacuuming, fishing, shoplifting, onychotillomania (nail picking), and excoriation (skin picking). Most patients reported pursuing these activities despite legal consequences, potential or actual harm to personal relationships and financial wellbeing, and risks to personal safety. Many patients also reported engaging in enabling behaviors, such as binge eating after family members have gone to sleep, hoarding of food, picking skin in areas not visible to others, and covertly pursuing their impulsive/compulsive activity to avoid observation by others.

Rate of Change in ICD Status Post-DBS

A substantial proportion of patients exhibited a conversion in ICD status after DBS (33.3% of GPi patients and 40% of STN patients; Figure 3-2). For the GPi, 23.3% of patients experienced resolution of a pre-existing ICD and 6.7% of patients experienced a new onset ICD. For the STN, 25% of patients experienced resolution of a pre-existing ICD and 15% of patients experienced a new onset ICD. The de novo ICDs in the GPi cohort included two cases of binge eating. One patient developed a new onset case of dopamine dysregulation syndrome (DDS). Although DDS is not an ICD, this was an important observation. The *de novo* ICDs in the STN cohort included two cases of hypersexuality and one case of hobbyism (model boat building). There were no

significant differences between the STN and GPi targets in terms of the proportions of patients who experienced any type of ICD status change (Fig 3-4). However, GPi patients had a significantly higher mean QUIP score at baseline than STN patients (3.9 vs. 1.6, p=.0486, Fig 3-4), suggesting a clinical bias in favor of targeting the GPi in patients with ICD symptoms.

Qualitative Changes in Impulse Control Post-DBS

A substantial proportion of patients reported meaningful qualitative changes in their ability to control impulsive behavior, even though they did not meet criteria for a change in diagnosis (Fig 3-5). During clinical interview, patients were asked whether they had experienced improvement, worsening, or no change in ICD symptoms since DBS. For the GPi, 20% of patients reported improvement and 16.7% reported worsening, in addition to those patients whose changes constituted a conversion in ICD status. For the STN, 5% of patients reported improvement and 15% reported worsening.

Changes in ICD Status and Dopaminergic Medication

Due to the well-established connection between dopamine medications (in particular DAA) and ICDs, we sought to determine the degree to which observed changes in ICD status could be attributed to DBS versus post-operative modifications in medication regimen. Special attention was paid to DAA. To accomplish this, we performed a multi-layered analysis. We first tested for a relationship between ICD symptom changes and changes in DAA regimen. We found that patients that changed ICD status were not more likely to have changed their dopamine agonist medication than those who maintained their ICD status (χ^2-test p=.1468). In addition, patients who changed ICD status *or* reported qualitative changes in their ICD symptoms were not more likely to have changed their dopamine agonist medication than those who

maintained their ICD status and reported no qualitative changes (χ^2-test, p=.2098). We then tested for a relationship between QUIP score (as a surrogate measure for ICD severity) and LEDD, and we repeated the analysis using LEDD for DAA only (DAA LEDD). Linear regression analysis revealed no significant correlation between QUIP score and LEDD for either pre-DBS or post-DBS measures (pre-DBS R^2=.204, post-DBS R^2=.006) or between QUIP score and DAA LEDD (pre-DBS R^2=.006, post-DBS R^2=.013). We also compared patients with a change in ICD status and those without a change in status in terms of the mean percent change in dopamine agonist dosage. We found no significant difference in this comparison (unpaired student's t test, p=.3716, Fig 3-3). Interestingly, pre-DBS and post-DBS LEDD for STN patients were remarkably similar. However, separate analysis of unilateral and bilateral procedures revealed a trend toward medication reduction for bilateral STN cases (1222±516.3 pre-DBS vs. 928±291 post-DBS, p=.252, Fig 3-6). The lack of statistical significance reflects both the small sample size of bilateral cases but also the bias but also the published philosophy of the UF center to employ conservative medication reduction strategies wherever possible to minimize adverse mood effects associated with dopamine withdrawal[117–119].

We note that patients who were ICD+ at baseline had significantly higher pre-operative LEDD compared to those who were ICD- at baseline (p=.019, Fig 3-4). These differences in LEDD were maintained at the post-operative assessment (p=.008, Fig 3-4). Interestingly, such differences were not observed for LEDD based on dopamine agonist only (pre-operative DAA LEDD, p=.479, post-operative DAA LEDD, p=.501; Fig 3-4). Importantly, of the patients who experienced a resolution of ICD symptoms, only

41.7% (5/12) decreased their dopamine agonist dosage. Of the patients who experienced a de novo ICD, 0% (0/6) increased their dopamine agonist dosage.

These findings suggest that while dopamine medications are strongly associated with ICDs in the pre-DBS PD population, they do not independently account for the changes in ICD symptoms observed following DBS.

Other Psychological Changes

During the follow-up clinical interview, patients were asked to describe any other changes in mood, cognition, or psychological functioning. One patient reported pathological crying (3-4 episodes per day) following STN DBS. Another patient reported euphoric episodes following STN DBS, however these issues resolved with changes in stimulation settings.

Discussion

Our data reveal that ICD symptoms can improve, worsen, emerge, or remain constant following STN and GPi DBS. There was resolution of ICDs in 60% of patients following surgery. This finding is close to the 65% observed in a retrospective study of STN DBS[73]. In our study, 20% of patients that did not have ICD at baseline developed ICD post-operatively. This finding paralleled the 13% rate that has been reported previously[73]. The combination of ICD resolution and emergence potentially explains the comparable prevalence of ICDs in the pre-operative and post-operative period.

The overall pre-operative prevalence of ICDs in our cohort was 40%. This was considerably higher than the ICD prevalence typically reported for the PD population at large (~15%)[105,116]. Higher prevalence of ICDs in the population of patients undergoing DBS has been described previously[116] and may be potentially explained by the bias of patients referred to DBS surgery tending to have higher LEDD, higher DAA LEDD, and

longer disease duration—all risk factors for the development of ICD[73]. Moreover, the pre-operative prevalence of ICDs appears to be largely dependent on the impulsive behavior scale used[120], and rates from 22.5%[73] to 50%[110] have been reported. The post-operative prevalence of ICDs in our cohort was 26%, and this was comparable to the 25.8% post-operative prevalence found in a retrospective study of STN DBS[73].

DBS has been associated with an increased risk of binge eating[121]. We therefore expected to observe a higher prevalence of binge eating in the post-DBS population. Although there were no significant differences in the prevalence of binge eating ICDs in the pre- and post-DBS periods, we observed considerable sub-threshold changes associated with eating impulsivity. Six patients reported worsening or sub-threshold onset of eating-related symptoms, with only one reporting improvement. While these results appear to corroborate previous findings, it is difficult to draw conclusions about binge eating given its low prevalence in the present cohort.

Our finding that differences in dopaminergic medications do not fully explain the changes in ICD symptoms following DBS is important. It corroborates pre-clinical findings suggestive of STN and GPi involvement in impulse control, and it aligns with reports that post-DBS changes in ICD symptoms do not always conform to expectations based on medication changes[116]. Pre-clinical studies in dopamine-naïve rodents revealed changes in impulsive behavior following high frequency electrical stimulation of the STN and GPi[78,79,82,83], and STN DBS in Parkinsonian humans increases measures of impulsivity independent of dopaminergic medication status[122].

The mechanisms underlying post-operative changes in impulse control are likely complex, with dopaminergic medications and electrical stimulation simultaneously

affecting behavior in ways that are dependent on a multitude of factors, including the type(s) and dosage of pre- and post-surgical medication, the location of the DBS lead, and the stimulation parameters—all of which, in clinical practice, tend to be modified in the months following DBS lead implantation to optimize outcomes. Exploring the relative impact of these factors while controlling variables in a limited clinical population remains a challenge.

Our study has some limitations. The QUIP cannot capture qualitative changes in ICD symptoms that do not constitute a diagnosis conversion. Indeed, our data regarding qualitative changes not captured by the QUIP suggests the need for a new instrument in the DBS population. Also, there was some heterogeneity in the time to follow-up. All efforts were made to re-administer evaluations within the intended 6 to 12 month window which was viewed as clinically feasible, but this was not always possible given the time required to complete the structured interview. Finally, our study had a male bias; however, our sampling method and previous studies[123,124] suggest that this bias was reflective of the DBS population at large. Finally, our sample includes patients who underwent both unilateral and bilateral DBS. The fact that our center has adopted a conservative approach to medication reduction, particularly following unilateral STN DBS, can be regarded as both a strength and weakness of the study. The similarity in dopamine therapy in the pre- and post-operative period for STN cases did permit a more controlled study of the effects of DBS, which would be skewed if both variables (medication and stimulation) had been modified. The STN patient population was thus ideal for demonstration that stimulation and medication effects could be independent. However, the study sample does limit the conclusions that can be drawn from

comparisons of STN and GPi targets, and it would be interesting to repeat the investigation in a center with a bias toward aggressive medication reduction post-DBS. The results of the study revealed that patients with more severe ICDs, as reflected in the QUIP score, were more likely to be implanted in the GPi. It would be interesting in a future study to match this variable in each group at baseline. Despite these limitations our study has several strengths, including its prospective approach, relatively large sample size, high rate of follow-up, and the fact that patients were enrolled consecutively from a single center.

In conclusion, we show that ICDs may improve, worsen, or emerge in PD patients following DBS surgery of either the STN or the GPi. Our prospective results thus confirm the findings of previous retrospective studies. There were no meaningful differences in the STN and GPi targets in terms of post-operative changes in ICD symptoms. Importantly, we provide evidence that post-DBS changes in impulsivity cannot be attributed solely to changes in dopaminergic medication. Overall, our findings suggest that STN and GPi DBS can evoke positive or negative changes in impulse control. Clinical approaches to DBS target and patient selection should take this into account.

	DBS Target						Pre- vs. Post-		
	GPi		STN		All		GPi	STN	All
	Pre-DBS	Post-DBS	Pre-DBS	Post-DBS	Pre-DBS	Post-DBS	*p* value		
ICD	13	9	7	3	20	12	0.41	0.14	0.14
Gambling	4	2	2	0	6	2	0.39	0.15	0.14
Sexual	7	4	3	3	10	7	0.16	1	0.42
Buying	7	5	0	0	7	5	0.52	1	0.54
Eating	4	5	0	0	4	5	0.72	1	0.73
Other	3	1	0	0	3	1	1	1	0.65
DDS	3	3	0	2	3	5	0.69	0.31	0.73

Figure 3-1. Comparison of Pre-DBS and Post-DBS Prevalence of ICDs. Data are represented as numbers of patients. *P* values in bold indicate statistical significant at 95% confidence (p<·05); p values were calculated using χ^2 statistics.

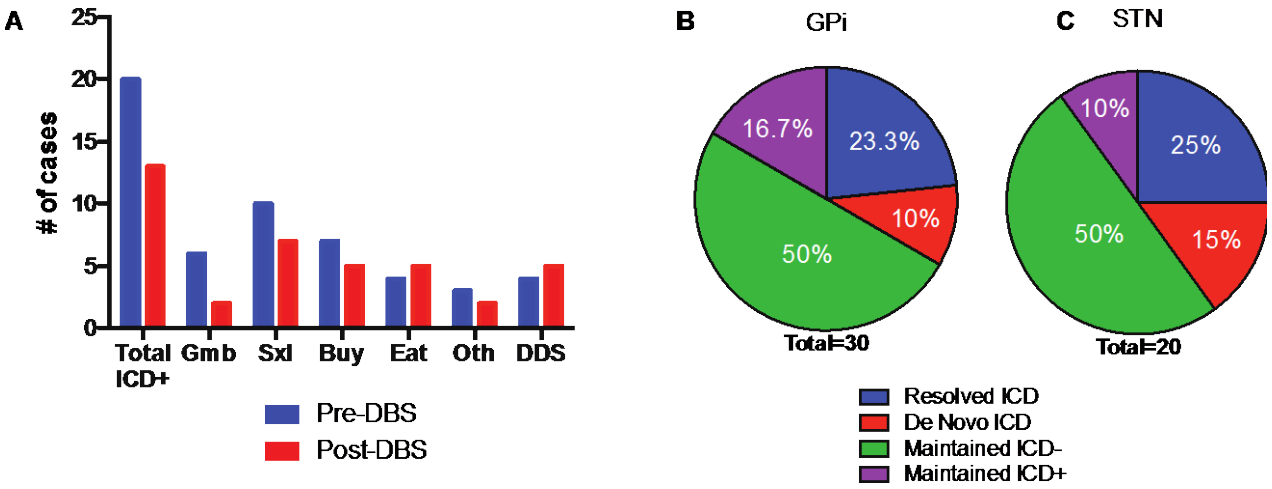

Figure 3-2. ICD changes after STN and GPi DBS surgery. Changes in prevalence of ICDs, ICD subtypes, and DDS after 6-12 months of unilateral or bilateral DBS of GPi or STN in 50 patients A). ICD diagnosis conversions following GPi B) and STN C) DBS. Abbreviations: ICD+= met diagnostic criteria for an impulse control disorder, Gmb=gambling, Sxl=hypersexuality, Buy=pathological buying/shopping, Eat=binge eating, Oth=other activity or hobbyism, DDS=dopamine dysregulation syndrome

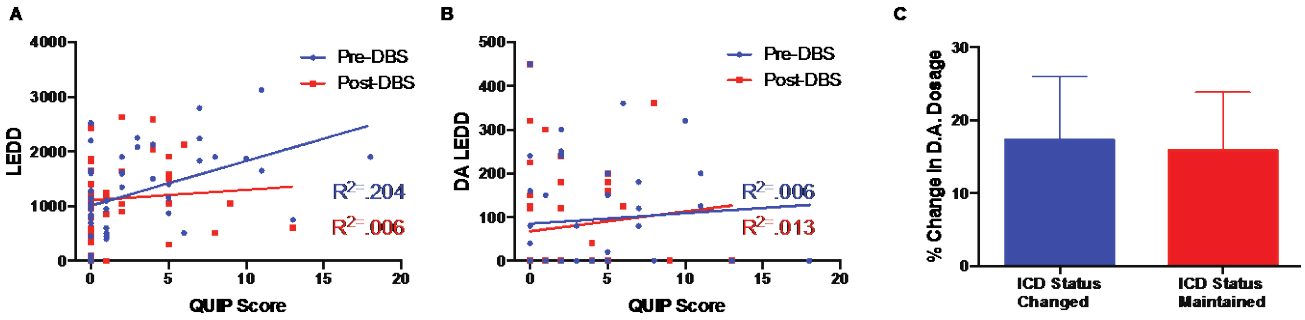

Figure 3-3. Change in ICD status following DBS is not dependent on dopamine therapy Linear regression plots between A) LEDD and QUIP score and between DA B) LEDD and QUIP score showed no significant correlation between the variables for pre-DBS or post-DBS periods. C) The mean percent change in dopamine agonist dosage was compared for patients who changed ICD status post-operatively and those for whom ICD status was maintained. Error bars indicate SEM.

Category	Variable	DBS Target			ICD+ vs. ICD-		
		GPi (n=30)	STN (n=20)	All Targets (n=50)	GPi	STN *p* value	All
Demographic	% Male	75.9	77.8	78	**0.008**	0.357	0.132
	Age	65.9 ± 8.9	60.6 ± 8.3	63.8 ± 9.1	0.187	0.144	0.075
	Diz. Dur. (yrs)	11 ± 5.1	7.3 ± 3.5	9.7 ± 4.9	**0.017**	0.659	**0.008**
	f/u (month)	9 ± 3.8	11.2 ± 5	9.8 ± 4.3	0.591	0.504	0.961
Physical Functioning	UPDRS OFF	43 ± 12.7	37.8 ± 6.7	41 ± 11	0.71	0.536	0.63
	UPDRS ON	27.1 ± 12.1	26.1 ± 8	26.6 ± 10.6	0.78	0.07	0.303
Cognitive Functioning	DRS-2	137 ± 4.1	139 ± 2	137.7 ± 3.7	0.234	0.586	0.161
	FSIQ	110.2 ± 9.8	112 ± 10.2	111.2 ± 9.9	**0.026**	0.478	**0.032**
	WMI	103.7 ± 15.7	103 ± 17.5	103.3 ± 16.1	0.177	0.282	0.074
	PSI-2	92.9 ± 9.6	96.1 ± 8.9	94.2 ± 9.3	0.266	0.488	0.522
Impulsivity Assessment	QUIP (Pre-DBS)	3.9 ± 4.8	1.6 ± 2	3.1 ± 4.2	**$1.9x10^{-6}$**	**0.001**	**$3.5x10^{-8}$**
	QUIP (Post-DBS)	2.5 ± 3.4	0.9 ± 2.2	1.9 ± 3	**0.02**	0.196	**0.005**
Medication	LEDD pre-DBS	1534 ± 765	881 ± 489	1309 ± 739.5	**0.015**	0.545	**0.019**
	LEDD post-DBS	1337 ± 765	862 ± 361	1191 ± 689.1	**0.038**	0.119	**0.008**
	DA LEDD pre-DBS	99.1 ± 130	78.8 ± 127	92.4 ± 129.4	0.952	0.244	0.479
	DA LEDD post-DBS	76.7 ± 109	68.3 ± 126	75.9 ± 117	0.897	0.434	0.501

Figure 3-4. Comparison of Impulsive vs. Non-Impulsive Patients in STN and GPi. Data are represented as mean ± standard deviation. Statistical comparisons between ICD+ and ICD- populations are based on pre-operative diagnosis. Bold p values indicate statistical significance at 95% confidence ($p<\cdot 05$). P values for proportions (% male) were calculated using χ^2 statistics. P values for continuous variables were calculated using unpaired t tests. Abbreviations: Diz. Dur= disease duration, yrs= years, f/u=follow-up, UPDRS=Unified Parkinson's Disease Rating Scale, OFF=off medication, ON=on medication, DRS=dementia rating scale, FSIQ=full scale intelligence quotient, WMI=Wechsler memory index, PSI=psychological screening inventory, QUIP=questionnaire for impulsivity in Parkinson's disease, LEDD= levodopa equivalent daily dosage, DA= dopamine agonist, DBS= deep brain stimulation, ICD=impulse control disorder, GPi=globus pallidus internus, STN=subthalamic nucleus.

	DBS Target			
	GPi	STN	All Targets	GPi vs. STN *p* value
Qualitative Improvement	3	3	6	0.6
Qualitative Worsening	6	1	7	0.05
Resolved ICD	7	5	12	0.75
de novo ICD	3	3	6	0.59
No Δ (orig. ICD-)	15	10	25	1
No Δ (orig. ICD+)	5	2	7	0.51

Figure 3-5. Changes in impulsivity following GPi and STN DBS. Comparison of changes in ICD symptoms by target, given in number of cases. Resolved and de novo ICDs indicate a change in ICD diagnosis based on quantitative changes in the QUIP score that passed pre-defined thresholds and corresponding findings during clinical interview. Qualitative improvement and worsening indicate directional changes in ICD symptoms that did not constitute a diagnosis conversion based on QUIP score and clinical interview. No Δ (orig. ICD-) indicates patients without ICD at baseline that did not convert diagnosis post-operatively. Bold p values indicate statistical significance at 95% confidence ($p<\cdot 05$). *P* values calculated using χ^2 test.

Category	Variable	DBS Target				Uni- vs.Bi-	
		GPi		STN		GPi	STN
		Unilateral	Biilateral	Unilateral	Biilateral	*p* value	
		n=23	n=7	n=14	n=6		
Impulsivity Assessment	# ICD+ at Baseline	10	3	4	3	0.9768	0.6488
	QUIP (Pre-DBS)	3.1 ± 4	6.1 ± 6.6	1.5 ± 2	1 ± 1	0.1487	0.5719
	QUIP (Post-DBS)	2.1 ± 3.2	3.6 ± 4.1	0.5 ± 1.5	0.6 ± 0.9	0.3173	0.8819
Medication	LEDD pre-DBS	1495.2 ± 748.8	1649 ± 945.6	829 ± 462.7	1222 ± 516.3	0.6575	0.1094
	LEDD post-DBS	1369.5 ± 760.1	1221.8 ± 845	872.2 ± 403.2	928.3 ± 291	0.6639	0.7629
	DA LEDD pre-DBS	107.4 ± 140.3	74.3 ± 96.4	17.3 ± 45.6	263.3 ± 32.1	0.5663	**<.0001**
	DA LEDD post-DBS	83.3 ± 115.4	45.7 ± 81.4	0 ± 0	221.7 ± 88.9	0.431	**<.0001**

Figure 3-6. Impulsivity outcomes and dopamine therapy in bilateral vs. unilateral DBS. Sub-analysis comparing patients who underwent unilateral and bilateral DBS. Bold p values indicate statistical significance at 95% confidence ($p<\cdot 05$). *P* values for categorical variables calculated using χ^2 test, continuous variables calculated using unpaired *t* test.

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