NATIONAL TECHNICAL UNIVERSITY OF ATHENS
SCHOOL OF ELECTRICAL AND COMPUTER ENGINEERING
DIVISION OF INFORMATION TRANSMISSION SYSTEMS AND MATERIAL TECHNOLOGY

Development of Stochastic Dynamical Models for Optimization of Deep Brain Stimulation in Movement and Neuropsychiatric Disorders

DOCTORAL DISSERTATION

Sofia D. Karamintziou

Doctoral Advisor: Prof. Konstantina S. Nikita

Athens, 2015

ΕΘΝΙΚΟ ΜΕΤΣΟΒΙΟ ΠΟΛΥΤΕΧΝΕΙΟ
ΣΧΟΛΗ ΗΛΕΚΤΡΟΛΟΓΩΝ ΜΗΧΑΝΙΚΩΝ ΚΑΙ ΜΗΧΑΝΙΚΩΝ ΥΠΟΛΟΓΙΣΤΩΝ
ΤΟΜΕΑΣ ΣΥΣΤΗΜΑΤΩΝ ΜΕΤΑΔΟΣΗΣ ΠΛΗΡΟΦΟΡΙΑΣ ΚΑΙ ΤΕΧΝΟΛΟΓΙΑΣ ΥΛΙΚΩΝ

Ανάπτυξη Μοντέλων Στοχαστικής Δυναμικής για τη Βελτιστοποίηση της εν τω Βάθει Εγκεφαλικής Διέγερσης σε Κινητικές και Νευροψυχιατρικές Διαταραχές

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

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There was a time I could see!

And I have seen boys like these, younger than these, their arms torn out, their legs ripped off!

But there is nothin like the sight of an amputated spirit. There is... no prosthetic for that.

Al Pacino as Lieutenant Colonel Frank Slade - Scent of a Woman (1992)

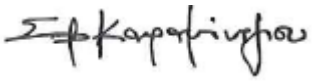
To my brothers, Ms. Konstantina (Nanti) Karamintziou - Mr. Nikos Karamintzios, and my parents, Mr. Dimitrios (Takis) Karamintzios - Ms. Presvia -Vassiliki Mamali, whom I adore.

To the members of the Biomedical Simulations and Imaging Laboratory (BIOSIM), wishing them a successful career.

To my dynamic, charismatic and inspirational mentor, Dr. Konstantina (Nantia) S Nikita, Professor of the NTUA.

To Dr. George Tsirogiannis and Dr. Olivier David (Grenoble University and Grenoble Institute of Neurosciences (INSERM-U836), Grenoble, France).

To the places where I grew up, Munich and Trikala of Thessaly, and my always-beloved Athens.



Abstract

The use of *electrical deep brain stimulation* (DBS), during approximately the last thirty years, has been proven to provide striking benefits for patients with advanced *Parkinson's disease* (PD), essential tremor (ET) and dystonia who have failed conventional therapies. In the interim, extended applications of this technique for the treatment of neuropsychiatric disorders have emerged, including *treatment-refractory obsessive-compulsive disorder* (OCD), Tourette's syndrome (TS), major depressive disorder (MDD), drug addiction and anorexia nervosa (AN). Challenges however exist and are principally related to the optimization of the efficiency of stimulation through refined strategies at multiple peri-operative levels. Particularly, in addition to appropriate patient selection and anatomical target determination, the outcome of DBS may be strongly influenced by the quality of post-operative clinical management, i.e. the adjustment of stimulation parameters and the selection of the optimal contact, usually over periods of weeks to months. This trial-and-error procedure entails important disantvantages: (a) it may not necessarily yield the optimal *therapeutic window* (i.e. the ratio of the threshold for stimulation-induced side-effects to the induction threshold for therapeutic benefit) (b) it is considerably time-consuming, while movement and neuropsychiatric disorder symptoms may fluctuate over time-scales of seconds to days (c) the open-loop nature and monomorph pattern of standard high-frequency stimulation (regular, 130Hz) appears chronically to favor tolerance/habituation phenomena, while being associated with maximal energy consumption. Against this background, *closed-loop neuromodulation* is emerging as a more robust alternative and one of the most promising breakthroughs in the field of DBS. Principally, any algorithm designed for a maximally efficient closed loop DBS system shall conceptually satisfy two core specifications: the reliable assessment of optimal *biomarkers for feedback control* that capture the patient's clinical state in real time and the identification of *temporally alternative stimulation protocols* that may be more therapeutically- and energy-efficient compared with the conventional pattern of stimulation.

In the framework of the current doctoral dissertation, *stochastic dynamical models* for the optimization of the clinical outcome of DBS in movement and neuropsychiatric disorders are

being developed. The ultimate goal is to algorithmically design a closed-loop DBS system for advanced PD and treatment-refractory OCD, ensuring optimal performance in terms of both *efficiency* and *selectivity* of stimulation, as well as in terms of *computational speed*. The main hypothesis we build upon is that temporally alternative DBS waveforms hold the potential to drive the neuronal dynamics within the basal ganglia back to the normal desynchronized state, thereby outperforming the action of standard DBS waveforms, the mechanism of which has been principally attributed to the reinforcement-driven regularization of neural firing patterns in the vicinity of the stimulated nucleus. On grounds of a stochastic phase model describing an ensemble of globally coupled chaotic oscillators driven by common noise, independent noise, and external forcing, and fitted to subthalamic MERs acquired during surgical interventions for PD and OCD, we first prove that the *desynchronizing* and probably also the *therapeutic effect* of low-frequency stochastic DBS waveforms may be significantly stronger compared with the effect of standard stimulation. Subsequently, relying upon a series of methods robust to the presence of measurement noise, we assess the presence of significant *nonlinear coupling* between beta and high-frequency subthalamic neuronal activity, as a biomarker for feedback control in the proposed closed-loop neuromodulation scheme, and further present a strategy, incorporating the application of a modified version of the stochastic phase model (phase-reduced bursting neuron model) and a derivative-free optimization algorithm (direct search optimization based on quadratic modeling), through which optimal stochastic patterns and parameters of stimulation for minimum energy desynchronizing control of neuronal activity are being identified. Cross-frequency coupling proves to be a consistently appropriate biomarker for feedback control in case of PD, but may display subject-specific applicability in case of OCD. We demonstrate the ability of the presented modeling approach to identify, at a relatively low computational cost, stimulation settings associated with a significantly higher efficiency and selectivity compared with stimulation settings determined during post-operative clinical management of patients with advanced PD and treatment-refractory OCD. Together, our data provide strong evidence for the applicability of *computational neurostimulation* to real-time, closed-loop DBS systems for movement and neuropsychiatric disorders.

Keywords: electrical deep brain stimulation, Parkinson's disease, obsessive-compulsive disorder, subthalamic nucleus, microelectrode recordings, stochastic dynamical model, desynchronizing effect of stimulation, invariant density measure, clinical effectiveness, temporally alternative stimulation protocols, closed-loop neuromodulation, biomarkers for feedback control, nonlinear coupling, efficiency of stimulation, selectivity of stimulation, computational speed, computational neurostimulation

Περίληψη

Η χρήση της *ηλεκτρικής εν τω βάθει εγκεφαλικής διέγερσης*, κατά τη διάρκεια των τελευταίων τριάντα ετών περίπου, έχει αποδειχθεί ότι παρέχει αξιοσημείωτα οφέλη σε ασθενείς με προχωρημένο στάδιο της *νόσου Πάρκινσον* (ΝΠ), ιδιοπαθή τρόμο ή δυστονία που δεν ανταποκρίνονται σε συμβατικές θεραπείες. Παράλληλα, αναδεικνύονται σταδιακά εκτεταμένες εφαρμογές της τεχνικής αυτής για τη θεραπεία νευροψυχιατρικών διαταραχών, συμπεριλαμβανομένης της *ανθεκτικής στη θεραπεία ιδεοψυχαναγκαστικής διαταραχής* (ΙΨΔ), του συνδρόμου Tourette, της μείζονος καταθλιπτικής διαταραχής, του εθισμού σε ουσίες και της νευρικής ανορεξίας. Ωστόσο υπάρχουν προκλήσεις οι οποίες σχετίζονται πρωταρχικά με τη βελτιστοποίηση της αποδοτικότητας της διέγερσης μέσω εκλεπτυσμένων στρατηγικών σε πολλαπλά περιεγχειρητικά επίπεδα. Συγκεκριμένα, εκτός από την κατάλληλη επιλογή των ασθενών και τον καθορισμό του ανατομικού στόχου, η έκβαση της εν τω βάθει εγκεφαλικής διέγερσης επηρεάζεται σημαντικά από την ποιότητα της μετεγχειρητικής κλινικής διαχείρισης, δηλ. την προσαρμογή των παραμέτρων διέγερσης και την επιλογή της βέλτιστης επαφής , συνήθως σε μία χρονική περίοδο εβδομάδων-μηνών. Αυτή η διαδικασία δοκιμής-σφάλματος συνεπάγεται σημαντικά μειονεκτήματα: πρώτον, ενδεχομένως να μην επιφέρει απαραίτητα το βέλτιστο *θεραπευτικό παράθυρο* (δηλ. το λόγο κατωφλίου για παρενέργειες προκαλούμενες από τη διέγερση προς το κατώφλι εμφάνισης θεραπευτικού οφέλους). Δεύτερον, είναι ιδιαίτερα χρονοβόρα, ενώ τα συμπτώματα των νευρολογικών και νευροψυχιατρικών διαταραχών παρουσιάζουν συνήθως διακυμάνσεις σε χρονικές κλίμακες δευτερολέπτων-ημερών. Τρίτον, η φύση ανοιχτού βρόχου και το μονομορφικό πρότυπο της συμβατικής διέγερσης υψηλής συχνότητας (περιοδική διέγερση 130Hz) φαίνεται χρόνια να ευνοεί φαινόμενα ανεκτικότητας, ενώ συσχετίζεται με μέγιστη κατανάλωση ενέργειας. Ενάντια σε αυτό το πλαίσιο, η *νευροδιαμόρφωση κλειστού βρόχου* ενδεχομένως να αποτελεί μία πιο ισχυρή εναλλακτική και μία από τις σημαντικότερες εξελίξεις στο πεδίο της εν τω βάθει εγκεφαλικής διέγερσης. Πρωταρχικά, οποιοσδήποτε αλγόριθμος που σχεδιάζεται για ένα μέγιστα αποδοτικό σύστημα εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου θα πρέπει να ικανοποιεί δύο σημαντικές προδιαγραφές: τον αξιόπιστο προσδιορισμό βέλτιστων *βιοδεικτών για τον έλεγχο ανάδρασης,* οι οποίοι να αποτυπώνουν την κλινική κατάσταση του ασθενή σε πραγματικό χρόνο και τον

καθορισμό *χρονικά εναλλακτικών πρωτοκόλλων διέγερσης* τα οποία να είναι θεραπευτικά και ενεργειακά πιο αποδοτικά σε σύγκριση με το τυποποιημένο πρότυπο διέγερσης.

Στο πλαίσιο της παρούσας διδακτορικής διατριβής, αναπτύσσονται *στοχαστικά δυναμικά μοντέλα* για τη βελτιστοποίηση του κλινικού αποτελέσματος της εν τω βάθει εγκεφαλικής διέγερσης σε κινητικές και νευροψυχιατρικές διαταραχές. Ο απώτερος στόχος είναι να σχεδιαστεί αλγοριθμικά ένα σύστημα εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου για προχωρημένο στάδιο της ΝΠ και ανθεκτική στη θεραπεία ΙΨΔ, διασφαλίζοντας βέλτιστη επίδοση τόσο ως προς την *αποδοτικότητα* και *επιλεκτικότητα* της διέγερσης, όσο και ως προς την *υπολογιστική ταχύτητα*. Η βασική υπόθεση πάνω στην οποία στηριζόμαστε είναι ότι οι χρονικά εναλλακτικές κυματομορφές εν τω βάθει εγκεφαλικής διέγερσης έχουν τη δυνατότητα να επανοδηγούν τη νευρωνική δυναμική εντός των βασικών γαγγλίων στη φυσιολογική αποσυγχρονισμένη κατάσταση, ξεπερνώντας με τον τρόπο αυτό την επίδοση των συμβατικών κυματομορφών εν τω βάθει εγκεφαλικής διέγερσης, ο μηχανισμός των οποίων έχει πρωταρχικά αποδοθεί στην κανονικοποίηση των προτύπων νευρωνικών εκφορτίσεων στη γειτονιά του διεγερμένου πυρήνα. Βάσει ενός στοχαστικού φασικού μοντέλου το οποίο περιγράφει ένα σύνολο ολικά συζευγμένων χαοτικών ταλαντωτών, οδηγούμενων από κοινό θόρυβο, ανεξάρτητο θόρυβο και εξωτερική επίδραση, και το οποίο προσαρμόζεται σε υποθαλαμικές μικροηλεκτροδιακές καταγραφές ανακτημένες κατά τη διάρκεια εγχειρητικών επεμβάσεων για ΝΠ και ΙΨΔ, αποδεικνύεται πρώτα ότι η *αποσυγχρονιστική* και πιθανόν επίσης η *θεραπευτική επίδραση* των χαμηλόσυχνων στοχαστικών κυματομορφών εν τω βάθει εγκεφαλικής διέγερσης είναι σημαντικά πιο ισχυρή συγκριτικά με την αντίστοιχη επίδραση της συμβατικής διέγερσης. Ακολούθως, βάσει μίας σειράς μεθόδων εύρωστων στην παρουσία του θορύβου μέτρησης, προσδιορίζεται η παρουσία σημαντικής *μη γραμμικής ζεύξης* μεταξύ της υποθαλαμικής νευρωνικής δραστηριότητας βήτα και της δραστηριότητας υψηλής συχνότητας, ως βιοδείκτη για τον έλεγχο ανάδρασης στο προτεινόμενο σχήμα νευροδιαμόρφωσης κλειστού βρόχου, και παρουσιάζεται περαιτέρω μία στρατηγική, η οποία ενσωματώνει την εφαρμογή μίας τροποποιημένης έκδοσης του στοχαστικού φασικού μοντέλου (εφαρμογή φασικώς αναγόμενου μοντέλου νευρώνα ξεσπασμάτων) και έναν αλγόριθμο βελτιστοποίησης ανεξάρτητο παραγώγου (βελτιστοποίηση απευθείας αναζήτησης βασιζόμενη σε τετραγωνική μοντελοποίηση), μέσω της οποίας καθορίζονται βέλτιστα στοχαστικά πρότυπα και βέλτιστες παράμετροι διέγερσης για τον αποσυγχρονιστικό έλεγχο της νευρωνικής δραστηριότητας με ελάχιστη κατανάλωση ενέργειας. Η διασυχνοτική ζεύξη αποδεικνύεται ότι είναι ένας σταθερά κατάλληλος βιοδείκτης για τον έλεγχο ανάδρασης στην περίπτωση της ΝΠ, αλλά ενδεχομένως να παρουσιάζει εφαρμοσιμότητα εξειδικευμένη κατ'ασθενή στην περίπτωση της ΙΨΔ. Αποδεικνύεται η ικανότητα της παρουσιαζόμενης προσέγγισης μοντελοποίησης να προσδιορίζει, με σχετικά χαμηλό υπολογιστικό κόστος, ρυθμίσεις διέγερσης που συσχετίζονται με μία σημαντικά

υψηλότερη αποδοτικότητα και επιλεκτικότητα σε σύγκριση με τις ρυθμίσεις διέγερσης που καθορίζονται κατά τη διάρκεια της μετεγχειρητικής κλινικής διαχείρισης ασθενών με προχωρημένο στάδιο της ΝΠ και ανθεκτική στη θεραπεία ΙΨΔ. Συνολικά, τα δεδομένα παρέχουν ισχυρές αποδείξεις για την εφαρμοσιμότητα της *υπολογιστικής νευροδιέγερσης* σε πραγματικού χρόνου συστήματα εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου για κινητικές και νευροψυχιατρικές διαταραχές.

Λέξεις κλειδιά: ηλεκτρική εν τω βάθει εγκεφαλική διέγερση, Νόσος Πάρκινσον, ιδεοψυχαναγκαστική διαταραχή, υποθαλαμικός πυρήνας, μικροηλεκτροδιακές καταγραφές, στοχαστικό δυναμικό μοντέλο, αποσυγχρονιστική επίδραση της διέγερσης, μέτρο αμετάβλητης πυκνότητας, κλινική αποτελεσματικότητα, χρονικά εναλλακτικά πρότυπα διέγερσης, νευροδιαμόρφωση κλειστού βρόχου, βιοδείκτες για τον έλεγχο ανάδρασης, μη γραμμική ζεύξη, αποδοτικότητα διέγερσης, επιλεκτικότητα διέγερσης, υπολογιστική ταχύτητα, υπολογιστική νευροδιέγερση

Εκτεταμένη Περίληψη

Οι κοινωνίες μεσαίου και υψηλού εισοδήματος χαρακτηρίζονται από έναν αξιοσημείωτο και αυξανόμενο φόρτο νευρολογικών και νευροψυχιατρικών ασθενειών, κυρίως λόγω της απουσίας αποτελεσματικών θεραπειών, αλλά και ενός αυξανόμενα γηράσκοντος πληθυσμού (Vos et al. 2012, Murray et al. 2012, World Health Organization 2004, Kowal et al. 2013). Συνεπώς, προβάλλει επιτακτική η ανάγκη για καινοτόμες μεθόδους πρόληψης και θεραπείας των ασθενειών αυτών. Η χρήση της χρόνιας, *εν τω βάθει εγκεφαλικής ηλεκτρικής διέγερσης* υψηλής συχνότητας κατά τη διάρκεια των τελευταίων 30 ετών περίπου έχει αποδειχθεί ότι παρέχει αξιοσημείωτα οφέλη για ασθενείς με νόσο Πάρκινσον (ΝΠ) (Deuschl et al. 2006), ιδιοπαθή τρόμο (Zhang et al. 2010) και δυστονία (Kumar et al. 1999), οι οποίοι δεν ανταποκρίνονται σε συμβατικές θεραπείες. Παράγοντες-κλειδί ανάπτυξης αυτής της πρωτοποριακής εφαρμογής αποτέλεσαν οι αξιοσημείωτες εξελίξεις στην δομική και λειτουργική εγκεφαλική απεικόνιση και την εγχειρητική τεχνολογία, αλλά και η καλλιέργεια μιας βαθύτερης κατανόησης της οργάνωσης και της παθοφυσιολογίας των βασικών γαγγλίων (Lozano and Lipsman 2013). Αυτοί οι παράγοντες προετοίμασαν το έδαφος για την μετατροπή ανατομικο-λειτουργικών αρχών σε βέλτιστα θεραπευτικέ εγχειρητικές στρατηγικές (Benabid 2012). Παράλληλα με την καθιέρωση της εν τω βάθει εγκεφαλικής διέγερσης ως μίας ασφαλούς και αποτελεσματικής θεραπευτικής μεθόδου για κινητικές διαταραχές, καινοτόμες εφαρμογές αυτής της τεχνικής για την αντιμετώπιση νευροψυχιατρικών διαταραχών εμφανίστηκαν κατά τη διάρκεια των τελευταίων 15 ετών συμπεριλαμβανομένης της ιδεοψυχαναγκαστικής διαταραχής (ΙΨΔ) (Nuttin et al. 1999), του συνδρόμου Tourette (Vandewalle et al.1999), της μείζονος καταθλιπτικής διαταραχής (Mayberg et al. 2005), του εθισμού σε ουσίες (Muller et al. 2009) και της νευρικής ανορεξίας (Lipsman et al. 2013). Η μη-αφαιρετική φύση της εν τω βάθει εγκεφαλικής διέγερσης , η προσαρμοστικότητα και η φαινομενική αναστρεψιμότητα (Benabid et al. 2009) έχουν μετατρέψει αυτή τη θεραπευτική επιλογή στο πιο ταχέως διευρυνόμενο πεδίο της νευροχειρουργικής. Μέχρι σήμερα, ο αριθμός των ασθενών που έχουν υποβληθεί σε εγχείρηση εν τω βάθει εγκεφαλικής διέγερσης εκτιμάται πως έχει ξεπεράσει τους 100,000 παγκοσμίως. Από επιστημονικής πλευράς, η εν τω βάθει εγκεφαλική διέγερση έχει αποτελέσει σημείο αναφοράς διακριτών επιστημονικών και ερευνητικών κλάδων. Κατά κύριο λόγο όμως έχει

συντελέσει σημαντικά στην ‘αναγέννηση’ των νευροεπιστημών, παρέχοντας τη δυνατότητα διεξαγωγής in vivo έρευνας σε εγκεφαλικά δίκτυα κινητικών, διανοητικών και συναισθηματικών λειτουργιών. Το γεγονός αυτό αντικατοπτρίζεται στις περισσότερες από 700 μελέτες σχετιζόμενες με την εν τω βάθει εγκεφαλική διέγερση, οι οποίες δημοσιεύονται κάθε χρόνο (Lozano and Lipsman 2013). Ωστόσο, αυτός ο ενθουσιασμός είναι απαραίτητο να μετριαστεί μέσω μιας προσεκτικής θεώρησης των σχετιζόμενων ηθικών αρχών. Παρόλο που οι υπάρχοντες ηθικοί κανόνες και το ρυθμιστικό πλαίσιο διασφαλίζουν σε ικανοποιητικό βαθμό την ορθή μεταχείριση της νευροχειρουργικής για κινητικές και νευροψυχιατρικές διαταραχές (Greenberg et al. 2010 (a)), παραμένει ακόμη επιτακτική η ανάγκη να σκιαγραφηθούν πλήρως οι σχετικές ηθικές και κοινωνικές προκλήσεις και να καθιερωθούν σε παγκόσμιο επίπεδο ηθικοί κανονισμοί για τις μελλοντικές κλινικές δοκιμές (Bell and Racine 2012, Fins et al. 2011, Lipsman et al. 2010). Η προστασία του ασθενή θα πρέπει αναμφίβολα να αποτελέσει τον κεντρικό άξονα ενός στέρεου πλαισίου αποτύπωσης ηθικών κανονιστικών αρχών (Clausen 2010).

Η εν τω βάθει εγκεφαλική διέγερση αποτελεί μία θεραπευτική προσέγγιση βασιζόμενη στην αρχή της νευροτροποποίησης, δηλ. της μεταβολής της παθολογικής νευρωνικής δραστηριότητας στον πυρήνα-στόχο και τα συνδεδεμένα νευρωνικά δίκτυα με χρήση ηλεκτρικού ρεύματος παρεχόμενου μέσω ενδοεγκεφαλικά εμφυτευμένων ηλεκτροδίων συνδεδεμένων σε έναν εμφυτεύσιμο παλμοδότη. Το σύστημα εν τω βάθει εγκεφαλικής διέγερσης Medtronic αποτελείται από έναν (ή δύο στην περίπτωση αμφίπλευρης διέγερσης) αγωγό (αγωγούς) με 4 κυλινδρικές επαφές (διαμέτρου 1.27mm, ύψους 1.5mm και απόστασης 1.5mm ή 0.5mm μεταξύ τους) που εμφυτεύονται εγχειρητικά στον επιλεγμένο πυρήνα του εγκεφάλου και συνδέονται υποδόρια με τον εμφυτεύσιμο παλμοδότη στην υποκλείδιο περιοχή. Ο εμφυτεύσιμος παλμοδότης είναι μία προγραμματιζόμενη και ενδεχόμενα επαναφορτιζόμενη διάταξη παρόμοια με τους μοντέρνους καρδιακούς παλμοδότες που παρέχει συνεχή διέγερση. Η εγχείρηση εν τω βάθει εγκεφαλικής διέγερσης βασίζεται στις αρχές της στερεοτακτικής και λειτουργικής νευροχειρουργικής και μπορεί να διεξαχθεί με ή χωρίς πλαίσιο (Lozano et al. 2009). Σε οποιαδήποτε από τις δύο προαναφερόμενες περιπτώσεις, η ακριβής τοποθέτηση του ηλεκτροδίου βασίζεται στην προεγχειρητική στερεοτακτική στόχευση και σε διεγχειρητικές τεχνικές ηλεκτροφυσιολογικής χαρτογράφησης που συνήθως εφαρμόζονται υπό τοπική αναισθησία (Abosch et al. 2013). Η προεγχειρητική στερεοτακτική στόχευση επιτυγχάνεται μέσω μοντέρνων τεχνικών οπτικοποίησης (απεικόνιση μαγνητικού συντονισμού χωρίς πλαίσιο και υπολογιστική τομογραφία βασιζόμενη σε πλαίσιο), ενώ οι διεγχειρητικές τεχνικές ηλεκτροφυσιολογικής χαρτογράφησης που συνήθως χρησιμοποιούνται αφορούν στις *μικροηλεκτροδιακές καταγραφές* νευρωνικής δραστηριότητας στον πυρήνα στόχο και στην μακροδιέγερση, δηλ. τη διεγχειτηρική διέγερση με αυξανόμενη τάση εφαρμοζόμενη μέσω ενός εξωτερικού παλμοδότη για τον καθορισμό του σημείου εμφύτευσης που συσχετίζεται με το

βέλτιστο *θεραπευτικό παράθυρο* (λόγος του κατωφλίου εμφάνισης δυσμενών αποτελεσμάτων-παρενεργειών προς το κατώφλι εμφάνισης κλινικής αποτελεσματικότητας) (Abosch et al. 2013, Marceglia et al. 2010, Krack et al. 2002). Ωστόσο αξίζει να σημειωθεί ότι σε ορισμένα χειρουργικά κέντρα έχουν υιοθετηθεί στρατηγικές που δε βασίζονται στην ηλεκτροφυσιολογική χαρτογράφηση (Foltynie et al. 2010). Εκτός από την ακριβή τοποθέτηση του ηλεκτροδίου, το αποτέλεσμα της εν τω βάθει εγκεφαλικής διέγερσης καθορίζεται σημαντικά από την μετεγχειρητική κλινική διαχείριση (Volkmann et al. 2004, Benabid et al. 2009). Συγκεκριμένα, μετά την εμφύτευση του συστήματος εν τω βάθει εγκεφαλικής διέγερσης, οι παράμετροι διέγερσης και η φαρμακευτική αγωγή θα πρέπει να καθοριστούν με τρόπο ώστε να οδηγούν στο βέλτιστο θεραπευτικό αποτέλεσμα. Οι δόσεις φαρμακευτικής αγωγής, που έχουν ήδη μειωθεί προεγχειρητικά, μειώνονται περαιτέρω και ρυθμίζονται με τρόπο συμβιβαστικό. Αναφορικά με τις παραμέτρους διέγερσης, αυτές σε πρώτη φάση συνήθως περιλαμβάνουν διάρκεια παλμού 60*μs*, συχνότητα διέγερσης 130 *Hz* και κυμαινόμενη τάση (Volkmann et al. 2004).

Κατά κύριο λόγο, η εν τω βάθει εγκεφαλική διέγερση έχει όχι μόνο αποτελέσει μια δυναμική κλινική προοπτική για την αντιμετώπιση κινητικών και νευροψυχιατρικών διαταραχών – βάσει της αντιστρεψιμότητας, της προσαρμοστικότητας και της συσχέτισής της με χαμηλούς δείκτες θνησιμότητας – αλλά και συντελέσει στην αποκρυπτογράφηση τόσο της λειτουργικότητας των πυρήνων-στόχων κατά τη διάρκεια της εκδήλωσης ή της υποχώρησης των συμπτωμάτων όσο και των μηχανισμών δράσης της διέγερσης αυτής καθεαυτής (Lozano et al. 2010 (a), Pollak et al. 2002). Αυτές οι μοναδικές δυνατότητες παρασχέθηκαν πρωταρχικά μέσω των διεγχειρητικών μικροηλεκτροδιακών καταγραφών και των τεχνικών λειτουργικής διέγερσης, όπως επίσης και μέσω των καταγραφών δυναμικών τοπικού πεδίου και της μετεγχειρητικά εφαρμοσμένης διέγερσης. Καταρχήν, κατά τη διάρκεια των διεγχειρητικών μικροηλεκτροδιακών καταγραφών που λαμβάνονται σε κατάσταση ηρεμίας ή ως απόκριση σε διάφορους κινητικούς και διανοητικούς χειρισμούς, μπορούν να προσδιοριστούν φυσιολογικά και παθολογικά μοτίβα νευρωνικής δραστηριότητας και να αποδοθούν σε έναν συγκεκριμένο πυρήνα στόχο ή σε μια υπο-περιοχή αυτού (Levy et al. 2000, Weinberger et al. 2006, Piallat et al. 2011, Wong et al. 2009, Rodriguez-Oroz et al. 2001, Lozano et al. 2010 (a), Zaghoul et al. 2009, 2012; Patel et al. 2012). Δεύτερον, κατά τη διάρκεια της διεγχειρητικής και της μετεγχειρητικής μακροδιέγερσης μπορούν να αποτιμηθούν τόσο οι ωφέλιμες όσο και οι δυσμενείς επιδράσεις της διέγερσης στους πυρήνες-στόχους και κατ'αυτόν τον τρόπο να αναδειχθεί ο λειτουργικός ρόλος των δομών αυτών (Pollak et al. 2002, Nuttin et al. 2003, Greenberg et al. 2006, Mayberg et al. 2005, Vandewalle et al. 1999, Lipsman et al. 2013, Mallet et al. 2008, Hershey et al. 2010, Greenhouse et al. 2011). Τέλος, η εκτίμηση της δραστηριότητας δυναμικών τοπικού πεδίου μετεγχειρητικά, δηλ. στο διάστημα μεταξύ της εμφύτευσης του ηλεκτροδίου διέγερσης και της συνακόλουθης σύνδεσής του στον υποδόριο

παλμοδότη αποτελεί μία προσέγγιση που έχει οδηγήσει σε σημαντικές διαπιστώσεις αναφορικά τόσο με το χαρακτηρισμό των παθοφυσιολογικών μηχανισμών που συνδέονται με την εμφάνιση των νευρολογικών διαταραχών (Brown et al. 2001, Lopez-Azcarate et al. 2010), όσο και με τους μηχανισμούς δράσης της διέγερσης (Kühn et al. 2008).

Ασθενείς με ιδιοπαθή προχωρημένο στάδιο της ΝΠ και με φαρμακολογικά ανθεκτικές κινητικές διακυμάνσεις, ανθεκτικό τρόμο, ή μη ανεκτικότητα στις δυσμενείς επιδράσεις της φαρμακολογικής θεραπείας, που επιπλέον δεν παρουσιάζουν σημαντικά ενεργά διανοητικά ή ψυχιατρικά προβλήματα, αποτελούν κατάλληλους υποψηφίους για εν τω βάθει εγκεφαλική διέγερση υψηλής συχνότητας. Η εγχείρηση θα πρέπει να διεξάγεται από έμπειρες πολυεπιστημονικές ομάδες (Bronstein et al. 2011, Lozano 2012). Ο υποθαλαμικός πυρήνας είναι συνηθέστερα ο προτεινόμενος στόχος διέγερσης για προχωρημένο στάδιο της ΝΠ (Benabid et al. 2009, Schuurman and Bosch 2007, Lozano 2012, Albanese and Romito 2011, Oderkerken et al. 2013, Foltynie and Hariz 2010). Μεγάλες τυχαιοποιημένες ελεγχόμενες μελέτες έχουν υποδείξει μία σημαντικά υψηλότερη αποτελεσματικότητα της εν τω βάθει εγκεφαλικής διέγερσης υποθαλαμικού πυρήνα για προχωρημένο στάδιο της ΝΠ σε σύγκριση με την αποκλειστική ιατρική διαχείριση (Williams et al. 2013, Deuschl et al. 2006, Weaver et al 2009, Okun et al. 2012). Συγκεκριμένα η εν τω βάθει εγκεφαλική διέγερση του υποθαλαμικού πυρήνα έχει αποδειχθεί ότι επιφέρει αξιοσημείωτη και μακράς διαρκείας βελτίωση των συμπτωμάτων που ανταποκρίνονται στη levodopa και του τρόμου, καθώς επίσης ότι εξαλείφει σημαντικά τη δυσκινησία και τις κινητικές διακυμάνσεις σε ασθενείς με προχωρημένο στάδιο της ΝΠ (Bronstein et al.2011, Castrioto et al. 2011 (a), Zibetti et al. 2011, Fasano et al. 2010, Rizzone et al. 2014, Moro et al. 2010, Vitek 2012 (a), Sturman et al. 2004, Hamani et al. 2011, Krack et al. 2003). Σε αντίθεση με τα περιφερικά συμπτώματα, ωστόσο, η εξέλιξη των αξονικών κινητικών συμπτωμάτων, συμπεριλαμβανομένων της ανθεκτικής στη levodopa διαταραχή της βάδισης και της αστάθειας της στάσης, παραμένει ανεξέλεγκτη ακόμη και μετά την επέμβαση της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα (Castrioto et al. 2011 (a), Zibetti et al. 2011, Fasano et al. 2010, Rizzone et al. 2014, Moro et al. 2010, Krack et al. 2003, Rodriguez-Oroz 2012). Έχει επίσης αναφερθεί η ανάπτυξη μη-κινητικών συμπτωμάτων συμπεριλαμβανομένων σημαντικών διανοητικών διαταραχών, κατάθλιψης ή άγχους, και μία αξιοσημείωτη επιδείνωση της καταληπτότητας της ομιλίας κατά τη διάρκεια μιας μακράς περιόδου μετά την επέμβαση εν τω βάθει εγκεφαλικής διέγερσης υποθαλαμικού πυρήνα (Rizzone et al. 2014, Zibetti et al. 2011, Tripoliti et al. 2011, Moro et al. 2010, Klostermann et al. 2008, Temel et al. 2006 (a), Voon et al. 2006, 2008, Guehl et al. 2006, Krack et al. 2003, Rodriguez-Oroz et al. 2012). Οι Rizzone et al (2014) έχουν αναφέρει ότι η προχωρημένη ηλικία κατά την έναρξη της ασθένειας, υψηλό αξονικό σκορ στην κατάσταση *off* και η παρουσία συμπεριφορικής διαταραχής του ύπνου συσχετίζονται με έναν υψηλότερο

κίνδυνο ανάπτυξης αναπηρίας με την πάροδο του χρόνου υπό την εν τω βάθει εγκεφαλική διέγερση του υποθαλαμικού πυρήνα. Παρολαυτά, η εν τω βάθει εγκεφαλική διέγερση του υποθαλαιμικού πυρήνα έχει αποδειχθεί ότι αποτελεί μία πιο αποτελεσματική θεραπεία συγκριτικά με την παλιδοτομή (Esselink et al. 2009). Γενικά, εκτιμάται ότι λιγότερο από το 5% των ασθενών με ΝΠ πληρούν τα κριτήρια επιλογής για την εν τω βάθει εγκεφαλική διέγερση του υποθαλαμικού πυρήνα. Το μεγαλύτερο μέρος των αποκλεισμών οφείλεται σε πρώιμη φάση της νόσου (Morgante et al. 2007). Ωστόσο, δύο αναμενόμενες, τυχαιοποιημένες κλινικές δοκιμές προσανατολίζονται προς την αποτίμηση της επίδρασης εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για ασθενείς σε πρώιμη φάση της νόσου (Deuschl et al. 2013, Kahn E et al. 2012). Η πρώτη δοκιμή ορίζει ως ασθενείς με πρώιμη ΝΠ όσους εμφάνισαν πρόσφατη έναρξη κινητικών επιπλοκών προκαλούμενων από levodopa (<3 χρόνια) (Deuschl et al. 2013), ενώ η δεύτερη δοκιμή συμπεριλαμβάνει ασθενείς που βρίσκονται υπό θεραπεία με αντιπαρκινσονική αγωγή (levodopa ή αγωνιστές ντοπαμίνης) για μία περίοδο μεγαλύτερη από 6 μήνες και μικρότερη από 4 χρόνια, χωρίς εκκίνηση κινητικών επιπλοκών προκαλούμενων από levodopa (Kahn E et al. 2012). Τα συμπεράσματα-κλειδί των μελετών αυτών αναμένεται να αφορέσουν, από τη μία πλευρά, στον καθορισμό της ασφάλειας και ανεκτικότητας της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα εφαρμοσμένης σε πρώιμη φάση της ΝΠ και, από την άλλη πλευρά, στην επιβεβαίωση μιας ενδεχόμενης νοσοτροποποιητικής επίδρασης, βάσει ενδείξεων νευροπροστατευτικής δράσης της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα (Temel et al. 2006 (b), Harnack et al. 2008, Wallace et al. 2007, Spieles-Engemann et al. 2010, deSouza et al. 2013, Albanese and Romito 2011). Αναφορικά με την μονόπλευρη εν τω βάθει εγκεφαλική διέγερση του υποθαλαμικού πυρήνα, αυτή έχει υποδειχθεί ότι βελτιώνει τα ετερόπλευρα κινητικά συμπτώματα της ΝΠ και ότι αποτελεί μία εναλλακτική της αμφίπλευρης διέγερσης, ιδιαίτερα για ασθενείς με εμφανή ασυμμετρία συμπτωμάτων (Alberts et al. 2008 (a), Alberts et al. 2008 (b), Castrioto et al. 2011(b), Walker et al. 2009, Brun et al. 2012), αλλά και για ηλικιωμένους ασθενείς, καθώς συνδέεται με έναν χαμηλότερο βαθμό διανοητικών επιπλοκών (Slowinski et al. 2007).

Παρά τη συνεχή ανάπτυξη των συστημάτων εν τω βάθει εγκεφαλικής διέγερσης , τα ποσοστά των δυσμενών επιδράσεων που συνδέονται με την εγχειρητική διαδικασία και τον τεχνικό εξοπλισμό παραμένουν ακόμη σχετικά υψηλά, αποτελώντας ένα μείζων μειονέκτημα της θεραπευτικής αυτής δυνατότητας (Shih and Tarsy 2011, Burdick et al. 2010, Lozano 2012, Morishita et al. 2013, Vergani et al. 2010, Chan et al. 2009, Rezai et al. 2006). Οι επιπλοκές που συνδέονται με την εγχειρητική διαδικασία συνήθως αφορούν στην ενδοκρανιακή αιμορραγία, ενώ έχουν αναφερθεί ακόμη περιπτώσεις διεγχειρητικής σύγχυσης, μετατόπισης του αγωγού, μόνιμης νευρολογικής βλάβης ή θανάτου (Zrinzo et al. 2011, 2012;Voges et al. 2007, Favre et al. 2002, Boviatsis et al. 2010, Pepper et al. 2013, Oh et al. 2002, Guridi et al.

2012, Linchares et al. 2013). Οι δυσμενείς επιδράσεις που συνδέονται με την εγχειρητική διαδικασία και τον τεχνικό εξοπλισμό παρατηρούνται περίπου στο 6.5 και 9% των ασθενών, αντιστοίχως (Vergani et al. 2010, Hamani et al. 2004). Επιπρόσθετα, περίπου στο 19% των ασθενών έχουν καταγραφεί δυσμενείς επιδράσεις που συνδέονται με τη διέγερση, όπως οι παραισθησίες, η δυσαρθρία και οι κινητικές επιπλοκές (Hamani et al. 2004). Ωστόσο, οι επιδράσεις αυτές είναι ήπιες και μπορούν να αναστραφούν μέσω της ορθής προσαρμογής των παραμέτρων διέγερσης. Η ειδική περίπτωση του μετεγχειρητικού εγκεφαλικού οιδήματος περιφερικά του αγωγού εν τω βάθει εγκεφαλικής διέγερσης θεωρείται μία μεταβατική δυσμενής επίδραση με αδιευκρίνιστη αιτιοπαθοφυσιολογία (Deogaonkar et al. 2011, Morishita et al. 2010).

Εκτιμάται ότι περίπου το 10% των ασθενών με ΙΨΔ εκδηλώνουν σοβαρά, ανθεκτικά στη θεραπεία συμπτώματα (Denys 2006). Για μία επιλεγμένη ομάδα αυτών των ασθενών η νευροχειρουργική αντιμετώπιση ενδεχομένως να αποτελεί μια αποτελεσματική εναλλακτική θεραπεία. Αξίζει να σημειωθεί ότι στην τρέχουσα πρακτική της ψυχιατρικής χειρουργικής , η ανθεκτική στη θεραπεία ΙΨΔ είναι η κατάσταση που αναφέρεται συχνότερα (Lipsman et al. 2011). Ωστόσο, παράγοντες όπως το κοινωνικό στίγμα ασθενών με ψυχιατρική νόσο, ο δισταγμός ψυχιάτρων να παραπέμψουν τους ασθενείς σε νευροχειρουργική θεραπεία, αλλά και η ιστορική αποτρόπαια χρήση της ψυχοχειρουργικής εμπόδισαν την εκτενή εφαρμογή της νευροχειρουργικής για ενδείξεις ανθεκτικής στη θεραπεία ψυχιατρικής νόσου. Η ασφάλεια και η αποτελεσματικότητα των παραδοσιακών αφαιρετικών διαδικασιών, συμπεριλαμβανομένης της πρόσθιας καψοτομής, της πρόσθιας προσαγωγιοτομής, της υποκερκοφόρας δεσμιδοτομής και της μεταιχμιακής λοβοτομής για σοβαρή, ανθεκτική στη θεραπεία ΙΨΔ υποστηρίζονται μόλις από επιπέδου ΙΙ ενδείξεις και παραμένουν στην ερευνητική κλίμακα ‘απόδειξης της ορθότητας της αρχής’, ενώ για την ακτινοχειρουργική gamma knife και τον στερεοτακτικά εστιασμένο υπέρηχο υπάρχει πλήρης έλλειψη ενδείξεων (Nuttin et al. 2014, National Collaborating Centre for Mental Health 2006). Επιπλέον, η εφαρμογή της εν τω βάθει εγκεφαλικής διέγερσης για την ανθεκτική στη θεραπεία ΙΨΔ και η επικύρωση των κατάλληλων ανατομικών στόχων παραμένουν ακόμη κατά μεγάλο μέρος σε πειραματική βαθμίδα (Blomstedt et al. 2013, Kohl et al. 2014, Morishita et al. 2014, Figee et al. 2010, de Koning et al. 2011, Lapidus et al. 2013, Williams and Okun 2013, Krack et al. 2010). Για τη δημιουργία κλινικής απόδειξης επιπέδου Ι αναφορικά με τις νευροχειρουργικές διαδικασίες για ψυχιατρικές διαταραχές, απαιτείται ο σχεδιασμός τυχαιοποιημένων και τυφλών ελεγχόμενων δοκιμών διασφαλίζοντας παράλληλα την ηθική διαγωγή και δίνοντας προτεραιότητα στην ασφαλή θεραπευτική αντιμετώπιση. Αντιστοίχως, απαιτούνται ανεξάρτητοι ειδικοί για έναν ολοκληρωμένο προεγχειρητικό έλεγχο χρησιμοποιώντας πρότυπες βαθμίδες αξιολόγησης και συμπεριλαμβάνοντας τον προσδιορισμό του βαθμού ανθεκτικότητας στη θεραπεία, αλλά και

την προσεκτική εκτίμηση του κινδύνου αυτοκτονίας. Θα πρέπει επίσης να διασφαλίζονται ορθές πρακτικές συναίνεσης . Εξίσου σημαντική είναι η διεξαγωγή της νευροχειρουργικής διαδικασίας από έμπειρη πολυεπιστημονική ομάδα αποτελούμενη από κατάλληλα εκπαιδευμένους νευροχειρουργούς, ψυχιάτρους, νευρολόγους και νευροφυσιολόγους. Τέλος, θα πρέπει οπωσδήποτε να διασφαλίζεται ένας ολοκληρωμένος μετεγχειρητικός έλεγχος (Nuttin et al. 2014).

Από το 1999, η εν τω βάθει εγκεφαλική διέγερση έχει αξιολογηθεί με βάση ένα σύνολο περίπου 100 ασθενών ως μία πλεονεκτικότερη θεραπευτική δυνατότητα συγκριτικά με αφαιρετικές διαδικασίες για σοβαρή, ανθεκτική στη θεραπεία ΙΨΔ, λόγω της αναστρεψιμότητας και της προσαρμοστικότητάς της (Sakas et al. 2007 (b)). Εξαιτίας περιορισμένης γνώσης της παθοφυσιολογίας της διαταραχής, η επιλογή του στόχου έχει κατά κύριο λόγο βασιστεί στην εμπειρία από παραδοσιακές διαδικασίες στερεοτακτικής τρώσης ή σε παρατηρήσεις κατά τη διάρκεια της επέμβασης εν τω βάθει εγκεφαλικής διέγερσης για κινητικές διαταραχές (Blomstedt et al. 2013, Benabid and Torres 2012). Στην πρώτη δημοσιευμένη αναφορά αμφίπλευρης εν τω βάθει εγκεφαλικής διέγερσης για ανθεκτική στη θεραπεία ΙΨΔ, ο επιλεγμένος στόχος βρισκόταν στην έσω κάψα, ακριβώς ρυγχοειδώς της πρόσθιας συμφύσεως επεκτεινόμενος στην προσκείμενη κοιλιακή κάψα και το κοιλιακό ραβδωτό σώμα (Nuttin et al. 1999). Ο επιλεγμένος στόχος ήταν ταυτόσημος της στοχευμένης περιοχής που χρησιμοποιείται στην καψοτομή. Σύμφωνα με την αναφορά αυτή, παρατηρήθηκαν άμεσες ευνοϊκές επιδράσεις στην κατάσταση ‘stimulation-on’ σε 3 από τους 4 ασθενείς. Ακολούθως, η μακροπορόθεσμη αποτελεσματικότητα της διέγερσης της πρόσθιας κάψας και του κοιλιακού ραβδωτού σώματος επικυρώθηκε από μία περαιτέρω σειρά μελετών μικρής κλίμακας (Nuttin et al. 2003, Gabriels et al. 2003, Abelson et al. 2005, Greenberg et al. 2006, Goodman et al. 2010). Σε μία συγκεντρωτική εκτίμηση του κλινικού αποτελέσματος αυτών των μελετών οι Greenberg et al. (2010 (b)) ανέφεραν ότι κατά τη διάρκεια της τελευταίας παρακολούθησης καταγράφηκε πλήρης αποκρισιμότητα (72% >35% μείωση στην κλίμακα YBOC-S) στην εν τω βάθει εγκεφαλική διέγερση κοιλιακής κάψας/ κοιλιακού ραβδωτού σώματος, αξιοσημείωτη υποχώρηση των συμπτωμάτων της κατάθλιψης, του άγχους και βελτίωση της συνολικής λειτουργικότητας στα περίπου 2/3 (17/26) των ασθενών, εξαιτίας της σταδιακής βελτιστοποίησης του σημείου εμφύτευσης. Συγκεκριμένα, ο βέλτιστος στόχος βρισκόταν στη συμβολή της πρόσθιας κάψας, της πρόσθιας συμφύσεως και του νωτιαίου κοιλιακού ραβδωτού σώματος. Καταγράφηκαν επίσης δυσμενή συμπτώματα συμπεριλαμβανομένων δύο ενδοκρανιακών αιμορραγιών, μίας κρίση επιληψίας, μίας μόλυνσης, δύο επιπλοκών εξαιτίας τεχνικού εξοπλισμού, αλλά και αναστρέψιμα συμπτώματα προκαλούμενα από τη διέγερση, όπως η υπομανία. Ωστόσο, διανοητική κατάπτωση δεν προκαλείται από την εν τω βάθει εγκεφαλική διέγερση της κοιλιακής κάψας/κοιλιακού ραβδωτού σώματος (Kubu et al. 2013).

Το 2003, η επιλογή της κελυφωτής περιοχής του δεξιού επικλινή πυρήνα ως στόχου για την εν τω βάθει εγκεφαλική διέγερση αναφέρθηκε ότι προκαλεί σημαντική βελτίωση της συμπτωματολογίας της ΙΨΔ (Sturm et al. 2003). Η συγκεκριμένη αυτή επιλογή στόχου βασίστηκε σε κλινικές παρατηρήσεις για τον πιθανό ρόλο του κοιλιακού-ουραίου μέρους της έσω κάψας προσκείμενης στον επικληνή πυρήνα στο κλινικό αποτέλεσμα της πρόσθιας καψοτομής, αλλά και σε παθοφυσιολογικές ενδείξεις για το ρόλο του επικληνή πυρήνα ως μίας κεντρική δομής ανάμεσα στο αμυγδαλοειδές σύμπλεγμα και τον υπερμεσολόβιο έλικα (de Koning et al. 2012). Σε μετέπειτα δοκιμές, η εφαρμογή της μονόπλευρης εν τω βάθει εγκεφαλικής διέγερσης του δεξιού επικληνή πυρήνα για την ανθεκτική στη θεραπεία ΙΨΔ, συμπεριλαμβανομένης μίας περίπτωσης ΙΨΔ με συννοσηρότητα σχιζοφρένειας, κατέληξε σε μέτρια μακροπρόθεσμα ευνοϊκά αποτελέσματα (Huff et al. 2010, Plewnia et al. 2008), ενώ η αμφίπλευρη εν τω βάθει εγκεφαλική διέγερση του επικληνή πυρήνα συσχετίστηκε με έναν σημαντικά μεγαλύτερο βαθμό μακροπρόθεσμης αποκρισιμότητας παρέχοντας ενδείξεις επιπέδου ΙΙ για τη χρήση αυτής της διαδικασίας στην κλινική πράξη (Denys et al. 2010, Hamani et al. 2014, Franzini et al. 2010, Mantione et al. 2014). Αξίζει να σημειωθεί πως σε όλες τις προαναφερόμενες κλινικές δοκιμές, απαιτήθηκαν υψηλές πλάτη τάσης διέγερσης (μέχρι 10.5V) για την επίτευξη σημαντικού κλινικού αποτελέσματος.

Αναφορικά με έναν διακριτό στόχο και σύμφωνα με μία πρόσφατη συστηματική ανασκόπηση των Hamani et al. (2014), υπάρχουν ενδείξεις επιπέδου Ι για τη χρήση της αμφίπλευρης εν τω βάθει έγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα στην ανθεκτική στη θεραπεία ΙΨΔ. Αυτές οι ενδείξεις βασίζονται στην έρευνα της ερευνητικής ομάδας ‘French Stimulation dans le Trouble Obsessionnel Compulsif (STOC)’ (Mallet et al. 2008), η οποία πρότεινε τη θεραπευτική αυτή επιλογή μετά την παρατήρηση ότι η διέγερση υψηλής συχνότητας του υποθαλαμικού πυρήνα μετρίασε ιδεοψυχαναγκαστικά συμπτώματα σε 2 ασθενείς με ΝΠ και ιστορικό σοβαρής ΙΨΔ (Mallet et al. 2002, Haynes and Mallet 2012). Περαιτέρω ώθηση για τη συγκεκριμένη επιλογή δόθηκε από πολλαπλές ενδείξεις για την εμπλοκή του υποθαλαμικού πυρήνα, ως βασικού κόμβου του έμμεσου μονοπατιού, στην παθοφυσιολογία της ΙΨΔ και άλλων συμπεριφορικών διαταραχών (Mallet et al. 2007, Winter et al. 2007, Winter et al. 2008(a), Haynes and Mallet 2012), όπως επίσης και από την αποδεδειγμένη αποτελεσματικότητα της διέγερσης υψηλής συχνότητας του υποθαλαμικού πυρήνα στο μοντέλο ΙΨΔ αρουραίου και θηλαστικού (Winter et al. 2008(b), Winter 2012, Klavir et al. 2009, Kupsch et al. 2004, Winter et al. 2007, Baup et al. 2008). Σύμφωνα με το αποτέλεσμα της μελέτης της γαλλικής STOC ερευνητικής ομάδας, οι ενεργές επαφές στο μετεγχειρητικό MRI ήταν τοποθετημένες στο μεσοπρόσθιο (συνειρμικό-μεταιχμιακό) μέρος του υποθαλαμικού πυρήνα, 2mm πρόσθια και 1mm μεσαία του στόχου που χρησιμοποιείται κατά τη διάρκεια της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για ΝΠ. Έπειτα από 3 μήνες ενεργής

διέγερσης παρατηρήθηκε σημαντική (p=0.01) μείωση κατά 31% στην κλίμακα YBOC-S. Οι Chabardès et al (2013) αποτίμησαν την επιλογή του ίδιου στόχου σε 4 ασθενείς με σοβαρή ΙΨΔ. Σε 3 από τους 4 ασθενείς, αναφέρθηκε μείωση 71-78% στην κλίμακα YBOC-S μετά από 6 μήνες διέγερσης, ενώ στην 4^{η} περίπτωση επιτεύχθηκε μικρότερη κλινική βελτίωση (~34% μείωση στην κλίμακα YBOC-S), ακόμη και έπειτα από την προσαρμογή των παραμέτρων διέγερσης, η οποία αποδίδεται στη λειτουργικώς εσφαλμένη τοποθέτηση των ηλεκτροδίων. Οι συγγραφείς επισήμαναν όχι μόνο τα κλινικά αποτελέσματα της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για την ανθεκτική στη θεραπεία ΙΨΔ, αλλά και τα πλεονεκτήματα που συνδέονται με μία ευρέως γνωστή περιοχή - στόχο, όπως επίσης τις χαμηλότερες ενεργειακές απαιτήσεις σε σύγκριση με τη χρήση των προαναφερόμενων εναλλακτικών στόχων.

Όπως έχει αναφερθεί, εκτός από την κατάλληλη επιλογή των ασθενών και τη βέλτιστη μετεγχειρητική διαχείριση, η ποιότητα του κλινικού αποτελέσματος της επέμβασης της εν τω βάθει εγκεφαλικής διέγερσης συσχετίζεται στενά με τον καθορισμό του κατάλληλου ανατομικού στόχου και την ακριβή τοποθέτηση του ηλεκτροδίου διέγερσης στην περιοχή αυτή (Lozano et al. 2010 (a), Volkmann et al. 2006). Σε αυτό το πλαίσιο, μετά την εφαρμογή του στερεοτακτικού πλαισίου, οι προεγχειρητικές μέθοδοι άμεσης στόχευσης, δηλ. η υπολογιστική τομογραφία, η 1.5T-απεικόνιση μαγνητικού συντονισμού και η κοιλιογραφία έχει αποδειχθεί ότι είναι στερεοτακτικά ακριβείς στην κλίμακα των χιλιοστών (Rezai et al. 2006). Αν και κάποιες χειρουργικές ομάδες επιλέγουν αποκλειστικά αυτές τις απεικονιστικές μεθόδους, στην πλειοψηφία των κλινικών κέντρων έχει υιοθετηθεί η επιπρόσθετη χρήση των μικροηλεκτροδιακών καταγραφών ως μία έμμεση μέθοδος στόχευσης για τη βελτιστοποίηση της ακριβούς τοποθέτησης του ηλεκτροδίου (Abosch et al. 2013, Weaver et al. 2009). Η επιλογή της μεθόδου αυτής απορρέει από συγκεκριμένα μειονεκτήματα που συνδέονται με την άμεση στόχευση, συμπεριλαμβανομένης της εγκεφαλικής μετατόπισης: η θέση του στόχου όπως καθορίζεται κατά τη διάρκεια της απεικόνισης μαγνητικού συντονισμού, όταν ο ασθενής βρίσκεται σε ύπτια θέση, δεν είναι η ίδια με τη θέση του στόχου που καθορίζεται διεγχειρητικά, όταν το κεφάλι του ασθενή βρίσκεται σε μία πιο όρθια θέση (Abosch et al. 2010). Ωστόσο, δεν έχουν ακόμη διεξαχθεί αναμενόμενες τυχαιοποιημένες μελέτες που να συγκρίνουν την μακροπρόθεσμη αποτελεσματικότητα των μικροηλεκτροδιακών καταγραφών έναντι των απεικονιστικών μεθόδων που προαναφέρθηκαν (Rezai et al. 2006, Senatus et al. 2006, Mc-Clelland III 2011, Gross and McDougal M E 2013). Σε κάθε περίπτωση, η τελική τοποθέτηση του ηλεκτροδίου καθορίζεται με βάση την απόκριση του ασθενή στην διεγχειρητική μακροδιέγερση (Lozano 2012, Bour et al. 2010).

Οι διεγχειρητικές μικροηλεκτροδιακές καταγραφές θωρούνται ένα σχετικά ασφαλές και εύρωστο εργαλείο για τη μείωση του κινδύνου ενός μη βέλτιστου προσδιορισμού του πυρήνα-

στόχου (Rezai et al. 2006, Reck et al. 2012, Lanotte et al. 2002, Chen et al. 2006, Schlaier et al. 2013). Αφού ανοιχτούν οπές πρόσθια της στεφανιαίας περίπαρσης, προωθούνται 1 έως 5 μικροηλεκτρόδια παράλληλα προς τον στόχο χρησιμοποιώντας έναν μικρο-οδηγό. Κατά τη διάρκεια αυτής της διαδικασίας, μπορεί να οπτικοποιηθεί η φυσιολογική ταυτότητα κάθε διαπερνόμενης πυρηνικής δομής, υποστηρίζοντας με τον τρόπο αυτό την κλινική απόφαση αναφορικά με τη βέλτιστη τροχιά καταγραφής, δηλ. την τροχιά που διαπερνά τον πυρήνα κατά το μεγαλύτερο μήκος (Lozano et al. 2010 (a), Marceglia et al. 2010). Αναφορικά με τον υποθαλαμικό πυρήνα, ένα αυξανόμενο επίπεδο θορύβου υποβάθρου, ένας υψηλός ρυθμός εκφορτίσεων και ένα πρότυπο μη ομαλής δραστηριότητας ή δραστηριότητας ξεσπασμάτων αποτελούν διαχωριστικά χαρακτηριστικά της στοχευμένης αυτής δομής συγκριτικά με γειτονικές εγκεφαλικές δομές (Bour et al 2010). Μετά τον προσδιορισμό των λειτουργικών ορίων του υποθαλαμικού πυρήνα, μπορεί να καθοριστεί το συνολικό του μήκος για κάθε τροχιά καταγραφής. Μία αποδεκτή τροχιά θα πρέπει να διαπερνά >= 3 mm του πυρήνα (Marceglia et al 2010). Η επέμβαση εν τω βάθει εγκεφαλικής διέγερσης βασιζόμενη σε πλαίσιο και τις μικροηλεκτροδιακές καταγραφές έχει παρόμοιο αποτέλεσμα συγκριτικά με τη στερεοταξία χωρίς πλαίσιο (Tai et al. 2010, Holloway et al. 2005, Bronte-Stewart et al. 2010, Rezai et al. 2006). Ωστόσο επί του παρόντος, δεν υπάρχουν πειστικές αποδείξεις για μία θετική συσχέτιση μεταξύ του αριθμού των ηλεκτροδίων καταγραφής που χρησιμοποιούνται και του βαθμού βελτίωσης των κινητικών συμπτωμάτων ή του κινδύνου ενδοκρανιακής αιμορραγίας (Temel et al. 2007, Gross et al. 2006, Chang et al. 2011, Zibetti et al. 2014). Επιπλέον, δεν έχουν εξαχθεί ακόμη στέρεα συμπεράσματα σχετικά με τις επιδράσεις της αναισθησίας στη μικροηλεκτροδιακή χαρτογράφηση (Lettieri et al. 2012, Maltete et al 2004, Rezai et al. 2006).

Εν τω μεταξύ, οι τεχνικές άμεσης οπτικοποίησης για προεγχειρητική ή διεγχειρητική χρήση βελτιώνονται συνεχώς με απώτερο στόχο τη βελτίωση της ακρίβειας του προσδιορισμού του ανατομικού στόχου ή ακόμη τον αποκλεισμό ενός ενδεχόμενου κινδύνου αιμορραγίας σχετιζόμενου με τη διαδικασία των μικροηλεκτροδιακών καταγραφών (Zrinzo et al 2012). Σε αυτό το πλαίσιο, η ακρίβεια που επιτυγχάνεται χρησιμοποιώντας απεικόνιση μοριακής επιδεκτικότητας στα 3 (3.0T-απεικόνιση μαγνητικού συντονισμού) ή 7 Tesla (7.0T-απεικόνιση μαγνητικού συντονισμού), επεμβατική απεικόνιση μαγνητικού συντονισμού υψηλού πεδίου, διεγχειρητική υπολογιστική τομογραφία, απεικόνιση βραχίονα Ο και τρακτογραφία απεικόνισης τανιστή διάχυσης φαίνεται να είναι τουλάχιστον συγκρίσιμη με την ακρίβεια που έχει αναφερθεί χρησιμοποιώντας συμβατικές μεθόδους στερεοτακτικής νευροχειρουργικής βασιζόμενες σε μικροηλεκτροδιακές καταγραφές (Patil et al. 2012, Abosch et al. 2010, Cho et al. 2010, Toda et al. 2009, Liu et al. 2013, Larson et al. 2012, Starr et al. 2010, Ostrem et al. 2013, Burchiel et al. 2013, Fiegele et al. 2008, Coenen et al. 2011, Holloway and Docef 2013, Henderson 2012, D'Albis et al. 2014, Sudhyadom et al. 2009). Ωστόσο για τους ανατομικούς

στόχους που αναμένεται να προκύψουν σε νέες εφαρμογές της στερεοτακτικής νευροχειρουργικής, η αποκλειστική χρήση τεχνικών άμεσης οπτικοποίησης ενδεχομένως να είναι λιγότερο κατάλληλη από την ηλεκτροφυσιολογικά οδηγούμενη νευροχειρουργική (Starr et al. 2010).

Θα πρέπει να τονιστεί ότι, ανεξάρτητα από την τεχνική στόχευσης που χρησιμοποιείται, η διεγχειρητική κλινική δοκιμή της μακροδιέγερσης αποτελεί ένα ισχυρό προαπαιτούμενο για τη βέλτιστη τελική τοποθέτηση του ηλεκτροδίου, διασφαλίζοντας την επίτευξη βέλτιστων θεραπευτικών επιδράσεων και την εμφάνιση ελάχιστων παρενεργειών της διέγερσης σε μία συγκεκριμένη θέση (Rezai et al. 2006, Abosch et al. 2010, Starr et al. 2010, Pollak et al. 2002, Kinfe and Vesper 2013). Η μακροδιέγερση εφαρμόζεται συνήθως μέσω της απόληξης χαμηλής αντίστασης του μικροηλεκτροδίου (Sakas et al. 2007 (a)), του μακροηλεκτροδίου (Coenen et al. 2011), ή του ηλεκτροδίου εν τω βάθει εγκεφαλικής διέγερσης (Chen C C et al. 2006) σε πολλαπλές θέσεις, προκειμένου να προσδιοριστεί ο βέλτιστος λόγος μεταξύ του κατωφλίου της έντασης για την εμφάνιση παρενεργειών και του κατωφλίου της έντασης για κλινική αποτελεσματικότητα, δηλ. το βέλτιστο θεραπευτικό παράθυρο (Marceglia et al. 2010). Κατ'αυτόν τον τρόπο η διεγχειρητική μακροδιέγερση παρέχει ένα περαιτέρω νευροφυσιολογικό 'φιλτράρισμα' του στόχου για την τελική τοποθέτηση του ηλεκτροδίου. Η διαισθητική αιτιολογία πίσω από αυτή την προσέγγιση έγκειται στο γεγονός ότι οι επιδράσεις προκαλούμενες από τη διεγχειρτηική μακροδιέγερση είναι παρόμοιες με τις μετεγχειρητικές επιδράσεις προκαλούμενες από το μόνιμο ηλεκτρόδιο διέγερσης. Για τον λόγο αυτό, οι παράμετροι διέγερσης που χρησιμοποιούνται διεγχειρητικά προσομοιώνουν τις αντίστοιχες παραμέτρους που εφαρμόζονται μετεγχειρητικά, δηλ. συνήθως περιλαμβάνουν συχνότητα 130Hz, εύρος παλμού 60μs και πλάτη τάσης μέχρι 5V (Pollak et al. 2002). Η διεγχειρητική κλινική δοκιμή διεξάγεται επί του παρόντος από νευροχειρουργούς, νευρολόγους και κλινικούς νευροφυσιολόγους (Rezai et al. 2006). Ένας αξιόπιστος προσδιορισμός των κλινικών οφελών κατά τη διάρκεια της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα συνήθως βασίζεται στην εκτίμηση του βαθμού βελτίωσης της δυσκαμψίας, της τμηματικής ακινησίας ή της εμφάνισης δυσκινησιών προκαλούμενων από τη διέγερση, οι οποίες πρέπει να γίνονται αισθητές σε χαμηλές ηλεκτρικές εντάσεις (Houeto et al. 2003, Pollak et al. 2002, Gross et al. 2006). Αναφορικά με συγκεκριμένες κινητικές και οφθαλμοκινητικές παρενέργειες (κινητικές συσπάσεις στον ετερόπλευρο χειλικό σύνδεσμο , το πρόσωπο ή το χέρι, και μονοφθαλμική παρέκκλιση ή μονόπλευρη μεταβολή στη διάμετρο της κόρης), αυτές θα πρέπει να προκαλούνται σε επίπεδα υψηλής έντασης (Pollak et al. 2002, Tommasi et al. 2008). Κατά τη διάρκεια της επέμβασης έχουν παρατηρηθεί βελτιώσεις σε κινητικά συμπτώματα της ΝΠ ή/και εμφάνιση δυσκινησιών μόλις μετά την εμφύτευση του ηλεκτροδίου εν τω βάθει εγκεφαλικής διέγερσης στον υποθαλαμικό πυρήνα, φαινόμενο που αποκαλείται 'επίδραση μικροτρώσεως'

(Chen C C et al. 2006, Yoshida et al. 2010). Αν και αυτό το φαινόμενο φαίνεται να είναι προγνωστκής σημασίας, δεν έχουν εξαχθεί ακόμη οριστικά συμπεράσματα (Rezai et al. 2006).

Στο γενικό πλαίσιο των μεθόδων στόχευσης που χρησιμοποιούνται κατά τη διάρκεια της επέμβασης της εν τω βάθει εγκεφαλικής διέγερσης έχει αναπτυχθεί μία ποικιλία αλγορίθμων και προχωρημένων συστημάτων λογισμικού για την διεγχειρητική υποστήριξη ή ακόμη την αυτοματοποίηση της κλινικής απόφασης. Συγκεκριμένα, βιοδείκτες και προσεγγίσεις μοντελοποίησης βασιζόμενες σε ηλεκτροφυσιολογικά δεδομένα ή προσανατολισμένες στην ανάπτυξη εξειδικευμένων κατ'ασθενή τρισδιάστατων μοντέλων της ανατομικής περιοχής-στόχου διευκολύνουν σημαντικά τον προσδιορισμό της βέλτιστης τροχιάς (Wong et al. 2009, Cagnan et al. 2011, Falkenberg et al. 2006, Chan et al. 2010, Novak et al. 2011, Pesenti et al. 2004, Pinzon-Morales et al. 2011, Holdefer et al. 2010, Danish et al. 2008, Snellings et al. 2009, Zaidel et al. 2009, 2010, Chen C C et al. 2006, Taghva et al. 2011, Abosh et al. 2013, Beriault et al. 2012). Επιπλέον, εξειδικευμένες κατ'ασθενή προσεγγίσεις μοντελοποίησης εφαρμόσιμες και στη διαδικασία της κλινικής μακροδιέγερσης παρέχουν τη δυνατότητα βελτιστοποίησης και επιτάχυνσης της τελικής τοποθέτησης του ηλεκτροδίου διέγερσης (Miocinovic et al. 2007, Butson et al. 2011, D'Haese et al. 2012, Maedler and Coenen 2012).

Ο υποθαλαμικός πυρήνας (*corpus Luysii*) είναι μία αμφίκυρτη δομή τοποθετημένη στο σύνδεσμο διεγκεφάλου-μεσεγκεφάλου (Luys 1865, Yelnik and Percheron 1979). Τα όρια του υποθαλαμικού πυρήνα ορίζονται από την αβέβαιη ζώνη, ένα τμήμα της φακοειδούς δεσμίδας, νημάτια της έσω κάψας , το πεδίο H του Forel, τον οπισθοπλευρικό υποθάλαμο, το εγκεφαλικό στέλεχος, τη δικτυωτή μοίρα μέλαινας ουσίας και τον ερυθρό πυρήνα (Schaltenbrand and Wahren 1977). Οι ζώνες νηματίων που περνούν πλησίον του ορίου του υποθαλαμικού πυρήνα περιλαμβάνουν την υποθαλαμική δεσμίδα, τη φακοειδή δεσμίδα, τη θαλαμική δεσμίδα, ντοπαμινεργικές μελανοραβδωτές δεσμίδες, το μεσαίο λημνίσκο και την σπονδυλοθαλαμική, τριδυμοθαλαμική και ακτινοθαλαμική ζώνη (Hamani et al. 2004). Ο όγκος του ανθρώπινου υποθαλαμικού πυρήνα έχει αναφερθεί ότι κυμαίνεται μεταξύ 175mm^3 και 240 mm^3 και ότι περιλαμβάνει κατά μέσο όρο 240,000-560,000 νευρώνες (Hardman et al. 2002, Levesque and Parent 2005). Το μήκος, πλάτος και ύψος του είναι 9.8 ± 1.6, 11.5 ± 1.6, και 3.7 ±0.7 mm, αντιστοίχως (Patil et al. 2012). Αξίζει να αναφερθεί ότι υπάρχουν ενδείξεις σημαντικών διατομικών διακυμάνσεων της ανατομικής θέσης και τωνν διαστάσεων του υποθαλαμικού πυρήνα (Daniluk et al. 2010, Reese et al. 2012).

Ο υποθαλαμικός πυρήνας είναι ο μόνος πυρήνας στο δίκτυο των βασικών γαγγλίων αποτελούμενος πρωταρχικά από προβάλοντες νευρώνες που ασκούν μία έντονη διεγερτική επίδραση σε άλλες δομές λόγω της ύπαρξης γλουταμινικού οξέως. Συγκεκριμένα, οι νευρώνες

προβάλουν κατά κύριο λόγο στην ωχρά σφαίρα, το ραβδωτό σώμα, τη μέλαινα ουσία, το σκελογεφυρικό πυρήνα και το ραχιαίο πυρήνα ραφής (Parent and Hazrati 1995, Hamani et al. 2004, Marani et al. 2008, Nambu et al. 2002, Levesque and Parent 2005). Αξίζει να σημειωθεί πως η προβολή υποθαλαμικού πυρήνα-ωχράς σφαίρας αποτελεί ένα βασικό στοιχείο του έμμεσου μοναπατιού (Parent and Hazrati 1995, Karachi et al. 2005). Η δομική και λειτουργική υποδιαίρεση των βασικών γαγγλίων στην αισθητηριοκινητική , συνειρμική και μεταιχμιακή περιοχή αντικατοπτρίζεται στην ύπαρξη τριών αντιστοίχων λειτουργικών ζωνών στον υποθαλαμικό πυρήνα, δηλ. την αισθητηριοκινητική, συνειρμική και μεταιχμιακή ζώνη που βρίσκονται στο οπίσθιο (ραχιαιοπλευρικό), μέσο (μεσοκοιλιακό) και πρόσθιο (μεσαίο) μέρος του πυρήνα, αντίστοιχα (Alexander and Crutcher 1990, Lambert et al. 2012, Hamani et al. 2004, Karachi et al. 2005, Parent and Hazrati 1995, Brunenberg et al. 2012, Tan et al. 2006, Sudhyadhom et al. 2007, Stathis et al. 2007). Συνεπώς, ο υποθαλαμικός πυήνας εμπλέκεται ενεργά όχι μόνο στη ρύθμιση της κίνησης, αλλά και την νοητική και συναισθηματική επεξεργασία (Péron et al. 2013, Le Jeune et al. 2010, Benedetti et al. 2004, Greenhouse et al. 2011, Drapier et al. 2008, Baláž et al. 2011, Bockova et al. 2011, Buot et al. 2013, Kopell and Greenberg 2008, Baunez et al. 2011, Burbaud et al. 1994). Ωστόσο, ενδιαφέρον παρουσιάζει το γεγονός ότι οι τρεις αυτοί μηχανισμοί ενδεχομένως να μην λαμβάνουν χώρα κατά έναν τοπογραφικά αυστηρό διαχωριστικό τρόπο, αλλά να δρουν συνεργιστικά στον μικρό όγκο του υποθαλαμικού πυρήνα (Mallet et al. 2007, Hershey et al. 2010, Baláž et al. 2011, Haynes and Haber 2013, Lalys et al. 2013).

Ιδιαίτερη αναφορά θα πρέπει να γίνει στην τοπογραφική οργάνωση των προτύπων της παθολογικής νευρωνικής δραστηριότητας στον υποθαλαμικό πυρήνα ασθενών με ΝΠ. Η επεξεργασία μονοκυτταρικών καταγραφών και καταγραφών δυναμικών τοπικού πεδίου έχει υποδείξει την ύπαρξη αυξημένων εκφορτίσεων ξεσπασμάτων, αυξημένης νευρωνικής δραστηριότητας σχετιζόμενης με την κίνηση, βήτα ταλαντωτικής δραστηριότητας και ταλαντωτικής δραστηριότητας σχετιζόμενης με τον τρόμο, αλλά και παθολογικού συγχρονισμού στο ραχιαίο συγκριτικά με το κοιλιακό μέρος του υποθαλαμικού πυρήνα ασθενών με ΝΠ (Kühn et al. 2005, Weinberger et al. 2006, Seifried et al. 2012, Contarino et al. 2011, Rodriguez-Oroz et al. 2001, Hamani et al. 2004, Guo et al. 2013, Lourens et al. 2013). Σε συμφωνία με αυτή την τοπογραφική οργάνωση, αλλά και το προαναφερόμενο πρότυπο λειτουργικής συνεκτικότητας στον υποθαλαμικό πυρήνα βρίσκεται το γεγονός ότι τα ηλεκτρόδια εν τω βάθει εγκεφαλικής διέγερσης που βρίσκονται τοποθετημένα στο κοιλιακό ή μέσο μέρος του υποθαλαμικού πυρήνα ασθενών με ΝΠ ενδέχεται να βελτιώνουν τα κινητικά συμπτώματα της νόσου, αλλά με το τίμημα της εμφάνισης λεκτικής, νοητικής ή συναισθηματικής βλάβης (Hershey et al. 2010, Astrom et al. 2010, Mikos et al. 2011, Mallet et al. 2007, Paek et al. 2008). Αντιθέτως, το ραχιαιοπλευρικό όριο του υποθαλαμικού πυρήνα

χαρακτηρίζεται σταθερά ως η στερεοτακτική θέση που συσχετίζεται με την μεγαλύτερη βελτίωση στην κλίμακα UPDRS-III (Herzog et al. 2004, Guo et al. 2013, Johnsen et al. 2010, Godihno et al. 2006, Lanotte et al. 2002, Maks et al. 2009, Zaidel et al. 2010), αν και υπάρχουν ακόμη κάποιες ενδείξεις ότι η διέγερση στην περιοχή αυτή μπορεί να επηρεάσει αρνητικά την καταληπτότητα του λόγου (Lalys et al. 2013). Επιπλέον, η διέγερση του πλευρικού μέρους του υποθαλαμικού πυρήνα έχει συσχετιστεί με μία χαμηλότερη θεραπευτική επίδραση στη βραδυκινησία συγκριτικά με τη δυσκαμψία (Cooper et al. 2011), ένα φαινόμενο που κατά πάσα πιθανότητα προκαλείται από την ενεργοποίηση νηματίων της πυραμιδικής ζώνης στην προσκείμενη έσω κάψα (Xu e al. 2011). Η προκαλούμενη από τη διέγερση ενεργοποίηση νηματίων της πυραμιδικής ζώνης έχει αναφερθεί ότι προκαλεί κρανιακές κινητικές συσπάσεις που αποτελούν μία από τις πιο κοινές παρενέργειες που παρατηρούνται κατά τη διάρκεια της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για ΝΠ (Tommasi et al. 2008, 2012).

Η αποσαφήνιση του μηχανισμού που συσχετίζεται με την κλινικά αποτελεσματική εν τω βάθει εγκεφαλική διέγερση είναι κρίσιμης σημασίας για τη βαθύτερη κατανόηση του λειτουργικού υποβάθρου αυτής της τεχνολογίας και τον καθορισμό του πλήρους θεραπευτικού της δυναμικού, που ενδέχεται εν συνεχεία να ευνοήσουν την ανάπτυξη και εξέλιξη πρωτότυπων και κλινικά πιο αποτελεσματικών προτύπων διέγερσης. Παραλλαγές στην προσέγγιση που χρησιμοποιείται (απεικόνιση, νευροφυσιολογία, μικροδιάλυση), στο είδος (με χρήση του συμβατικού ηλεκτροδίου εν τω βάθει εγκεφαλικής διέγερσης έναντι χρήσης ενός μικροηλεκτροδίου ή του βοηθητικού αγωγού ως ενεργού ηλεκτροδίου) και τις παραμέτρους της διέγερσης ή τη λανθάνουσα περίοδο (μικρή έναντι μεγάλης) των παρατηρούμενων επιδράσεων αποτελούν τους κύριους παράγοντες αναφοράς σχετικά αντικρουόμενων υποθετικών μηχανισμών δράσης της εν τω βάθει εγκεφαλικής διέγερσης (Lozano and Lipsman 2013). Η υπόθεση της ‘λειτουργικής τρώσεως’, δηλ. η υπόθεση ότι η διέγερση αδρανοποιεί τους παθολογικά υπερδραστήριους νευρώνες, προέκυψε από την παρατήρηση μιας συγκρίσιμης επίδρασης της διέγερσης με την επίδραση της εκτομής στο θάλαμο, τον υποθαλαμικό πυρήνα ή την έσω ωχρά σφαίρα (Benabid et al. 2000, Benazzouz et al. 1995, Beurrier et al. 2001). Η αρχική αυτή υπόθεση υποστηρίχθηκε εν συνεχεία από πιο πρόσφατες μελέτες βασιζόμενες μεθοδολογικά στη διεγχειρητική καταγραφή της νευρωνικής δραστηριότητας και την ταυτόχρονη εφαρμογή της διέγερσης υψηλής συχνότητας (Welter et al. 2004, Meissner et al. 2005, Filali et al. 2004, Toleikis et al. 2012). Σε γενικές γραμμές, η αναστολή της δραστηριότητας των στοχευμένων νευρώνων του υποθαλαμικού πυρήνα ή της έσω ωχράς σφαίρας μπορεί να οφείλεται σε αποπολωτικό αποκλεισμό (επιδράσεις Na, K), συναπτική ανεπάρκεια, εξάντληση των διεγερτικών νευροδιαβιβαστικών ουσιών (γλουταμινικού οξέος), υπερπόλωση των νευρωνικών κυτταρικών σωμάτων και δενδριτών, απελευθέρωση των

ανασταλτικών νευροδιαβιβαστικών ουσιών (γάμμα-αμινοβουτυρικού οξέως,αδενοσίνης) ή σε συναπτική αναστολή των προσαγωγών προβολών (Lozano and Lipsman 2013). Από την άλλη πλευρά, πειραματικές μελέτες και μελέτες υπολογιστικής μοντελοποίησης και λειτουργικής απεικόνισης έχουν υποδείξει μία πρωταρχικά διεγερτική επίδραση της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα στη δραστηριότητα του στοχευμένου πυρήνα (Garcia et al. 2005, Hilker et al. 2008, Garraux et al. 2011, Novak et al. 2009, So et al. 2012) ή, σε σημαντικότερο βαθμό, μία διαχωριστική δράση της διέγερσης στη σωματική και αξονική δραστηριότητα, δηλ. σωματική αναστολή και αδρανοποίηση των προσαγωγών, και αξονική διέγερση και δραστηριοποίηση των απαγωγών (McIntyre and Grill 2000, 2002, McIntyre et al. 2004 (a),(b),(c), McIntyre and Hahn 2010, Vitek 2002, Deniau et al. 2010, Johnson et al. 2013, Kringelbach et al. 2007, Grill and McIntyre 2001). Σε επίπεδο δικτύων νηματίων έχουν πλέον καταγραφεί ευρέως η αντιδρομική ενεργοποίηση ή οι συναπτικές επιδράσεις σε νευρωνικές δομές συνδεδεμένες στον υποθαλαμικό πυρήνα, συμπεριλαμβανομένης της συμπαγούς και δικτυωτής μοίρας της μέλαινας ουσίας, της ωχράς σφαίρας, του ετερόπλευρου υποθαλαμικού πυρήνα, του σκελογεφυρικού πυρήνα, του εγκεφαλικού φλοιού, του θαλάμου και του άνω διδυμίου (Burbaud et al. 1994, Benazzouz et al. 1995, 2000, Windels et al. 2005, Maurice et al. 2003, Tai et al. 2003, Degos et al. 2005, Shi et al. 2006, Maltete et al. 2007, Hashimoto et al. 2003, Dorval et al. 2010, Hahn et al. 2008, Hahn and McIntyre 2010, Hilker et al. 2008, 2004, Reese et al. 2008, 2011, Meissner et al. 2002, Lee et al. 2004, 2006 , Li et al. 2012, Gubellini et al.2006, Novak et al. 2009, Florio et al. 2007, Jech et al. 2006, Li et al. 2006, Pötter-Nerger et al. 2008, Eusebio et al. 2009, Kuriakose et al. 2010, Lehmkuhle et al. 2009, Xu et al. 2008, Bressand et al. 2002, Garraux et al. 2011, Geday et al. 2009, Guo et al. 2008, Moran et al. 2012, Rubin and Terman 2004, Santaniello et al. 2010, Sotiropoulos and Steinmetz 2007, Volonte et al. 2012, Walker et al. 2011, Whitmer et al. 2012, Zheng et al. 2011, Lafreniere-Roula et al. 2012).

Με βάση τα παραπάνω, η συνδυαστική επίδραση της διέγερσης σε υποκυτταρικό/νευρωνικό επίπεδο ή επίπεδο δικτύων νηματίων (συναπτική αναστολή, συναπτική και αντιδρομική διέγερση) ενδεχομένως να αποτελεί τη βάση της παρατηρούμενης τροποποίησης των παθοφυσιολογικών προτύπων της νευρωνικής δραστηριότητας τόσο στον διεγερμένο πυρήνα, όσο και στο κύκλωμα βασικά γάγγλια-θάλαμος-φλοιός (McIntyre and Hahn 2010, Grill et al. 2004, Montgomery and Gale 2008, Rosenbaum et al. 2014, Carlson et al. 2010, Deniau et al. 2010). Συγκεκριμένα, ο μηχανισμός δράσης της εν τω βάθει εγκεφαλικής διέγερσης για ΝΠ, μπορεί να αποδοθεί πρωταρχικά στην κανονικοποίηση των προτύπων νευρωνικών εκφορτίσεων και τη δημιουργία μίας ‘πληροφοριακής τρώσεως’ στην περιοχή του διεγερμένου πυρήνα (McConnell et al. 2012, Santaniello et al. 2015, Grill et al. 2004), ενώ υπάρχουν ακόμη ενδείξεις που δίνουν έμφαση στην ανασταλτική δράση της διέγερσης στην μη ομαλή νευρωνική

δραστηριότητα του φλοιού (de Hemptinne 2015). Αξίζει να σημειωθεί, ότι χρησιμοποιώντας τις συμβατικές κλινικές παραμέτρους διέγερσης, οι Carlson et al. (2010) παρατήρησαν ότι ένα υποσύνολο νευρώνων του υποθαλαμικού πυρήνα, που εκδήλωνε αρχικά εκφορτίσεις ξεσπασμάτων ή τονικές εκφορτίσεις, παρουσίασε μετά τη διέγερση ένα τυχαίο πρότυπο εκφορτίσεων. Το αποτέλεσμα αυτό συνδέεται στενά με τις παρατηρούμενες μεταβολές στο πρότυπο νευρωνικών εκφορτίσεων του υποθαλαμικού πυρήνα μετά την εν τω βάθει εγκεφαλική διέγερση του ετερόπλευρου πυρήνα (Walker et al. 2011), την αναφερθείσα αποσυγχρονιστική δράση της συμβατικής διέγερσης υψηλής συχνότητας (Hauptmann et al. 2007, Rubin et al. 2012), αλλά και με την υπόδειξη ότι η εν τω βάθει εγκεφαλική διέγερση του υποθαλαμικού πυρήνα τροποποιεί τα παθολογικά πρότυπα συγχρονισμένων ταλαντώσεων στον υποθαλαμικό πυρήνα (Bronte-Stewart et al. 2009, Eusebio et al. 2011, 2012, Meissner et al. 2002, Whitmer et al. 2012, Wingeier et al. 2006), επιδρώντας με τον τρόπο αυτό στο κινητικό αποτέλεσμα (Kuhn et al. 2008). Ακόμη πιο σημαντικό είναι το γεγονός ότι κλινικές μελέτες και μελέτες υπολογιστικής μοντελοποίησης υποδεικνύουν ότι τα *χρονικά εναλλακτικά πρότυπα διέγερσης* ενέχουν τη δυνατότητα να οδηγήσουν τη νευρωνική δυναμική των βασικών γαγγλίων πίσω στη φυσιολογική *αποσυγχρονισμένη κατάσταση* (Feng et al. 2007(a),(b), Adamchic et al. 2014). Εν τω μεταξύ, όπως έχει αναφερθεί, μία ενδεχόμενη νοσοτροποποιητική και νευροπροστατευτική δράση της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα (Temel et al. 2006 (b), Harnack et al. 2008, Wallace et al. 2007, Spieles-Engemann et al. 2010, deSouza et al. 2013, Albanese and Romito 2011, Shon et al. 2010, Van Gompel et al. 2010, Grahn et al. 2014) βρίσκεται επί του παρόντος υπό έρευνα από μία αναμενόμενη κλινική δοκιμή (Kahn et al. 2012).

Αναφορικά με τους μηχανισμούς που συσχετίζονται με τις νευροψυχιατρικές παρενέργειες της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα, οι υποθέσεις ποικίλουν σε μεγάλο βαθμό. Υπάρχουν στοιχεία που υποδεικνύουν τη μεταβολή της επεξεργασίας συναισθηματικής πληροφορίας ως έναν υποθάλπτοντα μηχανισμό της διέγερσης που οδηγεί σε διαταραχές συμπεριφοράς. Αυτή η μεταβολή μπορεί να ποσοτικοποιηθεί μέσω του σχετιζόμενου με γεγονότα αποσυγχρονισμού της υποθαλαμικής άλφα δραστηριότητας (Brücke et al. 2007, Huebl et al. 2011). Άλλες μελέτες έχουν τονίσει την προκαλούμενη από τη διέγερση αποσταθεροποίηση του συστήματος 5-υδροξυτρυπταμίνης ως παράγοντα εμφάνισης ψυχιατρικών παρενεργειών (Hartung et al. 2011, Tan et al. 2012 (a), (b)). Μία διαφορετική αλλά εξίσου εύλογη άποψη είναι ότι η διαρροή ρεύματος προς μη κινητικά δίκτυα εντός και περί του υποθαλαμικού πυρήνα μπορεί να είναι υπεύθυνη για μία ενδεχόμενη διανοητική και συναισθηματική βλάβη μετά την αμφίπλευρη εν τω βάθει εγκεφαλική διέγερση του υποθαλαμικού πυρήνα (Frankemolle et al. 2010, Alberts et al. 2010, Hershey et al. 2010, Mallet

et al. 2007, Daniels et al. 2012). Στην ίδια αιτία μπορεί να αποδοθεί η προκαλούμενη από τη διέγερση επιδείνωση της καταληπτότητας της ομιλίας (Mikos et al. 2011).

Όπως έχει αναφερθεί, στο πλαίσιο της μικροηλεκτροδιακής χαρτογράφησης, έχουν ερευνηθεί και προταθεί εκτενώς αυτοματοποιημένες μέθοδοι που παρέχουν αυξημένη αντικειμενικότητα και μειώνουν τη συνολική διάρκεια της επέμβασης (Falkenberg et al 2006, Danish et al 2008, Zaidel et al 2009, Wong et al 2009, Novak et al 2011, Cagnan et al 2011, Pinzon-Morales et al 2011). Συγκεκριμένα, έχει αξιολογηθεί η συνδυαστική εφαρμογή ποσοτικών χαρακτηριστικών σχετιζόμενων με τα δυναμικά τοπικού πεδίου και/ή το υψίσυχνο σήμα (δηλ. την υψίσυχνη δραστηριότητα του υποβάθρου ή τη δραστηριότητα των δυναμικών ενέργειας). Αν και οι προσεγγίσεις πολλαπλών χαρακτηριστικών παρέχουν αυξημένη ακρίβεια και αξιοπιστία για τη στόχευση του υποθαλαμικού πυρήνα, η χρήση ενός μοναδικού εύρωστου βιοδείκτη θα απλοποιούσε σημαντικά και θα επιτάχυνε τη διεγχειρητική ανίχνευση του πυρήνα. Επιπλέον, μία συμπληρωματική προσέγγιση με βάση έναν μοναδικό βιοδείκτη εφαρμόσιμη στη διαδικασία της διεγχειρητικής διέγερσης θα οδηγούσε σε σημαντική βελτίωση ολόκληρης της ηλεκτροφυσιολογικής διαδικασίας, βελτιστοποιώντας την κλινική απόφαση και μειώνοντας τη συνολική διάρκεια της επέμβασης.

Υπάρχουν αυξανόμενες ενδείξεις συσχέτισης του υποθαλαμικού ταλαντωτικού συγχρονισμού με την κλινική αναπηρία στη ΝΠ (Kühn et al 2009, Pogosyan et al 2010), και, αντιστρόφως, όπως προαναφέρθηκε, ενδείξεις συσχέτισης του αποσυγχρονισμού της νευρωνικής δραστηριότητας με το μηχανισμό δράσης της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα (Carlson et al 2010, Walker et al 2011, Hauptmann et al 2007, Modolo and Beuter 2009, Wilson et al 2011, Johnson et al 2013). Με βάση τις ενδείξεις αυτές, ο κύριος στόχος του 4^{ου} κεφαλαίου της διατριβής ήταν η αξιολόγηση συλλογικών δυναμικών ιδιοτήτων και ιδιοτήτων απόκρισης της υποθαλαμικής ταλαντωτικής δραστηριότητας ως κρίσιμων χαρακτηριστικών γνωρισμάτων για την επιλογή της βέλτιστης θέσης εμφύτευσης του ηλεκτροδίου διέγερσης στη ΝΠ. Ειδικότερα, επιχειρήθηκε ο προσδιορισμός της εφαρμοσιμότητας δύο συμπληρωματικών προσεγγίσεων βασιζόμενων σε μοναδικό βιοδείκτη στο πλαίσιο των πρωταρχικών τεχνικών χαρτογράφησης που χρησιμοποιούνται κατά κόρον διεγχειρητικά: των μικροηλεκτροδιακών καταγραφών και της εξέτασης της μακροδιέγερσης. Οι προσεγγίσεις βασίστηκαν σε μεθόδους στοχαστικής μη-γραμμικής δυναμικής. Αναλυτικά, με βάση τις μικροηλεκτροδιακές καταγραφές ανακτημένες κατά τη διάρκεια 10 χειρουργικών επεμβάσεων, προσδιορίστηκε αρχικά ένας δείκτης πολυμεταβλητού συγχρονισμού φάσης (Carmeli et al 2005, Allefeld et al 2007, Polychronaki 2011) ως ένα συνδυαστικό μέτρο τοπικού και χωρικά εκτεταμένου ταλαντωτικού συγχρονισμού (Moran and Bar-Gad 2010), διατηρώντας την ευαισθησία στο θόρυβο μέτρησης στο ελάχιστο (Rossberg et al 2004, Sun et al 2008). Ο

προτεινόμενος δείκτης εφαρμόστηκε με στόχο των προσδιορισμό των αποδεκτών μικροηλεκτροδιακών τροχιών, δηλ. των τροχιών στις οποίες θα μπορούσε σε δεύτερη φάση να εφαρμοστεί μακροδιέγερση (Marceglia et al 2010). Αυτό το χαρακτηριστικό χρησιμοποιήθηκε στη συνέχεια ως μία συστατική παράμετρος ενός *στοχαστικού φασικού μοντέλου* το οποίο προσαρμόστηκε κατάλληλα σε προεπιλεγμένες μικροηλεκτροδιακές καταγραφές. Με βάση το μοντέλο αυτό, προσδιορίστηκε ο εκθέτης Lyapunov (Pikovsky et al 2001), ως μία ποσότητα που αντικατοπτρίζει τη δυναμική υποθαλαμικού συγχρονισμού σε απόκριση περιοδικών παλμών διέγερσης (130Hz), και αξιολογήθηκε η προβλεπτική του ικανότητα στον προσδιορισμό των θέσεων όπου η διέγερση απέφερε το καλύτερο κλινικό αποτέλεσμα. Στη θεωρία της μη γραμμικής δυναμικής, ο εκθέτης Lyapunov χαρακτηρίζει τις ιδιότητες απόκλισης/σύγκλισης δύο κοντινών τροχιών στο χώρο των φάσεων (Pikovsky et al 2001). Θετικές τιμές του εκθέτη Lyapunov υποδηλώνουν αποσυγχρονισμό. Μέσω του στοχαστικού φασικού μοντέλου προσομοιώθηκε η παρουσία τόσο του ενδογενούς όσο και του εξωγενούς θορύβου. Η αυτοματοποιημένη μεθοδολογία αξιολογήθηκε με βάση τις κλινικές αποφάσεις που λήφθηκαν διεγχειρητικά από ειδήμονες.

Τα αποτελέσματα της ανάλυσης αυτής υπέδειξαν την υψηλή διακριτική ικανότητα του δείκτη πολυμεταβλητού συγχρονισμού φάσης στο πλαίσιο της διαδικασίας εντοπισμού του υποθαλαμικού πυρήνα, δηλ. του πρώτου μέρους της ηλεκτροφυσιολογικής παρακολούθησης. Η εφαρμογή ενός κατάλληλου μιγαδικού φίλτρου στα συνθετικά στοιχεία των καταγραφόμενων σημάτων (Rossberg et al 2004) σε συνδυασμό με τη μέθοδο εκτίμησης φάσης βασιζόμενης στη γειτονιά (Sun et al 2008) διασφάλισαν αξιοσημείωτη σταθερότητα της εξέλιξης του δείκτη εντός του υποθαλαμικού πυρήνα έναντι της παρουσίας θορύβου. Δεύτερον, το προτεινόμενο στοχαστικό μοντέλο αναπαρήγαγε επιτυχώς την υποτιθέμενη αποσυγχρονιστική δράση της περιοδικής διέγερσης. Το γεγονός αυτό επικυρώθηκε τόσο μέσω του μέτρου της *αμετάβλητης πυκνότητας*, δηλ. της κατανομής φάσης σταθερής κατάστασης, όσο και του εκθέτη Lyapunov υπολογιζόμενων βάσει του στοχαστικού φασικού χάρτη. Υπάρχουν δύο πρωταρχικοί λόγοι που μπορεί να οδήγησαν σε αυτό το αποτέλεσμα. Πρώτον, η επιλογή μίας καμπύλης απόκρισης φάσης τύπου II ως συνάρτησης φασικής ευαισθησίας στον κοινό (εξωγενή) θόρυβο (Abouzeid and Ermentrout 2009), διασφάλισε σε μεγάλο βαθμό την ικανότητα του μοντέλου να προσομοιώνει την παθολογική κατάσταση νευρωνικού συγχρονισμού απουσία διέγερσης, αποδίδοντας αρνητικό εκθέτη Lyapunov. Αντιθέτως, μία καμπύλη απόκρισης φάσης τύπου I θα συσχετιζόταν με τη φυσιολογική αποσυγχρονισμένη κατάσταση (Farries and Wilson 2012). Δεύτερον, η εφαρμογή μιας καμπύλης απόκρισης φάσης τύπου 0, που ενδεχομένως να είναι βέλτιστη για στοχαστικό αποσυγχρονισμό (Hata et al 2011), συνεισέφερε στην προσομοίωση ενός από τους υποθετικούς μηχανισμούς δράσης της διέγερσης υψηλής συχνότητας. Εν τέλει,

βάσει των προτεινόμενων προσομοιώσεων, ένας νευροχειρουργός ενδεχομένως να είναι σε θέση να καθορίσει τις βέλτιστες θέσεις διέγερσης με αυξημένο δείκτη ευαισθησίας.

Το προτεινόμενο φασικό μοντέλο αναπτύχθηκε ενσωματώνοντας πολλαπλούς παράγοντες που επιδρούν στη νευρωνική δυναμική: νευρωνική ζεύξη, πηγές ενδογενούς ανεξάρτητου και εξωγενούς κοινού θορύβου, και περιοδική διέγερση. Μία συνέπεια αυτού του γεγονότος είναι ότι ο εξαγόμενος εκθέτης Lyapunov συσχετίστηκε συνδυαστικά με το σύνολο των αντίστοιχων παραμέτρων και δεν καθορίστηκε μοναδικά από τον δείκτη πολυμεταβλητού συγχρονισμού φάσης που ποσοτικοποιεί τη νευρωνική ζεύξη. Μερικές προηγούμενες μελέτες (Tass et al 2006, Nabi et al 2013) έχουν προτείνει παρόμοια μοντέλα στο πλαίσιο της αποσυγχρονιστικής διέγερσης, ενσωματώνοντας ωστόσο μόνο την επίδραση του ενδογενούς θορύβου και παραβλέποντας τις πηγές εξωγενούς θορύβου (Teramae and Tanaka 2004). Επιπλέον, τα μοντέλα αυτά δε συνεκτίμησαν τη φασική εξάρτηση του θορύβου (Ermentrout and Saunders 2006) και κατά συνέπεια η επίδραση του θορύβου δεν ήταν απαραίτητα πολλαπλασιαστική (Ly and Ermentrout 2011). Ιδιαίτερης σημασίας είναι επίσης το γεγονός ότι, στην παρούσα ανάλυση, ο κοινός θόρυβος θεωρήθηκε έγχρωμος, δηλ. ως μία διαδικασία Ornstein-Uhlenbeck με συγκεκριμένο χρόνο συσχέτισης (Galán 2009). Για το λόγο αυτό, κατέστη απαραίτητος ένας μετασχηματισμός του αρχικού φασικού μοντέλου σε εξίσωση λευκού θορύβου Langevin εισάγοντας τους συντελεστές πραγματικής ολίσθησης και διάχυσης (Nakao et al 2010).

Στο 5^{ο} κεφάλαιο της διατριβής επιχειρείται η αξιολόγηση της αποτελεσματικότητας εναλλακτικών προτύπων εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για ΝΠ και ανθεκτική στη θεραπεία ΙΨΔ. Γίνεται πλέον αυξανόμενα αποδεκτό το γεγονός ότι η εφαρμογή χρονικά εναλλακτικών προτύπων διέγερσης μπορεί ενδεχομένως να οδηγήσει σε έναν πιο αποτελεσματικό έλεγχο των συμπτωμάτων, μειωμένες παρενέργειες, και χαμηλότερες ενεργειακές απαιτήσεις (Sarem-Aslani and Mullet 2011, Gross et al. 2013, Hess et al. 2013). Πράγματι, υπάρχουν αυξανόμενες πειραματικές αποδείξεις που υποδεικνύουν μία ισοδύναμη ή ακόμη βελτιωμένη κλινική αποτελεσματικότητα συγκεκριμένων χαρακτηριστικών χρονικά μη ομαλών προτύπων σε σύγκριση με ομαλά πρότυπα διέγερσης. Συγκεκριμένα, η χρονικά μη-ομαλή εν τω βάθει εγκεφαλική διέγερση του θαλάμου έχει αναφερθεί ότι περιορίζει τον τρόμο εξίσου αποτελεσματικά με την ομαλή διέγερση, στην περίπτωση που δεν υπάρχουν μακρές παύσεις (Birdno et al. 2012, Swan et al. 2013). Αντιθέτως, οι Kuncel et al. (2012) έχουν αναφέρει ότι η θαλαμική διέγερση που χαρακτηρίζεται από παύσεις μέγιστης διάρκειας 40% του συνολικού χρόνου παροχής ενδεχομένως να είναι εξίσου αποτελεσματική με την ομαλή διέγερση στη μείωση του τρόμου. Πολύ ενδιαφέρον είναι επίσης το γεγονός ότι η μη ομαλή εν τω βάθει εγκεφαλική διέγερση υψηλής συχνότητας του υποθαλαμικού πυρήνα, αν όχι εξαιρετικά ανώμαλη, απαλύνει τη βραδυκινησία στη ΝΠ πιο αποτελεσματικά από την ομαλή

διέγερση (Brocker et al. 2013, Swan et al. 2013). Επιπλέον, κλινικές μελέτες που αξιολογούν την αποτελεσματικότητα της υψίσυχνης ($\geq$ 130 Hz) έναντι της χαμηλόσυχνης ($\leq$ 80 Hz) εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για ΝΠ υποδεικνύουν μία μάλλον παρόμοια ή εξειδικευμένη κατ'ασθενή επίδραση της χαμηλόσυχνης διέγερσης σε σύγκριση με την υψίσυχνη διέγερση, όσον αφορά στα αξονικά συμπτώματα (Sidiropoulos et al. 2013, Vallabhajosula et al. 2014, Ricchi et al. 2012), τις ακούσιες κινήσεις (Merola et al. 2013) ή τη γενικότερη κινητική λειτουργία (Tsang et al. 2012, Khoo et al. 2014).

Οι κατάλληλα σχεδιασμένες κυματομορφές ενδεχομένως να είναι πλεονεκτικότερες σε σύγκριση με τον παραδοσιακό τετραγωνικό παλμό όσον αφορά τόσο στην κλινική αποτελεσματικότητα όσο και στην κατανάλωση ενέργειας (Foutz and McIntyre 2010, Hofmann et al. 2011, Wongsarnpigoon and Grill 2010). Επίσης, ο ένθετος προγραμματισμός με δύο διακριτά πλάτη διέγερσης ενδεχομένως να βελτιστοποιεί το κλινικό αποτέλεσμα της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για ΝΠ (Wojtecki et al. 2011). Τέλος, το πρωτόκολλο της 'διέγερσης συντονισμένης επαναφοράς' αποτελεί μία ριζική απόκλιση από τα συμβατικά πρότυπα εν τω βάθει εγκεφαλικής διέγερσης και έχει σχεδιαστεί με στόχο την πρόκληση ισχυρού νευρωνικού αποσυγχρονισμού και μακροπρόθεσμης τροποποίησης της συναπτικής πλαστικότητας (Tass 2003, Tass et al. 2006, 2012, Tass and Hauptmann 2007, 2009, Tass and Majtanik 2006, Hauptmann et al. 2009, Hauptmann and Tass 2007, 2009, 2010, Hauptmann et al. 2007, Lucken et al. 2013, Lysyansky et al. 2011 (a), (b), Popovych and Tass 2012). Η ενδεχόμενη αποτελεσματικότητα αυτού του παραδείγματος νευροτροποποίησης, που αποσπά αυξανόμενη προσοχή στο πεδίο της εν τω βάθει εγκεφαλικής διέγερσης τα τελευταία χρόνια (Rubin et al. 2012, DeLong and Wichmann 2012, McIntyre et al. 2014, Lourens et al. 2015), έχει υποδειχθεί από δύο μελέτες 'απόδειξης της ορθότητας της αρχής' (Tass et al. 2012, Adamchic et al. 2014).

Δεδομένου του γεγονότος ότι τα χρονικά εναλλακτικά πρότυπα διέγερσης ενδεχομένως να αποτελέσουν τον πυρήνα εφαρμογών εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου (Feng et al. 2007 (b), Wilson and Moehlis 2014), οι οποίες έχουν αποδειχθεί αποδοτικότερες στη θεραπεία του παρκινσονισμού (Rosin et al. 2011), περαιτέρω έρευνες φαίνεται να είναι απαραίτητες για τον καθορισμό των ιδιαίτερων χαρακτηριστικών που καθιστούν αυτά τα πρότυπα αποτελεσματικά στην αντιμετώπιση κινητικών και νευροψυχιατρικών διαταραχών. Χτίζοντας πάνω στην υπόθεση ότι τα συμβατικά και χρονικά εναλλακτικά πρότυπα διέγερσης ασκούν την τοπικού επιπέδου επίδρασή τους μέσω του αποσυγχρονισμού της υποθαλαμικής νευρωνικής δραστηριότητας , στη μελέτη του 5^{ου} κεφαλαίου, χρησιμοποιούνται μέθοδοι στοχαστικής μη γραμμικής δυναμικής (Gardiner 1985, Kuramoto 1984, Winfree 2001, Pikovsky et al. 2001) και δύο σύνολα δεδομένων μικροηλεκτροδιακών καταγραφών για το

συγκριτικό προσδιορισμό της αποσυγχρονιστικής επίδρασης της συμβατικής (ομαλής στα 130Hz) έναντι έντεκα χρονικά εναλλακτικών προτύπων εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για ΝΠ και ΙΨΔ, και για τον περαιτέρω καθορισμό των συγκεκριμένων χαρακτηριστικών των προτύπων που συσχετίζονται με μία σημαντικά ισχυρότερη αποσυγχρονιστική επίδραση. Συγκεκριμένα, με βάση το στοχαστικό φασικό μοντέλο που αναπτύχθηκε στο 4^{ο} κεφάλαιο, το οποίο περιγράφει ένα σύνολο ολικά συζευγμένων χαοτικών ταλαντωτών οδηγούμενων από κοινό, ανεξάρτητο θόρυβο και εξωτερική επίδραση, εκτιμάται για ένα σύνολο 2x96 μικροηλεκτροδιακών καταγραφών (κάθε υποσύνολο δεδομένων ανακτήθηκε κατά τη διάρκεια εν τω βάθει εγκεφαλικής διέγερσης για ΝΠ και ΙΨΔ, αντιστοίχως) η αμετάβλητη πυκνότητα (φασική κατανομή σταθερής κατάστασης) (Hata et al. 2010, Yamanobe 2011), ως μία ποσότητα που στην παρούσα μελέτη αντικατοπτρίζει την αποσυγχρονιστική δράση των εφαρμοζόμενων προτύπων διέγερσης στην υποθαλαμική νευρωνική δραστηριότητα. Επικυρώνεται η ευρωστία του μέτρου αυτού στη διάκριση σεναρίων αποσυγχρονισμού μέσω συγκρίσεων με μία εναλλακτική μεταβλητή, τον εκθέτη Lyapunov, και παρέχονται ενδείξεις για την ενδεχόμενη συσχέτισή του με την κλνικά αποτελεσματική διέγερση. Στο ίδιο πλαίσιο, εισάγονται συγκεκριμένες τροποποιήσεις αναφορικά με τη συλλογική δυναμική, τις παραμέτρους και τις συναρτήσεις του μοντέλου, οι οποίες αυξάνουν σημαντικά την ευαισθησία του. Για την εγκυρότητα της προσέγγισης, παρέχονται σημαντικά έμμεσα αποδεικτικά στοιχεία.

Τα πρότυπα διέγερσης σχεδιάζονται με στόχο το συγκριτικό προσδιορισμό της αποσυγχρονιστικής δράσης της διέγερσης με μεταβαλλόμενα χρονικά χαρακτηριστικά συμπεριλαμβανομένων της συχνότητας διέγερσης και της χρονικής ομαλότητας. Αντιστοίχως, τα χρονικά εναλλακτικά πρότυπα διέγερσης περιλαμβάνουν είτε υψίσυχνες (130Hz) μη ομαλές είτε χαμηλόσυχνες (80Hz), ομαλές ή μη ομαλές, χρονοσειρές. Στο ίδιο πλαίσιο, επιχειρείται ο καθορισμός των συγκεκριμένων χαρακτηριστικών των προτύπων μη ομαλής διέγερσης σχετιζόμενων με μία σημαντικά ισχυρότερη αποσυγχρονιστική επίδραση: η ανωμαλία αυτή καθ'αυτή, οι μακρές παύσεις ή τα ξεσπάσματα. Αντιστοίχως, τα μη ομαλά πρότυπα παράγονται είτε από μία διαδικασία γάμμα με αυξανόμενους βαθμούς χρονικής μεταβλητότητας (Dorval et al. 2010) είτε αποτελούνται από παλμούς σταθερού ρυθμού διακεκομμένους από μακρές πάυσεις (Kuncel et al. 2012) ή από ξεσπάσματα παλμών (Birdno et al. 2012, Brocker et al. 2013). Η αποσυγχρονιστική δράση των εξεταζόμενων προτύπων διέγερσης προσδιορίζεται περαιτέρω σε θέσεις ταλαντωτικής δραστηριότητας στη ραχιαιοπλευρική αισθητηριοκινητική περιοχή έναντι θέσεων μη ταλαντωτικής δραστηριότητας στη μεσοκοιλιακή μεταιχμιακή περιοχή του υποθαλαμικού πυρήνα ασθενών με ΝΠ.

Τα συγκεντρωτικά αποτελέσματα της προαναφερθείσας ανάλυσης παρέχουν σημαντικές πληροφορίες σχετικά με την ανάπτυξη θεραπευτικά και ενεργειακά αποδοτικών συστημάτων εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου. Συγκεκριμένα, δίνεται έμφαση στην ανώτερη αποτελεσματικότητα των υψίσυχνων (130Hz) και χαμηλόσυχνων (80Hz) μη ομαλών προτύπων διέγερσης, και της χαμηλόσυχνης περιοδικής διέγερσης διακεκομμένης από ξεσπάσματα παλμών, συγκριτικά με την συμβατική διέγερση (ομαλή, 130Hz) και με συγκεκριμένα εναλλακτικά πρότυπα, συμπεριλαμβανομένης της υψίσυχνης και χαμηλόσυχνης διέγερσης διακεκομμένης από μακρές παύσεις, της χαμηλόσυχνης περιοδικής διέγερσης και της υψίσυχνης διέγερσης διακεκομμένης από ξεσπάσματα παλμών. Ιδιαίτερα σημαντικό είναι το γεγονός ότι αυτό το συγκεκριμένο αποτέλεσμα ήταν ανεξάρτητο της υποκείμενης διαταραχής (ΝΠ/ΙΨΔ), ενώ η ανώτερη αποτελεσματικότητα των ανώμαλων προτύπων διέγερσης ήταν επιπλέον ανεξάρτητη της υποκείμενης νευρωνικής δραστηριότητας. Σε συνέπεια με τα αποτελέσματα αυτά, οι Birdno *et al.* (2012) και Brocker *et al.* (2013) υπέδειξαν ότι ούτε τα ξεσπάσματα ούτε η μη ομαλότητα αυτή καθεαυτή σχετίζονται με μειωμένη κλινική αποτελεσματικότητα της υψίσυχνης θαλαμικής και υποθαλαμικής εν τω βάθει εγκεφαλικής διέγερσης για ιδιοπαθή τρόμο και προχωρημένο στάδιο της ΝΠ, αντιστοίχως. Επιπρόσθετα, σε μία σύντομη κοινοποίηση, οι Baker *et al.* (2011) υπογράμμισαν την αποτελεσματικότητα της χαμηλόσυχνης (80Hz) ωχροσφαιρικής διέγερσης μεταδιδόμενης κατ'ακολουθία ενός ομαλού προτύπου με ξεσπάσματα στον περιορισμό της βραδυκινησίας στο μη ανθρώπινο θηλαστικό μοντέλο της ΝΠ. Η ανάλυση του 5^{ου} κεφαλαίου της διατριβής συμπληρώνει τις προαναφερόμενες μελέτες επεκτείνοντας την εγκυρότητά τους στην περίπτωση της χαμηλόσυχνης υποθαλαμικής εν τω βάθει εγκεφαλική διέγερση για προχωρημένο στάδιο της ΝΠ και παρέχοντας ενδείξεις για την αποτελεσματικότητα εναλλακτικών προτύπων υποθαλαμικής εν τω βάθει εγκεφαλικής διέγερσης για ανθεκτική στη θεραπεία ΙΨΔ. Ιδιαίτερα ενδιαφέρον είναι το γεγονός ότι η αποσυγχρονιστική δράση των εξεταζόμενων προτύπων διέγερσης στη ΝΠ αποδείχθηκε βέλτιστη στην ραχιαιοπλευρική ταλαντωτική περιοχή του υποθαλαμικού πυρήνα και ότι ενδεχομένως το πρωταρχικό μέτρο έκβασης διεξαγόμενο από το προτεινόμενο μοντέλο, δηλ. το μέτρο της αμετάβλητης πυκνότητας, να συσχετίζεται με την κλινική αποτελεσματικότητα της διέγερσης.

Σε αντίθεση με τους Brocker *et al.* (2013) και Kuncel *et al.* (2012), οι Birdno *et al.* (2012) ανέφεραν ότι η υψίσυχνη, χαρακτηριζόμενη από παύσεις διέγερση είναι σημαντικά λιγότερο αποτελεσματική από την ομαλή διέγερση για τον περιορισμό του τρόμου. Η υπόδειξη αυτή επικυρώνεται και επεκτείνεται μέσω της ανάλυσης του 5^{ου} κεφαλαίου, σύμφωνα με την οποία τόσο η υψίσυχνη όσο και η χαμηλόσυχνη διακεκομμένη από μακρές παύσεις διέγερση συσχετίστηκαν με μία ασθενέστερη αποσυγχρονιστική επίδραση σε σύγκριση με τη συμβατική διέγερση στη ΝΠ. Ωστόσο, στην περίπτωση της ΙΨΔ δεν προέκυψε παρόμοιο συμπέρασμα.

Συγκεκριμένα, η χαρακτηριζόμενη από παύσεις διέγερση αποδείχθηκε να ασκεί μία σημαντικά ισχυρότερη επίδραση στη νευρωνική δραστηριότητα συγκριτικά με τη συμβατική εν τω βάθει εγκεφαλική διέγερση για ΙΨΔ, ιδιαίτερα αν μεταδίδεται σε χαμηλή συχνότητα. Πολύ ενδιαφέρον είναι το γεγονός ότι πρόσφατα οι Gazit *et al.* (2015) υπέδειξαν ότι η χαμηλόσυχνη, χαρακτηριζόμενη από παύσεις διέγερση ενδεχομένως να απαλύνει τα συμπτώματα πιο αποτελεσματικά από την ομαλή διέγερση σε ένα ζωικό μοντέλο νευροψυχιατρικής διαταραχής. Ίσως ακόμη πιο σημαντικό είναι το γεγονός ότι όλα τα εναλλακτικά πρότυπα διέγερσης που θεωρήθηκαν στην μελέτη μας αποδείχθηκαν να συσχετίζονται με μία ισχυρότερη αποσυγχρονιστική επίδραση συγκριτικά με τη συμβατική εν τω βάθει εγκεφαλική διέγερση για ΙΨΔ. Επιπλέον, η συμβατική εν τω βάθει εγκεφαλική διέγερση συσχετίστηκε με μία σημαντικά ισχυρότερη αποσυγχρονιστική επίδραση στη ΝΠ σε σύγκριση με την ΙΨΔ. Αντιστρόφως, η χαμηλόσυχνη περιοδική διέγερση αποδείχθηκε πιο αποτελεσματική στην ΙΨΔ συγκριτικά με τη ΝΠ. Αυτή η εξαρτώμενη από τη διαταραχή επίδραση συγκεκριμένων χαρακτηριστικών προτύπων διέγερσης, που αποκαλύφθηκε από το υπολογιστικό μοντέλο, ενδεχομένως να πηγάζει από ένα ανόμοιο προφίλ νευρωνικής δραστηριότητας στις δύο υπό εξέταση παθολογικές καταστάσεις, δηλ. την ύπαρξη σημαντικά χαμηλότερων ρυθμών εκφόρτισης και ταλαντώσεις χαμηλότερης συχνότητας στην ανθεκτική στη θεραπεία ΙΨΔ συγκριτικά με την προχωρημένο στάδιο της ΝΠ (Piallat et al. 2011, Welter et al. 2011).

Εκτός από τα προαναφερόμενα γενικά συμπεράσματα, θα πρέπει να τονιστεί το γεγονός ότι, με εξαίρεση τα ανώμαλα πρότυπα, η σχετική αποσυγχρονιστική επίδραση των εξεταζόμενων εναλλακτικών προτύπων διέγερσης, με σημείο αναφοράς τη συμβατική εν τω βάθει εγκεφαλική διέγερση, εξαρτήθηκε στοιχειωδώς από την καταγραφόμενη νευρωνική δραστηριότητα. Το αποτέλεσμα αυτό υποδεικνύει ότι κατά το σχεδιασμό οποιουδήποτε σύστηματος εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου, θα πρέπει να εξετάζεται προσεκτικά κάθε πληροφορία για την υποκείμενη νευρωνική δυναμική, περικλειόμενη σε καταγραφές πραγματικού χρόνου, προτού καθοριστούν τα βέλτιστα χαρακτηριστικά των προτύπων διέγερσης.

Η προσέγγιση του 5^{ου} κεφαλαίου υπογραμμίζει την ανώτερη αποτελεσματικότητα της χαμηλόσυχνης περιοδικής διέγερσης συγκριτικά με την αποτελεσματικότητα της συμβατικής διέγερσης τόσο στη ΝΠ όσο και την ΙΨΔ, αν και – όπως έχει ήδη προαναφερθεί – πιο έντονα στη δεύτερη περίπτωση. Η κλινική εφαρμογή της χαμηλόσυχνης περιοδικής διέγερσης αντί του υψίσυχνου ομολόγου της έχει αποτελέσει θέμα αντιπαράθεσης στο πεδίο της εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα κατά τη διάρκεια των τελευταίων ετών (Sidiropoulos and Moro 2014). Αν και μερικά κλινικά στοιχεία φαίνεται να συγκλίνουν προς παρόμοια επίδραση των δύο τρόπων διέγερσης σε αξονικά (Sidiropoulos et al. 2013,

Vallabhajosula et al. 2015) ή περιφερικά συμπτώματα (Tsang et al. 2012), άλλες μελέτες υποδεικνύουν ότι μία μεγαλύτερη βελτίωση αξονικών συμπτωμάτων ή ακούσιων κινήσεων, μετά την μεταβολή της συχνότητας διέγερσης από 130 σε 80Hz, ενδεχομένως να είναι πιθανή, αλλά να εξαρτάται επίσης σε μεγάλο βαθμό από τον ασθενή (Ricchi et al. 2012, Merola et al. 2013). Η παρουσιαζόμενη προσέγγιση μοντελοποίησης ενισχύει περισσότερο τη δεύτερη υπόδειξη, αφού, από τη μία πλευρά δίνει έμφαση στην αποτελεσματικότητα της χαμηλόσυχνης διέγερσης, και από την άλλη πλευρά υποδεικνύει ότι η επίδραση των εναλλακτικών προτύπων διέγερσης εξαρτάται από την νευρωνική δραστηριότητα και συνεπώς και από τον ασθενή. Ακόμη πιο σημαντικό είναι το γεγονός ότι η παρουσιαζόμενη προσέγγιση παρέχει πρωτότυπες ενδείξεις για μία αξιοσημείωτη αποτελεσματικότητα της χαμηλόσυχνης εν τω βάθει εγκεφαλικής διέγερσης για την ανθεκτική στη θεραπεία ΙΨΔ.

Το $6^{ο}$ κεφάλαιο της διατριβής πραγματεύεται τον αλγοριθμικό σχεδιασμό ενός συστήματος εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου για προχωρημένο στάδιο της ΝΠ και ανθεκτική στη θεραπεία ιδεοψυχαναγκαστική διαταραχή, διασφαλίζοντας παράλληλα βέλτιστες επιδόσεις ως προς την *αποδοτικότητα* και *επιλεκτικότητα* της διέγερσης, και ως προς την *υπολογιστική ταχύτητα*.

Οι διαδικασίες που αφορούν στον καθορισμό της βέλτιστης επαφής του ηλεκτροδίου για μονοπολική (με αναφορά τον παλμοδότη) ή διπολική διέγερση, όπως επίσης στον καθορισμό των παραμέτρων διέγερσης που συνδέονται με το βέλτιστο θεραπευτικό παράθυρο συνεπάγονται έναν μεγάλο αριθμό δοκιμών-σφαλμάτων σε ένα μακρύ χρονικό διάστημα εβδομάδων-μηνών (Hunka et al. 2005, Kuncel et al. 2004). Επιπλέον, η διαδικασία αυτή δεν οδηγεί πάντα στο βέλτιστο συμβιβασμό μεταξύ μέγιστου θεραπευτικού οφέλους και ελάχιστων παρενεργειών προκαλούμενων από τη διέγερση (Kuncel and Grill 2004), ενώ δε συμβαδίζει με το γεγονός ότι τα συμπτώματα των κινητικών και νευροψυχιατρικών διαταραχών παρουσιάζουν διακυμάνσεις σε σημαντικά μικρότερες χρονικές κλίμακες δευτερολέπτων-ημερών. Μακροπρόθεσμα το μονομορφικό πρότυπο και η ανοιχτού βρόχου φύση της συμβατικής υψίσυχνης διέγερσης φαίνεται να ευνοεί φαινόμενα ανεκτικότητας, ενώ συσχετίζεται παράλληλα με μέγιστους ρυθμούς κατανάλωσης ισχύος (Carron et al. 2013). Ενάντια σε αυτό το πλαίσιο, η ‘κλειστού βρόχου’, ‘ελεγχόμενη με ανάδραση’ ή ‘προσαρμοζόμενη’ διέγερση αποτελεί καταλληλότερη εναλλακτική και ένα από τα πιο καινοτόμα σενάρια στο πεδίο της εν τω βάθει εγκεφαλικής διέγερσης (Leondopoulos and Micheli-Tzanakou 2010, Hariz et al. 2013).

Σε ένα βέλτιστο σενάριο εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου, η παροχή βέλτιστων προτύπων διέγερσης προσαρμόζεται στη δυναμική των συμπτωμάτων κινητικών και

νευροψυχιατρικών διαταραχών μέσω της αξιοποίησης συγκεκριμένων βιοδεικτών που αποτυπώνουν την κλινική κατάσταση του ασθενή σε πραγματικό χρόνο (Rise and King 1998). Το γεγονός αυτό θα διασφάλιζε με τη σειρά του ελάχιστη κατανάλωση ενέργειας και θα μείωνε το φυσικό μέγεθος της μπαταρίας (Grill 2015), τη συχνότητα των επεμβάσεων αντικατάστασης του παλμοδότη, το συνακόλουθο κίνδυνο μόλυνσης λόγω τεχνικού εξοπλισμού (Boviatsis et al. 2010, Pepper et al. 2013), ή το ρυθμό των διαδικασιών επαναφόρτωσης του παλμοδότη. Θα συσχετιζόταν επίσης με τη σημαντική εξοικονόμηση κλινικών πόρων (Gross and McDougal 2013, McIntosh et al. 2003). Κατ'αρχήν, οποιοσδήποτε αλγόριθμος σχεδιασμένος για ένα μέγιστα αποδοτικό σύστημα εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου θα πρέπει να ικανοποιεί δύο ουσιαστικές προδιαγραφές (Afshar et al. 2013): τον αξιόπιστο προσδιορισμό βέλτιστων βιοδεικτών για τον έλεγχο ανάδρασης και τον καθορισμό εναλλακτικών προτύπων διέγερσης τα οποία να είναι θεραπευτικά και ενεργειακά πιο αποδοτικά σε σύγκριση με το τυποποιημένο πρότυπο διέγερσης (Little and Brown 2012, Feng et al. 2007(a)).
Ένας από τους προτεινόμενους βιοδείκτες για την εν τω βάθει εγκεφαλική διέγερση κλειστού βρόχου για ΝΠ, καταγραφόμενος απευθείας από το ηλεκτρόδιο διέγερσης, ο οποίος χρησιμοποιείται επίσης ως υποκατάστατο του νευρωνικού συγχρονισμού, είναι η υποθαλαμική βήτα δραστηριότητα των δυναμικών τοπικού πεδίου (Brittain et al. 2014), βάσει ισχυρών ενδείξεων ότι η προκαλούμενη από τη διέγερση καταστολή της παθολογικής βήτα ταλαντωτικής δραστηριότητας συσχετίζεται με βελτιώσεις της βραδυκινησίας και της δυσκαμψίας (Kuhn et al. 2008, Eusebio et al. 2010, Priori et al. 2013). Επιπλέον, η ανάλυση των υποθαλαμικών δυναμικών τοπικού πεδίου μπορεί να επεκταθεί στη χρόνια κατάσταση (Rosa et al. 2010). Η ελεγχόμενη μέσω ανάδρασης διέγερση που βασίζεται στη βήτα ισχύ των δυναμικών τοπικού πεδίου έχει αποδειχθεί ότι είναι κλινικά πιο αποτελεσματική από ότι τόσο η συμβατική όσο και η τυχαιοποιημένη διακοπτόμενη διέγερση, και έχει συσχετιστεί με χαμηλές ενεργειακές απαιτήσεις σε μία πιλοτική κλινική μελέτη (Little et al. 2013). Παρολ'αυτά, η παρουσία, κατά τη διάρκεια της διέγερσης, μεγάλων σφαλμάτων στις καταγραφές δυναμικών τοπικού πεδίου, η σχετικά χαμηλή δυναμική πολυπλοκότητα του σήματος αυτού, το φαινόμενο της καταστολής της δραστηριότητας βήτα ζώνης των δυναμικών τοπικού πεδίου στον υποθαλαμικό πυρήνα και η βελτίωση στον τρόμο ή τη δυσκινησία πριν ή κατά τη διάρκεια της κίνησης, καθώς και η απουσία αναφοράς για μία θετική συσχέτιση μεταξύ της καταστολής της βήτα ταλαντωτικής δραστηριότητας στον υποθαλαμικό πυρήνα προκαλούμενης από τη διέγερση και τη βελτίωση στον τρόμο ή τη δυσκινησία υποδεικνύουν την ανάγκη διερεύνησης πιο ευαίσθητων βιοδεικτών (Starr and Ostrem 2013, Little and Brown 2012).

Μία εναλλακτική είναι η μακροπρόθεσμη καταγραφή φλοιϊκών δυναμικών τοπικού πεδίου (Ryapolova-Webb et al. 2014) χρησιμοποιώντας τον νευροδιεγέρτη Activa ® PC + S (Medtronic, Inc., Minneapolis, MN) (Afshar et al. 2013, Rouse et al. 2012), ο οποίος αποτελεί

μία ερευνητική διάταξη διπλής κατεύθυνσης παρέχοντας τη δυνατότητα τόσο θεραπευτικής διέγερσης όσο και καταγραφής δυναμικών τοπικού πεδίου (Sun and Morrell 2014). Η προσέγγιση αυτή προέκυψε από το γεγονός ότι τα φλοιϊκά δυναμικά τοπικού πεδίου μπορούν να καταγραφούν με ελάχιστη επέμβαση και σφάλμα διέγερσης , και ενδεχομένως να αποτυπώνουν αποτελεσματικά το βαθμό παθολογικής νευρωνικής δραστηριότητας στη ΝΠ, η οποία αντικατοπτρίζεται στη ζεύξη βήτα φάσης-γάμμα πλάτους στον πρωτογενή κινητικό φλοιό (de Hemptinne et al. 2013, Starr and Ostrem 2013). Επιπλέον, η χρήση φλοιϊκών καταγραφών ως σήματος ελέγχου στη διέγερση κλειστού βρόχου έχει συσχετιστεί με αυξημένη κλινική αποτελεσματικότητα συγκριτικά με τη συμβατική διέγερση ανοιχτού βρόχου σε μία προκλινική μελέτη 'απόδειξης της ορθότητας της αρχής' (Rosin et al. 2011). Η ανάλυση ηλεκτρομυογραφικών σημάτων κατά τη διάρκεια περιόδων κίνησης και ανάπαυσης αποτελεί μία περαιτέρω σημαντική δυνατότητα που παρέχεται από τον νευροδιεγέρτη Activa PC + S (Ryapolova-Webb et al. 2014). Μία προσέγγιση σχετιζόμενη με τον μη-επεβατικό έλεγχο ανάδρασης έχει προταθεί σε μία πιλοτική κλινική μελέτη που διεξήχθη από τους Basu *et al* (2013), κατά την οποία χρησιμοποιήθηκε το ηλεκτρομυογράφημα επιφανείας σε συνδυασμό με έναν καταλλήλως σχεδιασμένο αλγόριθμο με σκοπό την πρόβλεψη της απαρχής τρόμου κατά τη διάρκεια χρονικών διαστημάτων χωρίς διέγερση. Εν τω μεταξύ, εισάγονται σταδιακά καινοτόμοι νευρωνικοί καθετήρες οι οποίοι προσφέρουν τη δυνατότητα ταυτόχρονης εν τω βάθει εγκεφαλικής διέγερσης και καταγραφής (Lai et al. 2012, Stypulkowski et al. 2013). Με βάση ενδείξεις που αποδίδουν τον θεραπευτικό μηχανισμό της διέγερσης στην αποδέσμευση νευροδιαβιβαστών, τα 'έξυπνα' συστήματα εν τω βάθει εγκεφαλικής διέγερσης με ηλεκτροχημική ανάδραση ενδεχομένως να αποτελέσουν μία περαιτέρω ενδιαφέρουσα εφαρμογή νευροδιαμόρφωσης κλειστού βρόχου (Behrend et al. 2009, Grahn et al. 2014, Farina et al. 2014, Jackowska and Krysinski 2013, Gross and McDougal 2013). Σε αυτό το πλαίσιο διερευνάται η εφαρμογή του Ασύρματου Αισθητήριου Συστήματος Στιγμιαίας Νευροχημικής Συγκέντρωσης που ενσωματώνει τόσο την in vivo κυκλική βολταμετρία ταχείας σάρωσης και αμπερομετρία για την πραγματικού χρόνου ανίχνευση ντοπαμίνης, αδενοσίνης και σεροτονίνης (Van Gompel et al. 2010, Parpura et al. 2013).

Παράλληλα, δίνεται έμφαση σε ακόμη πιο ισχυρούς προγνωστικούς βιοδείκτες της παθοφυσιολογίας της ΝΠ και της ΙΨΔ, όπως στη *μη γραμμική ζεύξη δια πολλαπλών ζωνών συχνοτήτων* στα βασικά γάγγλια και σε φλοιϊκές δομές (Lopez et al. 2010, Yang et al. 2014, de Hemptinne et al. 2013, Shimamoto et al. 2013, Connolly et al. 2015(a), Bahramisharif et al. 2015). Ο προσδιορισμός των βιοδείκτη αυτού βασίζεται κατά ένα μεγάλο μέρος στην εκτίμηση της ζεύξης φάσης-πλάτους μέσω του μετασχηματισμού Hilbert (Tort et al. 2010). Αξίζει να σημειωθεί ωστόσο, ότι η αντίστοιχη μέθοδος ανακατασκευής φάσης ενδεχομένως να χαρακτηρίζεται από ένα υψηλό επίπεδο ευαισθησίας στο θόρυβο μέτρησης (Sun et al. 2008).

Για τον λόγο αυτό, ο περιορισμός της ευαισθησίας στο θόρυβο μέτρησης (Sun et al. 2008, Rossberg et al. 2005) και η χρήση μεθόδων που δε βασίζονται στην ανακατασκευή φάσης (Gottwald and Melbourne 2009) σε ένα αυτόματο σύστημα εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου ενδεχομένως να διευκολύνουν σημαντικά τον αξιόπιστο προσδιορισμό διασυχνοτικών αλληλεπιδράσεων.

Εν τω μεταξύ, διερευνώνται πολιτικές ελέγχου βασιζόμενες σε μοντελοποίηση για τον καθορισμό χρονικά εναλλακτικών πρωτοκόλλων διέγερσης (Wilson and Moehlis 2014, Danzl et al. 2009, Liu et al. 2011, Nabi et al. 2013, Lourens et al. 2015, Gorzelic et al. 2013, Dasanayke and Li 2015, Iolov et al. 2014, Tass and Hauptmann 2007, Tass et al. 2003, Hauptmann and Tass 2010, Tukhlina et al. 2007, Montaseri et al. 2015, Su et al. 2014), ενώ μία θετική 'απόδειξη της ορθότητας της αρχής' παρασχέθηκε πρόσφατα για τη νευροτροποποίηση συντονισμένης επαναφοράς (Adamchic et al. 2014). Ο κοινός παρονομαστής στην πλειοψηφία των προσεγγίσεων αυτών είναι ο αποσυγχρονιστικός έλεγχος της νευρωνικής δραστηριότητας με κατανάλωση ελάχιστης ενέργειας. Η λογική πίσω από το σκοπό αυτό έγκειται σε ενδείξεις ότι οι χρονικά εναλλακτικές κυματομορφές εν τω βάθει εγκεφαλικής διέγερσης έχουν τη δυνατότητα να οδηγήσουν τη νευρωνική δυναμική εντός των βασικών γαγγλίων πίσω στη φυσιολογική αποσυγχρονισμένη κατάσταση (Feng et al. 2007(a), (b)), ξεπερνώντας κατ'αυτόν τον τρόπο την επίδοση των συμβατικών κυματομορφών εν τω βάθει εγκεφαλικής διέγερσης, ο μηχανισμός των οποίων έχει πρωταρχικά αποδοθεί στην κανονικοποίηση των νευρωνικών προτύπων στην περιοχή του διεγερμένου πυρήνα (McConnell et al. 2012, Grill et al. 2004, Santaniello et al. 2015). Ίσως ακόμη πιο σημαντικό να είναι το γεγονός ότι η χρήση εναλλακτικών προτύπων διέγερσης να ευνοείται, ως προς τη βραχυπρόθεσμη και μακροπρόθεσμη κλινική αποτελεσματικότητα, από τη σταθεροποιητική επίδραση της εξαρτώμενης από το χρονισμό δυναμικών ενέργειας πλαστικότητας (spike-timing dependent plasticity, STDP) στην αποσυγχρονισμένη νευρωνική δραστηριότητα (Lourens et al. 2015).

Με βάση τις παραπάνω ενδείξεις, στην ανάλυση του κεφαλαίου 6 παραθέτουμε μία σειρά μεθόδων εύρωστων στην παρουσία θορύβου μέτρησης (Rossberg et al. 2005, Gottwald and Melbourne 2009), που χρησιμοποιούνται με σκοπό τον προσδιορισμό της παρουσίας σημαντικής μη γραμμικής ζεύξης μεταξύ της υποθαλαμικής δραστηριότητας βήτα και της δραστηριότητας υψηλής συχνότητας, ως βιοδείκτη ελέγχου ανάδρασης. Επιπλέον, προτείνουμε μία στρατηγική βασιζόμενη σε μοντελοποίηση μέσω της οποίας προσδιορίζονται βέλτιστα πρότυπα και παράμετροι διέγερσης για τον αποσυγχρονιστικό έλεγχο νευρωνικής δραστηριότητας με ελάχιστη κατανάλωση ενέργειας. Επιλέγουμε ένα φασικώς αναγόμενο μοντέλο νευρώνα χαρακτηριζόμενου από ξεσπάσματα (Sherwood and Guckenheimer 2010, Mauroy et al. 2014), δεδομένου ότι η αυξημένη νευρωνική δραστηριότητα χαρακτηριζόμενη

από ξεσπάσματα έχει συσχετιστεί με την παθοφυσιολογία τόσο της ΝΠ όσο και της ΙΨΔ (Piallat et al. 2011, Welter et al. 2011). Τα χρονικά πρότυπα διέγερσης παράγονται βάσει μίας τυχαίας (Poisson) διαδικασίας, αφού η αποσυγχρονιστική και ενδεχομένως η θεραπευτική επίδραση των στοχαστικών κυματομορφών εν τω βάθει εγκεφαλικής διέγερσης έχει αποδειχθεί στην ανάλυση του κεφαλαίου 5 ότι είναι σημαντικά ισχυρότερη σε σύγκριση με την επίδραση της συμβατικής διέγερσης. Επιπλέον, η αποδοτικότητα των στοχαστικών κυματομορφών έχει αποδειχθεί εύρωστη στις μεταβολές της νευρωνικής δραστηριότητας και ενδεχομένως επίσης στις ασταθείς συνθήκες που αναμένονται στην κλινική πράξη. Ο καθορισμός του ακριβούς βέλτιστου χρονικού προτύπου και των βέλτιστων παραμέτρων διέγερσης πραγματοποιείται μέσω της εφαρμογής ενός αλγορίθμου βελτιστοποίησης μη βασιζόμενου σε παράγωγο, συγκεκριμένα της βελτιστοποίησης απευθείας αναζήτησης βασιζόμενης σε τετραγωνική μοντελοποίηση (Custodio et al. 2010), βάσει του γεγονότος ότι η νευρωνική απόκριση στις παραμέτρους εν τω βάθει εγκεφαλικής διέγερσης ενδεχομένως να είναι μία πολύπλοκη, μη διαφορίσιμη συνάρτηση (Feng et al. 2007(a)). Οι προσομοιώσεις πραγματοποιούνται χρησιμοποιώντας μικροηλεκτροδιακές καταγραφές ανακτημένες κατά τη διάρκεια 8 και 8 επεμβάσεων εν τω βάθει εγκεφαλικής διέγερσης του υποθαλαμικού πυρήνα για ΝΠ και ΙΨΔ, αντιστοίχως. Τέλος, επεκτείνοντας τα αποτελέσματα της ανάλυσης του προηγούμενου κεφαλαίου, στην ανάλυση του κεφαλαίου 6, επιχειρούμε να παράσχουμε ενδείξεις για μία ενδεχόμενη συσχέτιση του πρωταρχικού μέτρου έκβασης διεξαγόμενου από το προτεινόμενο μοντέλο, δηλ. της αμετάβλητης πυκνότητας, με την κλινική αποτελεσματικότητα της διέγερσης στην ανθεκτική στη θεραπεία ΙΨΔ.

Οι Bikson et al. (2015) σημειώνουν: «Οι προσεγγίσεις διέγερσης κλειστού βρόχου είναι εγγενώς εξαρτώμενες από την κλινική κατάσταση και απαιτούν υπολογιστική νευροδιέγερση». Αναλύοντας την υπόδειξη αυτή σε συνδυασμό με τον αντίκτυπο της παρούσας προσέγγισης κάνουμε τις ακόλουθες δύο βασικές παρατηρήσεις: πρώτον, αν και οι ενδείξεις για την παθοφυσιολογία των ανθεκτικών στη θεραπεία νευρολογικών και νευροψυχιατρικών διαταραχών παραμένουν, έως την παρούσα στιγμή, κατά έναν μεγάλο βαθμό μη προσοδοφόρες, αυξανόμενες μελέτες υποστηρίζουν το σημαντικό ρόλο της μη γραμμικής ζεύξης μεταξύ της δραστηριότητας βήτα και της δραστηριότητας υψηλής συχνότητας στην παθοφυσιολογία της ΝΠ (Voytek and Knight 2015), υποδεικνύοντας κατά αυτόν τον τρόπο την ενδεχόμενη χρησιμότητα του μέτρου αυτού ως βιοδείκτη ‘κλινικής κατάστασης’ σε προσεγγίσεις νευροδιαμόρφωσης κλειστού βρόχου για ΝΠ. Τα αποτελέσματα της ανάλυσης του κεφαλαίου 6 τείνουν προς την υπόδειξη αυτή επικυρώνοντας την παρουσία διασυχνοτικής ζεύξης για κάθε ασθενή με προχωρημένο στάδιο της ΝΠ. Αντιθέτως, η καταλληλότητα του χαρακτηριστικού αυτού ως βιοδείκτη ‘κλινικής κατάστασης’ αποδείχθηκε μάλλον εξειδικευμένη κατ’ασθενή στην περίπτωση της ανθεκτικής στη θεραπεία ΙΨΔ. Για τον λόγο αυτό, κρίθηκε απαραίτητη η

εφαρμογή ενός εναλλακτικού βιοδείκτη σοβαρότητας της ΙΨΔ, δηλ. της έντονης υποθαλαμικής δραστηριότητας χαρακτηριζόμενης από ξεσπάσματα (Welter et al. 2011). Δεύτερον, μέσω της ανάλυσης του κεφαλαίου 6 επιχειρούμε να παράσχουμε πειστικές αποδείξεις για την εφαρμοσιμότητα της 'υπολογιστικής νευροδιέγερσης' σε συστήματα εν τω βάθει εγκεφαλικής διέγερσης κλειστού βρόχου. Αποδεικνύουμε ότι η προτεινόμενη στρατηγική βασιζόμενη σε μοντελοποίηση ενδεχομένως να υπερβαίνει την επίδοση της μετεγχειρητικής κλινικής διαχείρισης ως προς τη θεραπευτική αποδοτικότητα της διέγερσης και για τις δύο παθολογικές καταστάσεις. Αποφέροντας ένα μέσο βέλτιστο εύρος παλμού ίσο με 33μs, τιμές συχνότητας διέγερσης σημαντικά χαμηλότερες σε σύγκριση με τη συμβατική διέγερση και διατηρώντας το βέλτιστο πλάτος έντασης διέγερσης στην ελάχιστη τιμή, η στρατηγική βασιζόμενη σε μοντελοποίηση αποδεικνύεται περαιτέρω να επιτυγχάνει μία σημαντικά υψηλότερη επίδοση ως προς την επιλεκτικότητα και ενεργειακή αποδοτικότητα της διέγερσης. Εκτός από τη χρήση του φασικώς αναγόμενου μοντέλου νευρώνα χαρακτηριζόμενου από ξεσπάσματα, η ενσωμάτωση της βελτιστοποίησης απευθείας αναζήτησης βασιζόμενης σε τετραγωνική μοντελοποίηση συμβάλει σημαντικά στην εξαιρετική επίδοση της παρουσιαζόμενης προσέγγισης. Συγκεκριμένα, εκτός από τα προαναφερόμενα σημαντικά αποτελέσματα, η εφαρμογή της μεθόδου απευθείας αναζήτησης βασιζόμενης σε μοντελοποίηση συσχετίζεται με μία σημαντικά υψηλότερη υπολογιστική ταχύτητα συγκριτικά με ομόλογους αλγορίθμους βελτιστοποίησης (γενικευμένη μέθοδος αναζήτησης προτύπων, γενετικός αλγόριθμος).

Contents

Figures

Tables

List of Abbreviations

ΝΠ	νόσος Πάρκινσον
ΙΨΔ	ιδεοψυχαναγκαστική διαταραχή
5-HT	5-hydroxytryptamine
ACC	anterior cingulate cortex
AD	Alzheimer's disease
AN	anorexia nervosa
ANOVA	analysis of variance
APA	american psychiatric association
BDD	body dismorphic disorder
CBT	cognitive-behavioral therapy
CI	confidence interval
COMT	catechol-O-methyl transferase
CSTC	cortico-striato-thalamo-cortical
CT	computed tomography
cZi	caudal zona incerta
DBS	deep brain stimulation
DLB	dementia with Lewy bodies
DLPC	dorsolateral prefrontal cortex
DM	dorsomedial
DSM	diagnostic and statistical manual of mental disorders
ECT	electroconvulsive therapy
EMG	electromyography
ERP	exposure and response prevention

ET	essential tremor
FDA	food and drug administration
FNR	false negative rate
FPR	false positive rate
FWR	full-wave rectification
GABA	gamma-aminobutyric acid
GAF	global assessment of functioning
GPi	internal globus pallidus
GPe	external globus pallidus
HDE	humanitarian device exemption
HSD	honestly significant difference
IC	internal capsule
IPG	implantable pulse generator
IPI	inter-impulse interval
ISI	interspike interval
ITP	inferior thalamic peduncle
L-dopa	levodopa
LFP	local field potential
LOFC	lateral orbitofrontal cortex
MAO-b	monoamine oxidase type B
MER	microelectrode recording
MDD	major depressive disorder
MDS	movement disorder society
MPTP	1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSA	multiple system atrophy
MSNs	medium spiny neurons
Nacc	nucleus accumbens
NJRE	‘not just right’ experience
NPE	neighbourhood-based phase estimation
OCD	obsessive-compulsive disorder
OCPD	obsessive-compulsive personality disorder
OCRDs	obsessive-compulsive and related disorders
PD	Parkinson’s disease
PDD	PD-related dementia
PDF	probability density function
PET	positron emission tomography
PIGD	postural instability/gait difficulty
PPN	pedunculopontine nucleus
PPTg	pedunculopontine tegmental nucleus
PRC	phase response curve
RBD	sleep behavioral disorder
REM	rapid eye movement
RR	relative risk

SEM	standard error mean
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRIs	selective serotonin reuptake inhibitors
STN	subthalamic nucleus
STOC	stimulation dans le trouble obsessionnel compulsif
TMS	transcranial magnetic stimulation
TS	Tourette's syndrome
TTM	trichotillomania
UPDRS	unified Parkinson's disease rating scale
VA	ventral anterior nucleus of the thalamus
VC/VS	ventral capsule/ventral striatum
Y-BOCS	Yale–Brown obsessive-compulsive scale

1

Introduction

1.1. Deep Brain Stimulation

1.1.1. Introduction

…never before have practicioners and scientists been able to actively intervene in, modulate, correct, and investigate dysfunctional neuroanatomical circuits believed to underlie much of human thought and behavior…

N. Lipsman et al. (2010)

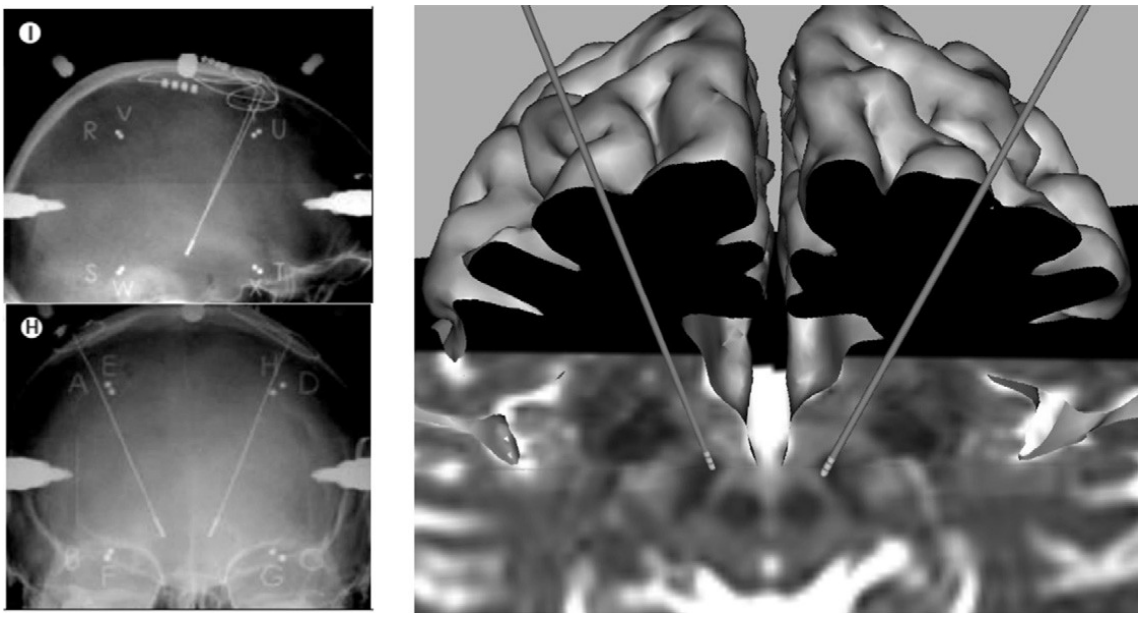
Middle- and high-income societies are being characterized by a considerable and rising burden of neurological and psychiatric disorders, mainly due to an absence of effective treatments along with an increasingly elderly population (Vos et al. 2012, Murray et al. 2012, World Health Organization 2004, Kowal et al. 2013). Accordingly, there is an urgent need for innovative treatments to prevent, delay onset, or alleviate symptoms of the respective diseases. With respect to the latter, the use of chronic, high-frequency, electrical deep brain stimulation (DBS), during approximately the last 30 years, has been proven to provide striking benefits for patients with Parkinson's disease (PD) (Deuschl et al. 2006), essential tremor (ET) (Zhang et al. 2010)

and dystonia (Kumar et al. 1999) who have failed conventional therapies. Key factors for the emergence of this groundbreaking application have been considerable advances in structural/functional brain imaging and surgical technology coupled with the development of a deeper understanding of the organization and the pathophysiology of the basal ganglia (Lozano and Lipsman 2013). These factors paved the way for the translation of the anatomofunctional concepts into therapy-oriented surgical strategies (Benabid 2012). Further, while DBS has been established as a safe and effective therapeutic option for movement disorders (Williams et al. 2010), novel applications of this technique for the treatment of neuropsychiatric disorders have emerged over the last 15 years, including treatment-refractory obsessive-compulsive disorder (OCD) (Nuttin et al. 1999), Tourette's syndrome (TS) (Vandewalle et al.1999), major depressive disorder (MDD) (Mayberg et al. 2005), drug addiction (Muller et al. 2009) and anorexia nervosa (AN) (Lipsman et al. 2013). Eventually, '*just as DBS has revolutionized the practice of movement disorder surgery, its application to psychiatric illness has become the cutting edge of functional neurosurgery*' (Kopell and Greenberg 2008). The non-ablative nature of DBS, its adaptability and virtual reversibility (Benabid et al. 2009) have converted this treatment option into the most rapidly expanding field in neurosurgery. As yet, the number of patients who have undergone deep brain stimulation surgery is estimated to have exceeded 100,000 worldwide. From a scientific point of view, DBS has provided a common touchstone of hitherto separate disciplines and research areas. Ultimately, it has significantly contributed to a 'renaissance' in systems neuroscience offering the potential for conducting in vivo research on specific brain networks subserving motor, affective and cognitive function. The above facts are being reflected within the over 700 DBS-related manuscripts being published every year (Lozano and Lipsman 2013). Meanwhile, however, this enthusiasm needs to be tempered by a careful consideration of ethical principles. Though the existing ethical norms and regulatory context provide certain safeguards against misuse of neurosurgery for movement and neuropsychiatric disorders (Greenberg et al. 2010 (a)), there is still a need in this field to more clearly address the related ethical and social challenges and to establish universal ethical guidelines for the newly emerging clinical trials (Bell and Racine 2012, Fins et al. 2011, Lipsman et al. 2010). Undoubtedly, patient protection should be the kingpin of a solid framework for ethical evaluation (Clausen 2010).

1.1.2. What is Deep Brain Stimulation?

Undoubtedly the most striking progress in neuromodulation using DBS can be attributed to the enormous progress in anatomical, functional, and network visualization provided by MRI techniques.

F.L.H. Gielen and G.C. Molnar (2012)



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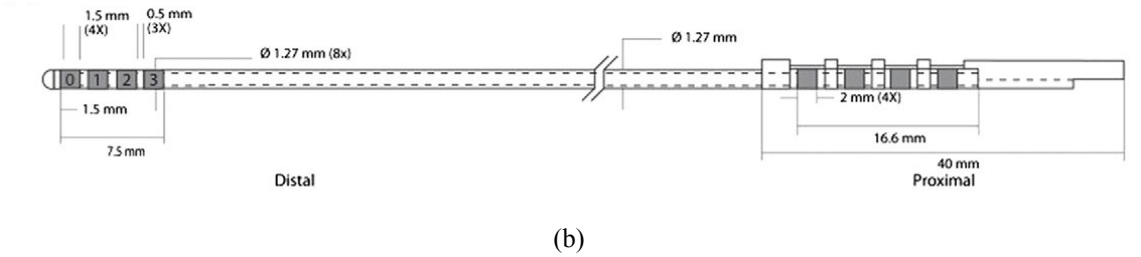


(b)

Figure 1.1. (a) Example of preoperative radiographic control and postoperative magnetic resonance imaging control scans in a patient with treatment-refractory OCD. A 3389 electrode (Medtronic, Minneapolis, Minnesota, USA) was used for deep brain stimulation (adapted with permission from Chabardes et al. 2013) (b) Medtronic DBS lead (Medtronic Inc.-Lapidus)

Deep brain stimulation is a therapeutic approach based on the concept of neuromodulation, i.e. the alteration of pathological neuronal activity in the target nucleus and associated neural networks by means of an electric current delivered through intracerebrally implanted electrodes that are connected to an implantable pulse generator (IPG). The Medtronic DBS system consists of one (or two in case of bilateral stimulation) lead(s) with four cylindrical contacts (each 1.27 mm diameter, 1.5 mm height, 1.5 mm or 0.5 mm spacing between contacts) that is (are) surgically implanted in the selected brain nucleus (or nuclei) (figure 1.1) and subcutaneously connected in the subclavicular region to an IPG. The IPG is a programmable and possibly rechargeable device similar to modern cardiac pacemakers that delivers continuous stimulation. Deep brain stimulation surgery embraces the principles of stereotactic and functional neurosurgery and may be frameless or frame-based (Lozano et al. 2009). In either case, precise electrode localization is based on pre-operative stereotactic targeting and intra-operative electrophysiological mapping techniques usually applied under local anesthesia (Abosch et al. 2013). Pre-operative stereotactic targeting is achieved via modern visualization techniques

(frameless magnetic resonance imaging (MRI) and frame-based computed tomography (CT)), while electrophysiological mapping techniques most commonly applied are microelectrode recording (MER) of neuronal activity in the target area and intra-operative macrostimulation, i.e. stimulation at increasing voltage applied through an external pulse generator for determination of the site associated with the best therapeutic window (i.e. threshold for adverse effects/ threshold for clinical effects) (Abosch et al. 2013, Marceglia et al. 2010). Importantly, non-MER strategies have also been adopted (Foltynie et al. 2010). In addition to precise electrode localization, post-operative clinical management strongly influences the outcome of DBS for a specific treatment (Volkmann et al. 2004, Benabid et al. 2009). Thus, following the implantation of a DBS system, stimulation parameters and medication are optimally adjusted. Medication doses, already reduced pre-operatively, are further decreased, and set at a compromise level. With respect to stimulation settings, a pulse width of 60μs, a stimulation frequency of 130 *Hz* and a variable voltage amplitude are commonly applied at initial stages (Volkmann et al. 2004). The procedures related to the determination of the optimal contact within the electrode array for monopolar (against the IPG case) or bipolar stimulation, as well as to the determination of the stimulation parameters that produce the best therapeutic window (Marceglia et al. 2010, Krack et al. 2002) entail a great amount of trials and errors and are therefore considerably time consuming (Hunka et al. 2005, Kuncel et al. 2004). Against this framework, the concepts of 'closed-loop', 'feedback controlled', or 'adaptive' stimulation are interchangeably emerging as robust 'on-demand' alternatives, constituting one of the most revolutionary scenarios in the field of DBS (Leondopoulos and Micheli-Tzanakou 2010, Hariz et al. 2013) (figure 1.2).

Principally, DBS has not only constituted a dynamic clinical perspective for the treatment of movement and refractory neuropsychiatric disorders - by virtue of its reversibilty, adaptability and association to a low morbidity - but also a powerful tool for delineating the functionality of the targeted nuclei in the course of symptom manifestation and remission, as well as for disentangling the effects and mechanisms of stimulation *per se* (Lozano et al. 2010 (a), Pollak et al. 2002). These unique opportunities have been primarily provided through both intraoperative MER and functional stimulation techniques, as well as local field potential (LFP) recordings and stimulation applied post-operatively. First, during intraoperative microelectrode recording performed at rest or in response to various motor and cognitive tasks, physiological and pathological patterns of neuronal activity can be assessed and ascribed to a specific targeted nucleus or nucleus subterritory (Levy et al. 2000, Weinberger et al. 2006, Piallat et al. 2011, Wong et al. 2009, Rodriguez-Oroz et al. 2001, Lozano et al. 2010 (a), Zaghoul et al. 2009, 2012; Patel et al. 2012). Secondly, during intraoperative and postoperative macrostimulation, the beneficial, but also adverse effects of stimulation on the target nuclei can

(a) (b) (c)

Figure 1.2. (a) General device architecture for a bi-directional neural interface system incorporating the built-in capability to make real-time therapy adjustments in a closed-loop mode (Rouse et al. 2011) (b) The Activa® PC+S deep brain neurostimulator (Medtronic, Minneapolis, MN, USA) (c) The Activa® RC neurostimulator, the first rechargeable deep brain stimulation device and the thinnest available on the market today with 9-year longevity (Medtronic, Minneapolis, MN, USA).

be evaluated, thereby elucidating the functional role of these structures (Pollak et al. 2002, Nuttin et al. 2003, Greenberg et al. 2006, Mayberg et al. 2005, Vandewalle et al. 1999, Lipsman et al. 2013, Mallet et al. 2008, Hershey et al. 2010, Greenhouse et al. 2011). Finally, the assessment of LFP activity post-operatively, i.e. in the interval between DBS electrode implantation and subsequent connection to the subcutaneous stimulator, is an approach that has yielded important findings with respect to the characterization of pathophysiological mechanisms underlying neurological disorders (Brown et al. 2001, Lopez-Azcarate et al. 2010), as well as the mechanisms of action of stimulation (Kühn et al. 2008).

1.1.3. From Ablation to Stimulation

Although the enthusiasm with which psychiatric neurosurgery is sometimes greeted hearkens back to that in the beginning of the era of freehand 'psychosurgery', when prefrontal lobotomy saw wide, indiscriminate use, the parallels are quite limited. Those crude operations had some therapeutic effects, but were accompanied by unacceptable and even tragic adverse effects. Techniques, procedures, and practices have evolved steadily since then.

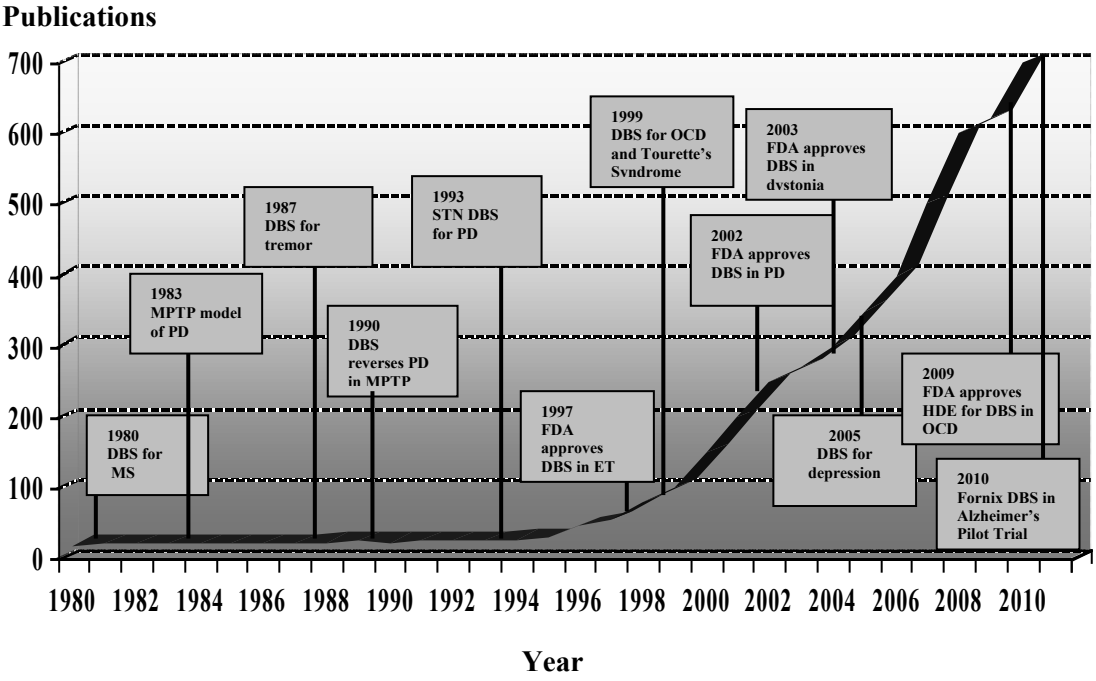
B. Greenberg et al. (2010 (a))

Surgery for movement and neuropsychiatric disorders was initiated in the late 19th century involving distinct ablative procedures that, although being unrefined, were correlated with certain therapeutic effects. These procedures included the removal of the motor cortex for the

treatment of chorea by neurosurgeon Victor Horsley (Horsley 1890) and the excision of sections of the frontal, temporal or temporoparietal lobe for the treatment of chronic mania, primary dementia and schizophrenia by the Swiss psychiatrist Gottlieb Burckhardt (Kotowicz 2005). Almost half a century later, in 1949, the Portuguese neurologist Egas Moniz was awarded the Nobel Prize in Physiology and Medicine for performing a surgical intervention in patients with certain neuropsychiatric disorders (Moniz 1936), that was subsequently modified in an uncritical and erratic manner by neurologist Walter Freeman evolving into the most maligned medical practice in history: the prefrontal lobotomy (Malone and Pandya 2006).

In the meantime, with the groundbreaking introduction of stereotactic functional neurosurgery by neurologist Ernst Spiegel and neurosurgeon Henry Wycis (Spiegel et al 1947), and the subsequent work of neurosurgeon Lars Leksell (Bingley et al 1977), substantially more refined ablative interventions, first for neuropsychiatric disorders and later for movement disorders, were becoming possible: thalamotomy, pallidotomy, capsulotomy and subthalamotomy were some of the stereotactic surgical procedures performed based on the principle of making focal lesions in the pertinent nuclei, while resulting in significant improvements without producing paralysis and the unacceptable or even tragic adverse effects of prefrontal lobotomy.

During approximately the same period, the use of temporary electrodes for the application of DBS in patients with neuropsychiatric, pain or movement disorders was being reported for the first time (Hariz et al. 2010). In almost all of these cases, stimulation was performed intraoperatively as a means of physiological evaluation of the subcortical brain target prior to lesioning, but also in order to assess its possible therapeutic value for the treatment of the respective disorders. With respect to the application of DBS in neuropsychiatric disorders, as opposed to Spiegel and Wycis who performed ethically and scientifically sound trials (Spiegel et al. 1947), psychiatrist Robert Heath was rightfully criticized for acting in isolation and for violating ethical principles (Laitinen 1977). In the mid-1970s, as a consequence of studies related to the assessment of the therapeutic value of stimulation in the treatment of chronic pain (Reynolds 1969), the term ‘DBS’ was trademarked by Medtronic, Inc. (Minneapolis, MN, USA) for the first commercially marketed devices (Coffey 2009). Paradoxically, however, DBS for chronic pain has not been to date approved by the US Food and Drug Administration (FDA) due to the absence of controlled trials demonstrating its clinical efficacy. In 1974, Quadee reported on the application of stimulation and lesion of the lateral hypothalamic area in patients with comorbid obesity (Quadee 1974). During the period 1972-1977, neurophysiologist Bechtereva and colleagues aimed at chronic stimulation of the ventrolateral and the centromedian thalamus as a ‘permanent’ therapy for patients with PD, without however reaching this end due to poor technological equipment in the USSR at that time (Bechtereva et al. 1975, Hariz et al. 2010).



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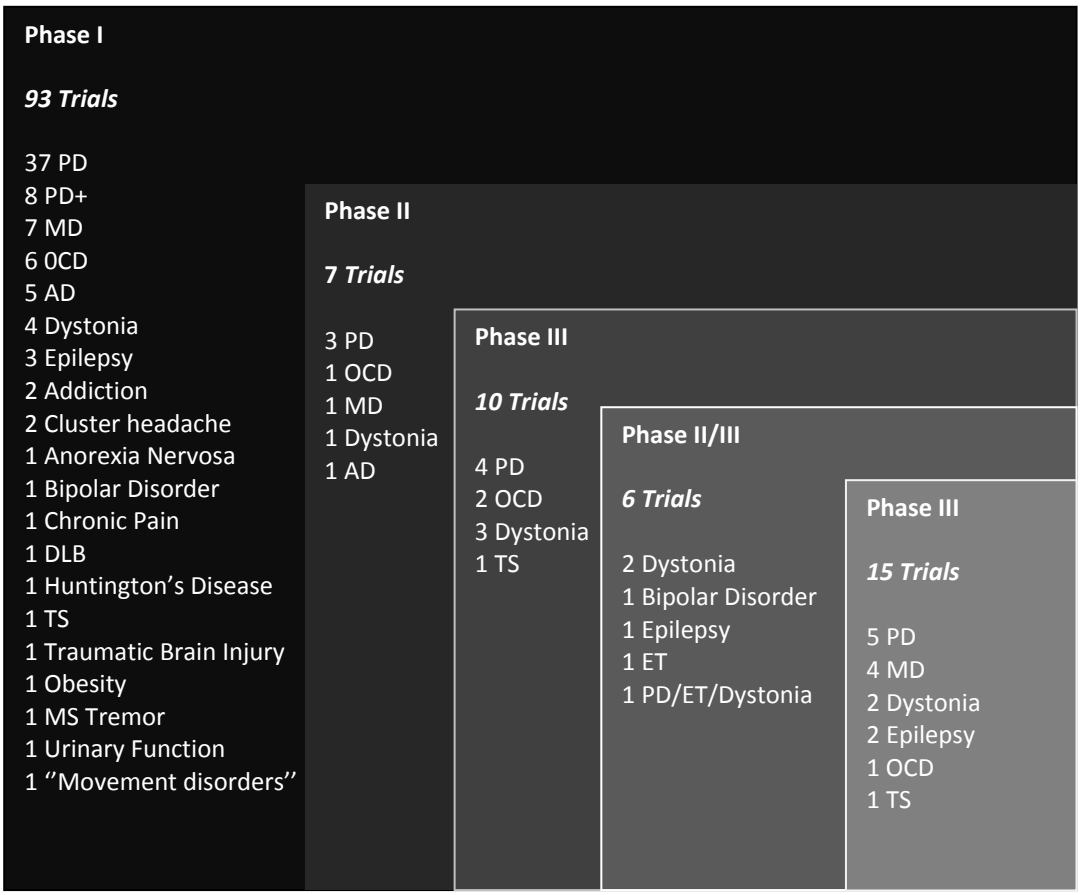


(b)

Figure 1.3. (a) Significant DBS milestones since 1980 (b) Registered Phase I to Phase III DBS Trials as of September 2012 (adapted with permission from Lozano and Lipsman 2013). PD+: PD plus an additional disorder (depression, dystonia, tremor).

In 1977, Professor Fritz Mundinger reported on the permanent implantation of a Medtronic DBS system for the treatment of cervical dystonia. Stimulation was intermittently delivered via a radiofrequency coupled external stimulator, at frequencies of up to 390 Hz (Mundinger 1977). In fact, however, the introduction of two major breakthroughs, the chlorpromazine- and the levodopa-based pharmacological therapy, during the 1950s (Turner 2007) and 1960s (Cotzias et al. 1069), respectively, along with the virtual abandonment of surgery for psychiatric disorders due to the wide and indiscriminate use of prefrontal lobotomy, were pushing surgical therapy for movement and neuropsychiatric disorders, by the 1970s, almost completely into the background.

In the 1980s, the awareness of the fact that many patients with advanced PD showed reduced clinical benefit with levodopa therapy or developed medication-related adverse effects began to increase. This evolution combined with significant technological and functional imaging breakthroughs and a vastly superior knowledge of neural pathophysiology was setting the stage for a resurgence of interest for functional neurosurgical and deep brain stimulation approaches (Starr et al. 1998). In the early 1980s, Cooper, Brice and Andy evaluated the therapeutic effectiveness of DBS for intractable movement disorders reporting its reversibility and superiority to lesioning for the first time (Cooper 1980, Brice and McLellan 1980, Andy 1983). Against this background, the modern form of DBS was heralded in 1987, by the French neurosurgeon/neurologist team of Benabid and Pollak and their colleagues who applied thalamic DBS at frequencies higher than 100Hz in the one side and thalamotomy in the most disabled side in patients with tremor due to PD (Benabid et al. 1987) (figure 1.3). The team corroborated the triad of hallmarks characterizing modern DBS: reversibility, adaptability and low morbidity. Thereby, they portended the potential to establish thalamic DBS as an alternative equally effective to ablative stereotaxy for PD (Schuurman et al. 2008). Importantly, several years before, Burns et al (1983) had developed the non-human primate model of PD on the basis of the discovery of the neurotoxin 1-methyl-4- phenyl-1,2,3,6-tetrahydropyridine (MPTP) by Langston et al (1983). This model, as well as the functional model of the basal ganglia established by Alexander and colleagues (Alexander et al. 1986, Alexander and Crutcher 1990) are considered major milestones in the development of new approaches in the field of DBS. In 1990, Hagai Bergman reported the reversal of parkinsonism by focal lesions and electrical stimulation of the subthalamic nucleus (STN) in MPTP-treated non-human primates. On the basis of this observation, in 1993, Benabid *et al* corroborated the effectiveness of STN DBS in two patients with PD (Benabid et al. 1994).The Grenoble group established 130 Hz as the 'ideal' stimulation frequency. The documentation of the safety and efficacy of this method eventually led to the displacement of the posteroventral pallidotomy for PD in the 1990s (Limousin et al. 1995, Limousin et al. 1998, Laitinen 1977). In 1997, the US FDA issued an

approval for the use of thalamic DBS for ET (Koller et al. 1997), while DBS of the STN or globus pallidus for the treatment of PD was approved in 2002 (Deep Brain Stimulation for Parkinson's Disease Study Group 2001). In 2000, Coubes and colleagues reported on the effectiveness of DBS of the internal globus pallidus (GPi) for the treatment of DYT1 generalized dystonia (Coubes et al. 2000). Three years later, a Humanitarian Device Exemption (HDE) was granted by the FDA for pallidal DBS for the treatment of primary dystonia (Coubes et al. 2004).

Undoubtedly, the current era of DBS has been principally characterized by applications for the treatment of movement disorders. Nonetheless, the corroboration of the safety and clinical effectiveness along with the evolving refinement of this technology have served as an impetus for the resurgence of psychiatric neurosurgery and the initiation of clinical trials exploring application of DBS for treatment-refractory neuropsychiatric disorders. A synergetic factor for this evolution has been the exponentially growing literature correlating dysfunctional neuroanatomical and physiological circuits to psychiatric symptoms and explicitly pointing to the biological roots of psychiatric disorders (Kopell and Greenberg 2008). In 1999, Nuttin and colleagues observed beneficial effects of DBS of the anterior limbs of the internal capsule (IC) in three of four patients with treatment-refractory OCD (Nuttin et al. 1999). In the same year, Vandewalle and colleagues reported on the effectiveness of thalamic DBS in one patient with TS (Vandewalle et al. 1999).Ten years later, a humanitarian device exemption was granted by the FDA for DBS of the anterior limb of the IC for the treatment of OCD, an action that has been fiercely criticized by Fins and colleagues for entailing great risks for patient safety and research integrity (Fins et al. 2011(b)). In 2005, Mayberg and colleagues stated that DBS of the subgenual cingulate white matter (Cg25) effectively reversed symptoms in four of six patients with treatment-refractory MDD (Mayberg et al. 2005). The first report on the clinical effectiveness of DBS of the nucleus accumbens (NAcc) for the treatment of refractory addiction was published in 2009 by Müller and colleagues (Müller et al. 2009) following an observation of remarkable alleviation of a patient's comorbid alcohol dependency after DBS of the NAcc (Kuhn et al. 2007). Finally, in 2013, Lipsman *et al* designed a phase I pilot trial through which they assessed the safety and the clinical benefits of subcallosal cingulated DBS in patients with treatment-refractory AN (Lipsman et al. 2013). Remarkably, Laxton *et al* had meanwhile conducted the first phase I pilot trial of fornix/hypothalamic DBS for the treatment of Alzheimer's disease (AD) (Laxton et al. 2010), thereby extending the spectrum of DBS applications to cognitive disorders (figure 1.3).

1.2. Thesis Structure

The ultimate objective of this dissertation is the algorithmic design of a therapeutically- and energy-efficient closed-loop DBS system for movement and neuropsychiatric disorders, with special focus on advanced PD and treatment-refractory OCD, through the employment of stochastic dynamical modeling.

The dissertation is organized as follows.

Chapter 2 presents an analysis of the symptomatology, the pathophysiology and the neurocircuitry of PD, as well as of DBS for the advanced clinical stage of this condition.

Chapter 3 presents an analysis of the symptomatology, the pathophysiology and the neurocircuitry of OCD, as well as of DBS for the treatment-refractory form of this condition.

Chapter 4 introduces a data-driven model of stochastic nonlinear dynamics and evaluates collective dynamical and response properties of the subthalamic oscillatory activity in the pathological state, as crucial hallmarks for the selection of the optimal stimulation site during DBS for advanced PD. Specifically, the objective is to determine the applicability of the model within the framework of the principal mapping techniques that are commonly used intraoperatively: MER and macrostimulation testing.

Chapter 5 focuses on the evaluation of the efficiency of alternative STN-DBS protocols for advanced PD and treatment-refractory OCD. A modified version of the model introduced in chapter 4 is employed along with two MER datasets for the comparative assessment of the desynchronizing and therapeutic effect of standard (regular at 130Hz) versus eleven temporally alternative patterns of STN-DBS for PD and OCD, and for the determination of the particular pattern characteristics correlated with a significantly stronger desynchronizing and therapeutic effect.

Chapter 6 is devoted to the algorithmic design of a closed-loop STN-DBS system for advanced PD and treatment-refractory OCD, ensuring optimal performance in terms of both efficiency and selectivity of stimulation, as well as in terms of computational speed. The system incorporates the application of a phase-reduced bursting neuron model and direct search optimization based on quadratic modeling, through which optimal stochastic patterns and parameters of stimulation for minimum energy desynchronizing control of neuronal activity are being identified.

Chapter 7 concludes the dissertation with a summary of the main contributions of the thesis and a reference to future perspectives.

2

Parkinson's Disease

... the aspect of the patient is very characteristic. The head is bent forward, and the expression of the face is anxious and fixed, unchanged by any play of emotion. The arms are slightly flexed at all joints from muscular rigidity, and (the hands especially) are in constant rhythmical movement, which continues when the limbs are at rest so far as the will is concerned. The tremor is usually more marked on one side than on the other. Voluntary movements are performed slowly and with little power. The patient often walks with short quick steps, leaning forward as if about to run…

Gowers (1901)

2.1. Definition, Classification and Epidemiology

Parkinson's disease (PD), also known as idiopathic or primary parkinsonism, hypokinetic rigid syndrome (HRS), or paralysis agitans is the second most common neurodegenerative disorder after Alzheimer's disease (AD), pathologically characterized by the loss of dopaminergic cells of the substantia nigra pars compacta (SNc) in association with the presence of alpha-synuclein deposits (Lewy bodies) in the cytoplasm of neurons, and clinically by four cardinal symptoms: resting tremor, bradykinesia, rigidity, and postural instability (de Lau and Breteler 2006, Lang and Lozano 1998, Nussbaum and Ellis 2003). First descriptions of parkinsonian symptoms are found in ancient Egyptian and ayurvedic literature, but also in the Bible (Manyam 1990, Garcia Ruiz 2004). In 1817, the English scientist and political activist James Parkinson, published his

seminal work 'An Essay on the Shaking Palsy', describing the characteristic resting tremor, the abnormal posture and gait, paralysis and the diminished muscle strength in six cases (Parkinson 1817). In the second half of the nineteenth century, Jean-Martin Charcot pioneered in making the distinction between rigidity, weakness and bradykinesia, and further suggested the disease to be renamed in honor of James Parkinson (Charcot 1872).

Prevalence of PD in industrialised countries is generally estimated at 0,3% of the entire population with rates increasing to 1% to 2% and 4% to 5% for persons over age 65 and over 85, respectively (de Lau and Breteler 2006, Lang and Lozano 1998, Kowal et al. 2013). According to Zhang and Román (1993), with the exception of China, Japan and Africa, which have the lowest prevalence ratios, the actual prevalence variation for PD in geographically diverse populations is relatively low. However, ratios may be significantly influenced by local environmental risk factors. Five to ten percent of patients displays initial symptoms of PD between ages 21 and 39 (young-onset PD) (Bhidayasiri and Tarsy 2012). The significantly higher incidence of PD in men than in women has been attributed to the neuroprotective effects of estrogens, the higher frequency of intensity of occupational toxin exposure as well as of minor head trauma in men, and to recessive susceptibility genes on the X chromosome (Saunders-Pullman 2003, Wooten et al. 2004).

2.2. Clinical Signs and Symptoms

Resting tremor is the most easily recognized motor symptom of PD, occurring at a frequency of 3-8 Hz in the distal part of an extremity and disappearing with action or during sleep (Jankovic 2008). James Parkinson described tremor as '*involuntary tremulous motion, with lessened voluntary muscular power, in parts, not in action…*' (Parkinson 1817). Resting tremor is substantially differentiated from ET. About 69% of patients with PD demonstrate rest tremor at disease onset, 75% have tremor during the course of the disease, while tremor vanishes in 9% of patients in late-stage disease (Hughes et al. 2001). In addition to resting tremor, postural tremor may also occur in patients with PD (Jankovic et al. 1999).

Bradykinesia refers to the slowness of a performed movement or prolonged reaction time to initiate a movement (Hallett and Khoshbin 1980) and is often used as a synonym of akinesia and hypokinesia, despite certain differences in the meaning of these terms. Specifically akinesia refers to a reduction in the amount of spontaneous or associated movements and to freezing, while hypokinesia refers to the performance of slow and small movements. Difficulty in sustaining complex movements, i.e. repetitive, sequential or simultaneous movements, is a further characteristic of bradykinesia in PD (Agostino et al. 1994, Benecke et al. 1986, Scwab et

al.1954). Notably, while in PD bradykinesia may coexist with akinesia and hypokinesia, in dystonia and in Huntington's disease bradykinesia occurs in conjunction with *hyperkinesia*. Muscle weakness, rigidity, tremor, movement variability and bradyphrenia may contribute to bradykinesia in PD (Berardelli et al. 2001). Bradykinesia can be assessed through finger tapping, hand gripping or hand pronation-supination (Jankovic 2008, Kühn et al. 2008). It has been reported that bradykinesia is the motor manifestation of PD that correlates best with the degree of nigrostriatal dopaminergic deficiency (Vingerhoets et al. 1997).

Rigidity is defined as an increase in muscle tone and enhanced resistance to passive movements (Broussolle et al. 2007). It may occur proximally (neck, shoulders) or distally (ankles, wrists) (Jankovic 2008). Two types of parkinsonian rigidity exist: the leadpipe rigidity that is uniform throughout the entire movement and the cog-wheel rigidity that is regularly interrupted at the frequency of resting or postural temor (Broussolle et al. 2007). Rigidity was first recognized by Charcot (Charcot 1872) (figure 2.1) and further investigated at the beginning of the twentieth century by Negro, Moyer and Froment (Negro and Treves 1901, Moyer 1911, Froment and Gardere 1926). The 'Froment maneuver' facilitates the detection of rigidity through a voluntary movement of the contralateral limb (Froment and Gardere 1926a, Froment and Gardere 1926b). Shoulder pain is a clinical manifestation of PD associated with rigidity (Stamey and Jankovic 2007).

Postural instability, or impaired balance, can be present at early stages of untreated idiopathic PD, but becomes inevitably more prevalent with disease progression (Kim et al. 2013). In the Sydney Multicentre Study of Parkinson's disease, 34% of patients demonstrated postural instability within 2 years of diagnosis (Hely et al. 1989), while symptom manifestation was reported in 71% of the surviving patients within 10 years of diagnosis (Hely et al. 1999) and in 92% of the surviving patients within 15 years of diagnosis (Hely et al. 2005). Principally, postural instability along with freezing of gait are the motor manifestations of PD that are least responsive to dopaminergic medication and have been characterized as risk factors for PD dementia and falls, hence constituting two of the most disabling features of the disease (Müller et al. 2013, Plotnik et al. 2011, Kim et al. 2013, Bloem et al. 2004). It has been suggested that non-dopaminergic mechanisms, like increased neocortical b-amyloid deposition, even at low-range levels, are associated with higher severity of postural instability and cognitive impairment (Müller et al. 2013). Long latency to onset, but not duration, of recurrent falls is a characteristic with significant diagnostic validity, as it differentiates PD from other neurodegenerative disorders, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), and corticobasal degeneration (CBD) (Wenning et al. 1999).

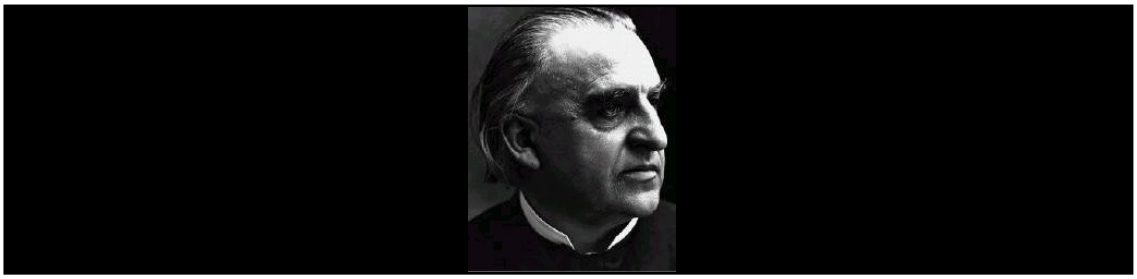


Figure 2.1. Neurologist Jean-Martin Charcot (1825-1893)

Freezing of gait is a form of akinesia typically manifested as a sudden and transient inability to initiate walking or to continue to move forward (Jankovic 2008, Bloem et al. 2004). Schaafsma et al (2003) described five subtypes of freezing: start hesitation, turn hesitation, hesitation in tight quarters, hesitation upon reaching a destination and hesitation in an open runway.Most freezing of gait episodes last less than 10 seconds, however with disease progression they become more frequent and disabling, and a greater risk factor for falls (Bloem et al. 2004). Levodopa helps in reducing the frequency and duration of off- but not on- related freezing of gait episodes (Schaafsma et al. 2003). About 47% of patients experience freezing regularly, while patients with the tremor dominant form of PD are likely to experience freezing less frequently (Macht et al. 2007).

Other postural deformities include rigidity of the neck and trunk (axial rigidity) (Jankovic 2008). Striatal hand represents an abnormal hand posture in PD, unresponsive to medication treatment (Spagnolo et al. 2014) (figure 2.2). Camptocormia, is a condition characterized by the extreme forward flexion of the thoracolumbar spine, which increases during walking and abates in the sitting and recumbent positions. In addition to PD, other causes of camptocormia include dystonia, myasthenia gravis, amyotrophic lateral sclerosis and extensor truncal myopathy (Sakas et al. 2010).

Other motor abnormalities include dysarthria, hypophonia, dysphagia and sialorrhoea, neuro-ophthalmological abnormalities and respiratory disturbances (Hoehn and Yahr 1967, Jankovic 2008). Many of these complications are equally or more disabling than the cardinal motor symptoms.

Non-levodopa responsive non-motor symptoms dominate the clinical picture of advanced PD, and have been classified among its most disabling features (Hely et al. 2005). Non-motor symptoms include sleep disturbances, cognitive and neuropsychiatric symptoms, autonomic dysfunction, and sensory symptoms (Chaudhuri et al. 2006).

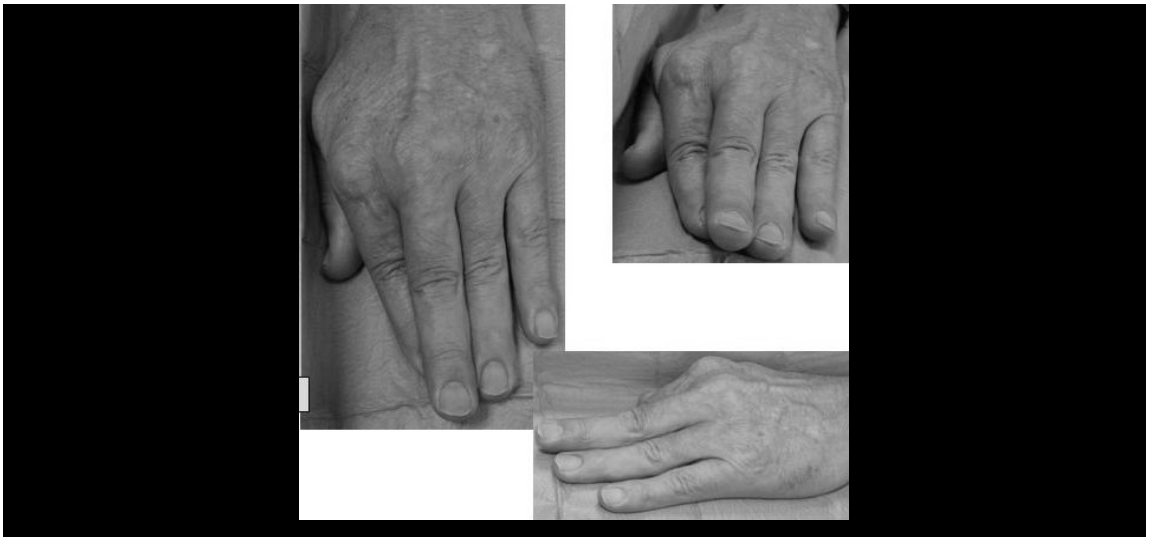


Figure 2.2. Striatal hand in PD (adapted with permission from Spagnolo et al. 2014)

Sleep disturbances in PD most commonly refer to rapid eye movement (REM) sleep behavioral disorder (RBD) and insomnia (Chaudhuri and Schapira 2009). RBD is a form of parasomnia characterized by an increase in frightening dream content accompanied by simple or complex movements (Schenck et al. 1986). Symptoms of RBD can predate the diagnosis of PD and may be associated with degeneration of the pedunculopontine and peri-ceruleal nucleus (Chaudhuri and Schapira 2009). Sleep-onset insomnia and sleep-maintenance insomnia are common in PD, but their occurrence is highly variable among patients (Gjerstad et al. 2006).

Cognitive decline has been reported to occur in about 84% of patients with advanced PD (Hely et al. 2005), while prevalence of dementia in advanced PD ranges from 48%-80% (Hely et al. 2005, Aarsland et al. 2011). The risk for developing dementia in PD-patients is up to six times higher compared to controls (Aarsland et al. 2001). A progressive dysexecutive syndrome, hallucinations, attentional deficits and fluctuating cognition characterize the neuropsychological profile of PD-related dementia (PDD) (Bosboom et al. 2004). Age-related neuropathological processes, cortical Lewy bodies, degeneration of the nucleus basalis of Meynert, and diseases like stroke and AD are correlated with the pathology of PDD (Helly et al. 2005).

Neuropsychiatric symptoms most commonly include depression, anxiety, apathy and hallucinations (Chaudhuri et al. 2006, Chaudhuri and Schapira 2009, Gallagher and Schrag 2012). These symptoms are more common in patients with PDD (Aarsland et al. 2007). According to a systematic review on the prevalence rates of depression in PD, the weighted prevalence of MDD appears to be about 17%, which is substantial, but less than the prevalence rates that are usually quoted (Reijnders et al. 2008). According to the same study the weighted prevalence of minor depression is 22% and of clinically significant depressive symptoms 35%. In cross-sectional studies, prevalence of anxiety in PD ranges from 20% to 49% (Aarsland et al.

2007, Dissanayaka et al. 2010, Negre-Pages et al. 2010, Riedel et al. 2010, Chen Y K et al. 2010). Generalized anxiety disorder, panic disorder and social phobia are the most common subtypes of anxiety in PD (Dissanayaka et al. 2010, Chen Y K et al. 2010). Comorbid depression and anxiety before the appearance of motor symptoms has also been reported (Shiba et al. 2000). It is generally considered that depression and anxiety in PD are more than just a reaction to the limitations of the disease, as there is evidence for a significant role of dysfunctional dopaminergic, serotoninergic, and norepinephrinergic pathways in manifestation of these symptoms (Gallagher and Schrag 2012, Remy et al. 2005, Chaudhuri and Schapira 2009). Apathy has been established as a distinctive feature of PD, whose underlying pathophysiological mechanism most probably involves limbic and ventral striatal dopamine deficiency (Czernecki et al. 2008) and contributions from cholinergic mechanisms (Gallagher and Schrag 2012). Visual hallucinations in PD have been reported to occur in 30-60% of treated patients, whereas auditory hallucinations occur more rarely and are almost always accompanied by visual hallucinations (Diederich et al. 2005). Moreover, delirium can occur in advanced dementia (Chaudhuri et al. 2006). There is no clear association between dopaminergic medication and the development of visual hallucinations (Papapetropoulos et al. 2005). Impaired visual input, cognitive impairment and impairment of the brainstem-regulated sleep-wake cycle are considered contributing factors for the development of psychosis in PD (Gallagher and Schrag 2012).

Autonomic dysfunction is a key feature in MSA, but occurs with varying severity in PD. The prevalence of orthostatic hypotension, bladder dysfunction, constipation, erectile dysfunction and hyperhidrosis has been reported to be significantly higher in PD compared with controls (Magerkurth et al. 2005).

Sensory symptoms in PD refer to olfactory dysfunction, visual impairment, central pain and pain related to motor fluctuations or dyskinesias secondary to dopaminergic treatment (Chaudhuri and Schapira 2009). According to the cross-sectional french DoPaMiP survey, about 39.3% of patients with PD have chronic pain related to PD (Negre-Pages et al. 2008).

2.3. The Hoehn and Yahr Scale, and the Unified Parkinson's Disease Rating Scale (UPDRS)

At present, there exists no single gold standard index to evaluate the severity of the motor and non-motor symptoms of PD. Instead, clinically based rating tests are employed. The

Hoehn and Yahr Scale was introduced in 1967, classifying disease progression into five stages based on the severity of motor impairment and compromised balance/gait (Hoehn and Yahr 1967). Thereby the disorder could be charted from unilateral (Stage 1) to bilateral disease without balance difficulties (Stage 2), to bilateral disease with postural instability (Stage 3),to severely disabling disease with loss of physical independence (Stage 4), and being wheelchair- or bed-bound (Stage 5) (Goetz et al. 2004). This five-point scale was subsequently modified to a seven-point scale during the 1990s (Jankovic et al. 1990) (table 2.1). Though over 40 years old, the scale continues to be used widely (Zhao et al. 2010). The Unified Parkinson's Disease Rating Scale (UPDRS) was originally developed in 1987 (version 3.0) evolving into the most widely used and tested clinical rating scale for comprehensive evaluation of both motor impairment and disability in PD, by virtue of its high internal consistency and inter-rater variability, moderate construct validity and stable factor structure (Fahn et al. 1987, Ramaker et al. 2002). In 2003, the Movement Disorder Society (MDS) sponsored Task Force for Rating Scales in PD suggested the development of an improved version of the UPDRS that would retain the strengths of the original version, but would further display a higher sensitivity incorporating the assessment of many important non-motor symptoms of PD (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease 2003). This modified version, termed the MDS sponsored UPDRS revision (MDS-UPDRS) (Goetz et al. 2007) (figure 2.3), successfully passed initial clinimetric testing in a series of over 800 native English-speaking patients, evolving into the official benchmark scale for PD (Goetz et al. 2008). According to Gallagher et al (2011), the MDS-UPDRS Part I total score has a strong relationship with a composite score of validated scales for the non-motor symptoms of PD.

Remarkably, reviews based on the use of the UPDRS or other rating scales to track the progression of PD (Post et al. 2007, Marras et al. 2002), or findings based on longitudinal follow-up data (Jankovic and Kapadia 2004), have suggested that the rate of progression of the disease may be nonlinear. Particularly higher age, postural instability/gait difficulty (PIGD) and lack of rest tremor at onset have been associated with a higher rate of disease progression.

2.4. Mortality

An approximately two-fold increased mortality rate (1.3-2.3) among patients with PD compared with the general population has been reported by studies referring to cohorts of patients with symptom onset after the introduction of the levodopa treatment (de Lau et al. 2005, D'Amelio et al. 2006, Herlofson et al. 2004, Driver et al. 2008). Different methodologies may account for the

Table 2.1. Comparison between the original and modified Hoehn and Yahr scale (adapted with permission from Goetz et al. 2004)

Hoehn and Yahr scale	Modified Hoehn and Yahr scale
1:Unilateral involvement only usually with minimal or no functional disability	1.0: Unilateral Involvement only
	1.5: Unilateral and axial involvement
2: Bilateral or midline involvement without impairment of balance	2.0: Bilateral involvement without impairment of balance
	2.5: Mild bilateral disease with recovery on pull test
3: Bilateral disease: mild to moderate disability with impaired postural reflexes, physicallyindependent	3.0:Mild to moderate bilateral disease; some postural instability; physically independent
4: Severely disabling disease; still able to walk or stand unassisted	4.0:Severe disability; still able to walk or stand unassisted
5:Confinement to bed or wheelchair unless aided	5.0:Wheelchair bound or bedridden unless aided

observed rate variability. A systematic review conducted by Ishihara et al (2007) showed that life expectancy in PD compared with the general population is reduced for all onset ages but this reduction is higher in individuals with young-onset PD: for patients with PD diagnosed between age 25 and 39 mean life expectancy was 38 years versus 49 years for the general population; for patients with PD diagnosed between age 40 and 64, life expectancy was 21 years versus 31 years for the general population and for patients with PD diagnosed at age 65 years or above, life expectancy was 5 years versus 9 years. Dementia, PIGD and lack of rest tremor at onset are associated with a significantly increased mortality risk (de Lau et al. 2005, de Lau and Breteler 2006, Diem-Zangerl et al. 2009). Specifically, the development of dementia is associated with a twofold increased mortality risk in PD (Levy G et al. 2002).

2.5. Pathophysiology of Parkinson's Disease

A hallmark pathologic feature of idiopathic PD is a selective degeneration of neuromelanin-laden dopaminergic neurons in the SNc (Zigmond and Burke 2002), that project to the striatum, but also to other basal ganglia nuclei, such as the external and internal segments of the globus pallidus (GPe, GPi, respectively), the subthalamic nucleus (STN), and the substantia nigra pars reticulata (SNr) (McIntyre and Hahn 2010). This feature has been correlated with a decrease in the level of expression of mRNA encoding the dopamine D1 receptor and an elevation in expression of mRNA encoding the dopamine D2 receptor (Gerfen et al. 1990). There is evidence pointing to the loss of dopaminergic neurons exclusively within the SNc, as the underlying cause of the cardinal motor manifestations of PD, based on

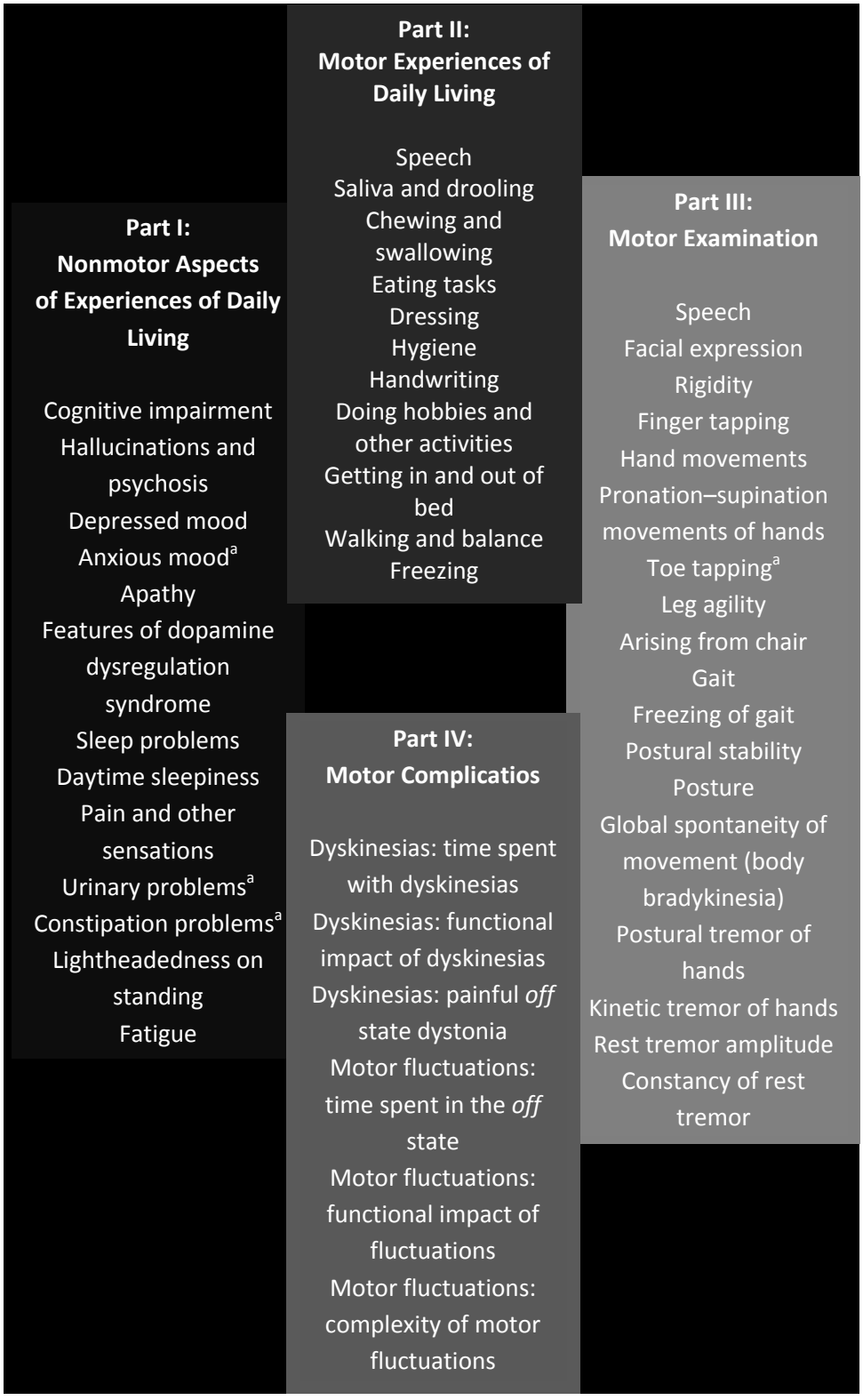


Figure 2.3. The Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al. 2007)

observations that the *N*-methyl- 4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), a neurotoxin selective for dopamine neurons of the SNc in humans and nonhuman primates, induces the development of the full spectrum of motor signs of PD (Langston et al. 1983). The greater neuronal loss in the ventrolateral tier (average loss 91%) of the SNc, compared with the medial ventral and dorsal tier (average loss 71% and 56%, respectively) of the nucleus (Fearnley and Lees 1991), is specific to PD, and accounts for a more severe loss of dopamine in the caudal portions of the putamen. These data suggest that the motor symptoms of PD are for the most part a consequence of dopamine loss in the putamen (Kish et al. 1988). Neuronal loss in PD, however, is not restricted to dopaminergic neurons, but also to populations of neurons in the locus coeruleus, the hypothalamus, the cingulate gyrus and entorhinal cortex, the olfactory bulb, sympathetic ganglia and parasympathetic neurons in the gut, as well as to serotoninergic neurons of the raphe nuclei and cholinergic neurons of the nucleus basalis of Meynert (Lang and Lozano 1998, Zigmond and Burke 2002). These neurodegenerative changes have been correlated with the development of the non-motor symptoms of PD (Lang and Lozano 1998, Zigmond and Burke 2002). However, there is evidence that a host of active compensatory processes serve to delay the onset of motor and non-motor symptoms in PD and that gross neurological deficits do not occur until the loss of dopamine is extreme (Zigmond 1997). Among the factors that have been implicated in neuronal degeneration in PD are mitochondrial dysfunction, oxidative stress, excitotoxins, deficient neurotrophic support, and immune mechanisms, probably induced by non-genetic factors in interaction with susceptibility genes (Lang and Lozano 1998, de Lau and Breteler 2006).

Another salient pathologic feature of idiopathic PD is the presence of Lewy bodies, eosonophilic inclusions that occur in the cytoplasm of selectively vulnerable neurons (Pollanen et al. 1993) and the presence of Lewy neurites, thread-like proteinaceous inclusions observed in affected brainstem regions, particularly in the dorsal motor nucleus of the vagus (Gai et al. 1995). Lewy bodies are generally 5 to 25 μm in diameter, with an electron dense granular core, a clear halo, and often a targetoid appearance. They are composed of radially oriented neurofilaments and are commonly observed in the SN, locus coeruleus, the dorsal motor nucleus of the vagus, the nucleus basalis of Meynert, the hypothalamus, but also in the neocortex, diencephalon, spinal cord, and peripheral autonomic ganglia (Gibb and Lees 1988). It has been hypothesized that formation of Lewy bodies from neurofilament subunits could alter the critical structural functions of neurofilaments in axons, leading to a disruption of axonal connections from the SNc to the striatum in PD (Lang and Lozano 1998, Trojanowski and Lee 1994). Neurofilaments of Lewy bodies in PD are tagged with ubiquitin, an antigen involved in protein degradation (Kuzuhara et al. 1988), and aggregates of α-synuclein (Spillantini et al. 1998, Spillantini et al. 1997, Mezey et al. 1998, Baba et al. 1998). Both proteins are found in the

core of Lewy bodies, but tendrils of synuclein make up the periphery (Mezey et al. 1998). The discovery of abnormal accumulations of α-synuclein in Lewy bodies along with the identification of mutations in the gene for α-synuclein in familial forms of PD (Polymeropoulos et al. 1997, Krüger et al. 1998) have highlighted the central role of this protein in the pathogenesis of PD**.** Notablly, α-synuclein has been identified not only in Lewy bodies of PD, but also the Lewy bodies of Hallervorden–Spatz syndrome (Arawaka et al. 1998), AD (Hamilton, Lippa), and diffuse Lewy body disease (Baba et al. 1998). In addition to α-synuclein, β-synuclein and γ-synuclein have also been implicated in the onset/progression of PD (Galvin et al. 1999). Besides, proteasomal proteins, synphilin, neurofilaments and microtubule-associated proteins have been identified within Lewy bodies in PD (Maries et al. 2003).

2.6. Neurocircuitry of Parkinson's Disease

…the basal ganglia can no longer be thought of as an unidirectional linear system that transfers information based solely on a firing-rate code. Rather, we propose that the basal ganglia are a highly organized network, with operational characteristics that simulate a non-linear dynamic system.

J. Obeso et al (2000)

Selective degeneration of heterogeneous populations of neurons in PD has proven to induce electrophysiological changes in the basal ganglia, thalamus and cortex. These changes include altered firing rates, altered processing of proprioceptive input, increased incidence of burst discharges, abnormal oscillatory activity, synchrony and cross-frequency coupling (Galvan and Wichmann 2008, Wichmann and DeLong 2002, Bergman and Deuschl 2002, DeLong and Wichmann 2009, Rubin et al. 2012, Lopez-Azcarate et al. 2010). Propagation of this abnormal activity throughout neural networks of the basal ganglia-thalamo-cortical loops has been suggested to be strongly correlated with the cardinal motor symptoms of PD (Bergman and Deuschl 2002, Kühn et al. 2009). The significant progress in our understanding of the mechanisms underlying the motor abnormalities of PD, through which parkinsonism has emerged as a complex network disorder (DeLong and Wichmann 2007), has been achieved on the basis of three notable accomplishments: the development of models of the functional organization of the basal ganglia (Alexander et al. 1986, Alexander and Crutcher 1990, Penney and Young 1986, Albin et al. 1989, DeLong 1990), the discovery that nonhuman primates treated with MPTP develop behavioral alterations that closely mimic motor symptoms of PD in humans (Burns et al. 1983), and the unique opportunity provided by functional neurosurgery to directly record from the human basal ganglia (Brown and Williams 2005).

The basal ganglia are a group of functionally related subcortical nuclei that include the neostriatum (composed of the caudate nucleus and the putamen), the GPe, the GPi, the STN, the SNr, and the SNc. The basal ganglia participate in anatomically and functionally segregated loops that subserve the function of the 'motor', 'associative' and 'limbic' cortical areas. The striatum and, to a less extent, the STN are the main entries for cortical and thalamic inputs into the basal ganglia. The main basal ganglia output nuclei are the GPi and the SNr, that project to the ventral anterior and ventrolateral nuclei of the thalamus (VA/VL), which then send efferents back mainly to frontal cortical areas (Alexander et al. 1986, Alexander and Crutcher 1990). The projections between the striatum and GPi/SNr are thought to be organized into two distinct pathways, a monosypatic 'direct' pathway, and a polysynaptic 'indirect' pathway involving the GPe and the STN (Alexander and Crutcher 1990, Penney and Young 1986, Albin et al. 1989, DeLong 1990). These pathways originate from separate populations of striatal medium spiny neurons (MSNs), whose activity is differentially modulated by prominent dopaminergic input from the SNc. The direct pathway is an inhibitory projection from MSNs that include neuropeptides (substance-P and dynorphin) and dopamine D1-receptors to the GPi/SNr. The indirect pathway is a polysynaptic inhibitory projection from MSNs that contain dopamine D2-receptors and enkephalin to the GPe followed by inhibitory projections between GPe and GPi/SNr, either directly or via the glutamatergic STN. The segregation of D1and D2 receptors reflects the dual action of striatal dopamine release that over the direct pathway reduces the inhibitory output from GPi/SNr, thereby disinhibiting the activity of thalamocortical projection neurons and *facilitating* movements, and over the indirect pathway increases the inhibitory output from GPi/SNr, inhibiting the thalamocortical activity and s*uppressing* movements (Gerfen et a. 1990). Eventually, the net effect of dopamine release from the nigrostriatal projection is the reduction of basal ganglia output to the thalamus, disinhibiting thalamocortical activity, and, through greater activation of the cerebral cortex, facilitating movement (Wichmann and DeLong 2002). In addition to the direct and indirect pathways, the hyperdirect pathway, a cortico-subthalamic projection, evokes an increase of the basal ganglia output, producing the same effect as the indirect pathway, but in significantly less time (Wichmann et al. 2011, Nambu et al. 2002) (figure 2.4).

Studies of dopamine-depletion induced metabolic changes in the basal ganglia of MPTP-treated non-human primates carried out by Alan Crossman and colleagues demonstrated that 2-deoxyglucose (2DG) is increased in both pallidal segments (Crossman et al. 1985, Mitchell et al. 1989, Scwartzman and Alexander 1985). Subsequent microelectrode recordings of neuronal activity showed that MPTP-induced parkinsonism in nonhuman primates is associated with reduced spontaneous neuronal activity in the GPe and increased neuronal discharge in the STN and GPi, as compared to normal controls (Miller and DeLong 1985, Filion and Tremblay 1991).

Analogous studies pointed to reduced basal ganglia output in nonhuman primate models of experimentally induced chorea, hemiballism, and dyskinesias (Crossman 1990, Mitchell et al. 1985). Together, these important early studies gradually led to the development of the 'rate model' of the pathophysiology of movement disorders by Albin et al. (1989) and DeLong (1990). In this seminal work, firing rate changes observed in basal ganglia nuclei in movement disorders are considered to reflect a modulated inhibitory output from the GPi to the thalamus, resulting from unbalanced activity in the basal ganglia-thalamo-cortical 'motor' circuit. In particular, striatal dopamine depletion leads to increased inhibitory activity over the indirect pathway and decreased activity over the direct pathway, resulting in inhibition of the GPe, and subsequent disinhibition of the STN and the GPi/SNr. Conversely, decreased output from the GPi to the thalamus underlies the manifestation of hyperkinetic disorders. Thereafter, further insights into the pathophysiology of PD corroborated the findings of increased neuronal activity in the GPi and STN (Bergman et al. 1994, Hassani et al. 1994). Moreover, lesions of the STN or GPi were proven to reverse the cardinal motor disturbances of parkinsonism in MPTP-treated non-human primates, thereby implicitly supporting the postulated role of excessive activity in the GPi and STN in PD (Bergman et al. 1990, Wichmann et al. 1994(b), Aziz et al. 1991, Guridi et al. 1996). Despite these breakthroughs, however, the main assumptions and predictions of the classical Albin-DeLong rate model were contradicted by a number of additional observations, including evidence that GPe or thalamic lesions may not consistently induce parkinsonism (Soares et al. 2004, Marsden and Obeso 1994), and that DBS may ameliorate parkinsonian symptoms by increasing the GPi output to the thalamus (Hashimoto et al. 2003) or by suppressing pathological synchronization (the 'noisy signal' hypothesis) (Brown and Eusebio 2008), suggesting a pivotal role of additional contributing factors in the development of the behavioral manifestations of PD .

One of the most prominent pattern abnormalities in MPTP-treated nonhuman primates and in patients with PD is a greater incidence of burst discharges in the GPe, STN,GPi, SNr, and basal ganglia-receiving areas of the thalamus compared to the physiological state (Miller and DeLong 1987, Filion and Tremblay 1991, Wichmann et al. 1999, Wichmann and Soares 2006, Bergman et al. 1998, Hutchison et al. 2004, Magnin et al. 2000), observed early in the course of dopamine depletion (Ni et al. 2001, Vila et al. 2000, Breit et al. 2007) (figure 2.5(a)). Post-inhibition rebound bursting due to dopamine depletion, demonstrated to occur in the GPe, GPi, STN, and thalamic neurons (Bevan et al. 2006, Bevan et al. 2007, Shen and Johnson 2005, Beurrier et al. 1999, Cooper and Stanford 2000, Gillies et al. 2002), and modulation of the function of the STN-GPe 'pacemaker' (Plenz nad Kitai 1999) are considered the main physiological mechanisms underlying the development of neuronal burst firing in PD.

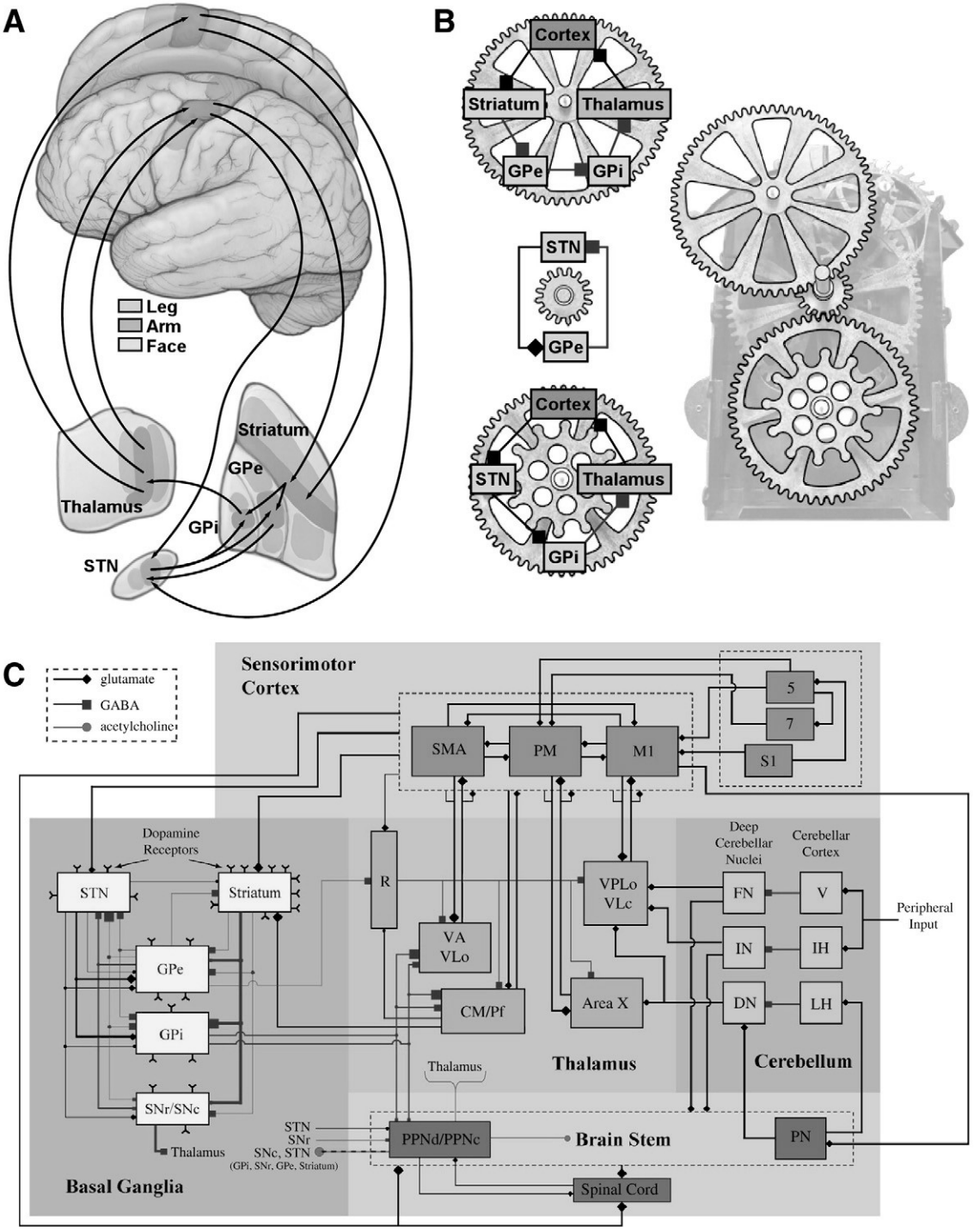
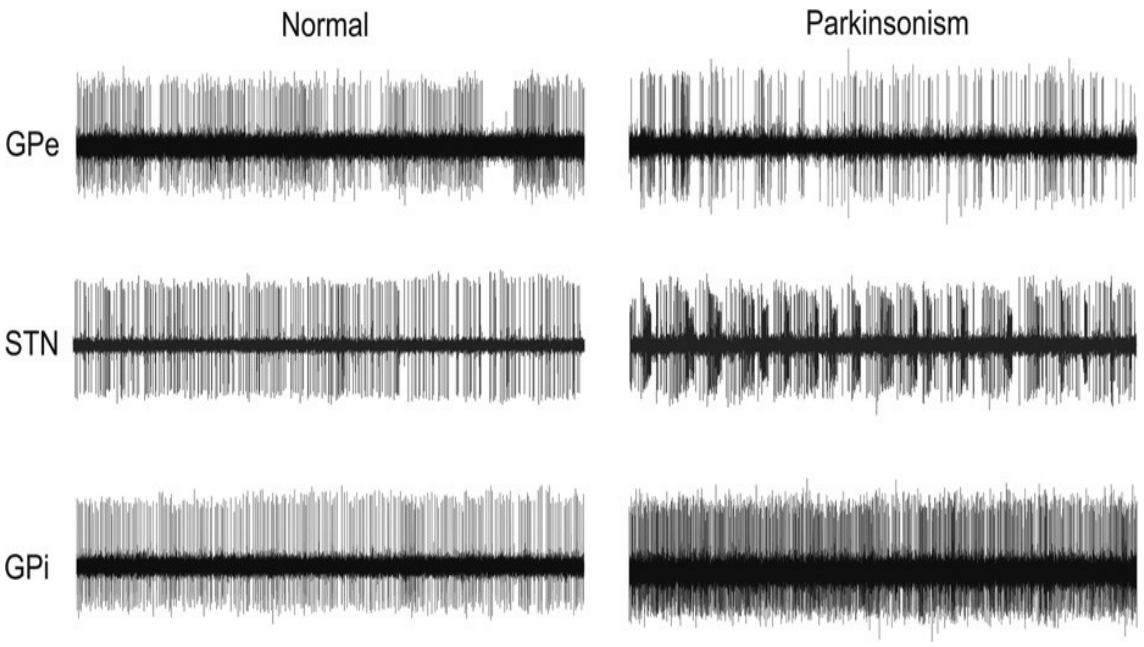
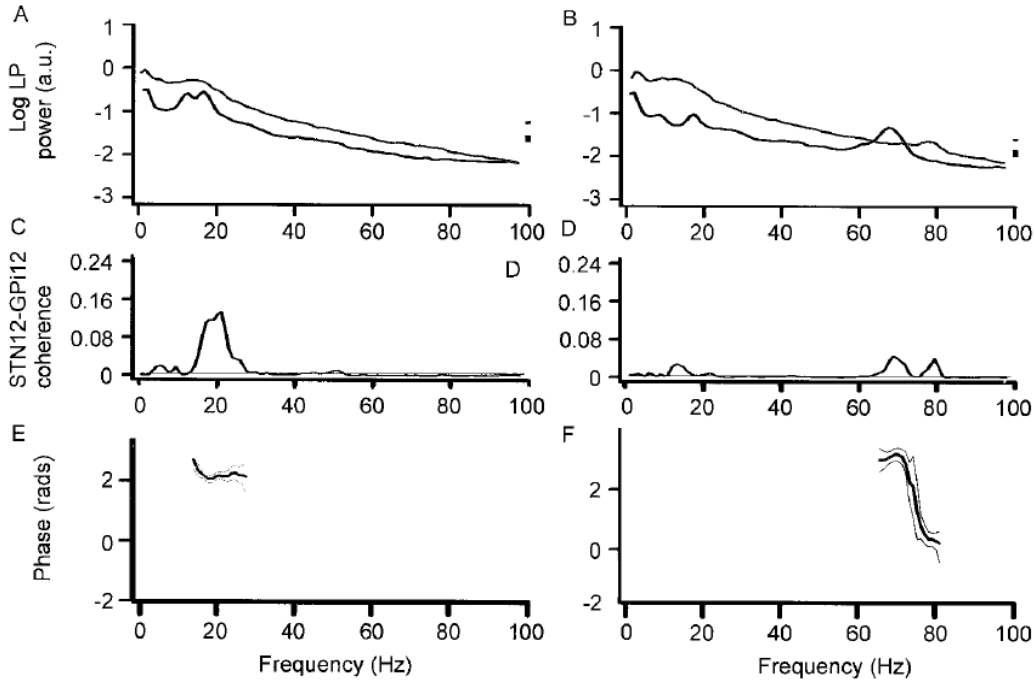


Figure 2.4. Detailed schematic of the sensorimotor network (adapted with permission from Johnson et al. (2008))

Secondly, the presence of abnormal oscillatory activity in single neurons of the basal ganglia, thalamus and cortex, particularly in the alpha (~4-8Hz) and beta (~11-30Hz) frequency bands, has been documented based on microelectrode recordings obtained during DBS surgery for PD (Levy et al. 2000, Weinberger et al. 2006, Moran et al. 2008), and MPTP-treated nonhuman primates (Bergman et al. 1994, Rivlin-Etzion et al. 2006, Raz et al. 2000). Furthermore, in local field potential (LFP) recordings, considered to reflect the synaptic input to a large neuronal population (Logothetis 2002), prominent beta oscillatory activity in the STN and GPi of patients with PD undergoing functional neurosurgery has also been demonstrated (Brown et al. 2001). LFP recordings are either obtained intraoperatively from microelectrodes or postoperatively from DBS macroelectrodes, in the interval between implantation and subsequent connection to a subcutaneous stimulator (Brown and Williams 2005). According to Brown et al (2001), who originally assessed LFP recordings from the STN and GPi in patients with PD (therein referred to under the term 'local potentials' (LPs)), beta oscillatory activity in these nuclei is reduced by levodopa treatment, whereas gamma-band (>30Hz) oscillatory activity is increased (figure 2.5(b)). This latter finding is in agreement with evidence that the degree of pallidal gamma oscillations is positively correlated with basal ganglia control of motor performance (Brücke et al. 2012). Further studies have corroborated the presence of abnormal oscillatory activity in PD based on LFP recordings obtained either intra- or postoperatively (Weinberger et al. 2006, Moran and Bar-Gad 2010, Kühn et al. 2004, Kühn et al. 2005, Kühn et al. 2008, Kühn et al. 2009, Pogosyan et al. 2006). Remarkably, the LFP spectrum at rest may be characterized by a 'signature' rhythm for an individual with PD (Tsirogiannis et al. 2009). Despite data that abnormal oscillations do not develop in the early phase of parkinsonism (Leblois et al. 2007), the existence of a possible correlation between alpha- and beta-band oscillatory activity and specific motor and non-motor manifestations in PD has been well documented. In this regard, it has been reported that anticholinergics, which fail to treat bradykinesia, but can ameliorate rigidity and tremor, do not suppress beta LFP activity in the STN of patients with PD. This implies that dopaminergic suppression of beta oscillatory activity is selective and may be linked to bradykinesia, but not to tremor (Priori et al. 2004, Brown and Williams 2005). This assumption has been validated and extended by further studies that have reported a positive correlation between treatment-induced suppression of beta oscillatory activity in the STN and improvement in both bradykinesia and rigidity, but not tremor (Kühn et al. 2006, Kühn et al. 2008, Kühn et al. 2009, Ray et al. 2008). Additionally, it has been proven that the complexity of LFPs in the beta-frequency band correlates negatively with bradykinesia and rigidity in untreated patients (Chen C C et al. 2010), and that 10- or 20-Hz DBS stimulation of the STN in patients with PD results in deterioration of akinesia/bradykinesia (Timmermann et al. 2004, Timmermann and Florin 2012, Chen C C et al. 2007). On the other hand, though parkisonian tremor may not be strictly correlated with



(a)



(b)

Figure 2.5. (a) Extracellular electrophysiologic recordings in the GPe, STN, and GPi of normal and MPTP-treated non-human primates. Each data segment is 5 s in duration (reproduced with permission from Galvan et al. 2008). (b) First report on the assessment of LFP recordings from the STN and Gpi of patients with PD (reproduced with permission from Brown et al. 2001). Autospectra of STN LP power (A, B) coherence spectra between STN and GPi (C, D), and respective phase spectra (E, F) after withdrawal (A, C, E) or reinstitution (B, D, F) of levodopa treatment. Data pooled from records at rest in four patients with PD.

oscillations in basal ganglia networks (Rivlin-Etzion et al. 2006, Wichmann and DeLomg 2002), oscillatory activity in the alpha and theta frequency ranges appears to play an efferent role in rest tremor generation (Levy et al. 2000, Levy R et al. 2002 (a), Hurtado et al. 1999, Raz et al. 2000, Bergman et al. 1994, Contarino et al. 2011, Tass et al. 2010). Last, the development of certain dopaminergic-mediated motor or behavioral abnormalities, namely dyskinesias and impulse control disorders, has been reported to be significantly correlated with 4-10Hz oscillations in the STN of patients with PD (Alonso-Frech et al. 2006, Rodriguez-Oroz et al. 2010). The presence of abnormal oscillatory activity in basal ganglia neurons or neuronal populations may be attributed to the interplay in the STN-GPe network (Tsirogiannis et al. 2009, Pavlides et al. 2012, Galvan and Wichmann 2008, Nevado Holgado et al. 2010).

Closely related to the incidence of burst and oscillatory discharges, is the marked change in the synchronization of discharge of basal ganglia and thalamic neurons in the parkinsonian state, thought to reflect a breakdown of functional segregation in the basal ganglia-thalamo-cortical circuitry (Levy et al. 2000, Raz et al. 2000, Moran et al. 2008, Moran and Bar-Gad 2010, Weinberger et al. 2006, Hammond et al. 2007, Terman et al. 2002, Heimer et al. 2002, Goldberg et al. 2010, Bergman et al. 1994, Bergman and Deuschl 2002, Pessiglione et al. 2005). This is in contrast to the virtual absence of correlated activity between these neurons under normal conditions (Wichmann et al. 1994(a), Nini et al. 1995, Heimer et al. 2002, Raz et al. 2000, Bar-Gad et al. 2003). LFPs are considered a surrogate marker of synchronization of neuronal discharge within and between basal ganglia nuclei (Brown et al. 2001). Thereupon, beta-band oscillatory synchronization has been reported in the STN of patients with PD (Levy R et al. 2002 (b), Weinberger et al. 2006, Moran and Bar-Gad 2010, Kühn et al. 2005). Interestingly, in the same studies it is further suggested that neuronal discharges in the STN of patients with PD are locked to beta oscillatory activity in the LFPs, thereby pointing to an even stronger biomarker of pathological synchronization. Moran et al (2008) and Moran and Bar-Gad (2010) have originally introduced the term 'background unit activity' considered to reflect spiking activity of small localized subpopulations, in order to estimate the degree of coherence between the respective signal and single-unit activity or LFPs, and thereby to optimally evaluate synchronization in the STN of patients undergoing functional neurosurgery for PD. Treatment-induced modulation of pathological patterns of synchronized oscillations in the STN of patients with PD, specifically the suppression of beta oscillatory activity, has been correlated with improvement in bradykinesia and rigidity (Kühn et al. 2008, Eusebio et al. 2010), while a direct association between finely tuned oscillatory synchronization in the beta frequency band and motor impairment in PD has also been reported (Kühn et al. 2009, Pogosyan et al. 2006). In addition, there is a substantial body of evidence that the degree of synchronization of subthalamic nucleus activity in the beta frequency band is strongly involved in motor

programming, movement initiation and REM sleep (Levy R et al. 2002 (b), Williams et al. 2010, Cassidy et al. 2002, Doyle et al. 2005, Kühn et al. 2004, Joundi et al. 2012, Jenkinson and Brown 2011, Tzagarakis et al. 2010, Foffani et al. 2005, Androulidakis et al. 2008 (a), Amirnovin et al. 2004, Urrestarazu et al. 2009). Striatal dopamine depletion has been suggested as an underlying cause of pathological synchronization in the basal ganglia in PD, on the basis of the observation that dopaminergic medication reverses abnormal synchrony in MPTP-treated nonhuman primates and patients with PD (Heimer et al. 2002, Levy et al. 2002 (b), Brown et al. 2001). Similar to the previous cases, the coupling architecture and dynamic interactions within the subthalamopallidal circuit appear to be additional self-sustaining mechanisms for the emergence of correlated rhythmic activity in the pathological condition (Terman et al. 2002, Tsirogiannis et al. 2009).

Documentation of excessive and unselective neuronal responses to passive joint manipulation in the STN, GPi and thalamus of patients with PD, raises the hypothesis that a loss of functional segregation in the basal ganglia-thalamo-cortical circuitry and the disinhibition of competing motor mechanisms underlie the core signs of parkinsonism (Mink 1996). In particular, studies on movement-related neuronal activity based on microelectrode recordings in the basal ganglia or the thalamus of MPTP-treated nonhuman primates, demonstrated an increase in number, amplitude and non-specificity of movement-related responses, compared with the normal untreated state (Filion et al. 1988, Bergman et al. 1994, Boraud et al. 2000, Pessiglione et al. 2005, Leblois et al. 2007).

Last, special reference should be made to the pathophysiological changes observed outside the basal ganglia-thalamo-cortical network, specifically in the PPN. The PPN is a component of the reticular formation located at the junction of the midbrain and pons (Olszewski and Baxter 1954) involved in the processing of gait (Piallat et al. 2009). It has been suggested that factors including disruption of the extensive interconnections between this brainstem region and the basal ganglia or the spinal cord, along with significant degeneration of cholinergic PPN neurons are associated with postural instability and gait dysfunction in PD (Pahapill and Lozano 2000, Mena-Segovia et al. 2004, Nandi et al. 2002, Rinne et al. 2008, Karachi et al. 2010). Furthermore, it has been demonstrated that administration of levodopa strongly promotes oscillatory synchronization in the alpha frequency band, in the PPN of patients with PD (Androulidakis et al. 2008 (b), Androulidakis et al. 2008 (c), Fraix et al. 2013), while attenuation of this oscillatory activity has been associated with gait freezing (Thevathasan et al. 2012, Fraix et al. 2013). Thus, synchronization in the alpha frequency band in the PPN area may represent a physiological pattern of activity substantially correlated with regulation of locomotion.

2.7. Current and Projected Economic Burden in the USA

The progressive nature of PD, with respect to the severity of both motor and non-motor disabilities, exerts a major negative impact on activities of daily living and health –related quality of life (Rahman et al. 2008). Absence of pharmacological interventions with enduring disease-modifying properties, along with an increasing longevity and ageing population, translates into a substantial and growing economic burden on patients, care-givers and the healthcare system, due to both medical (direct) and non-medical (indirect) costs (Chen J J 2010) (figure 2.6). Medical (direct) costs mainly refer to expenditures on hospitalization, nursing home care and pharamaceutical therapies, whereas non-medical (indirect) costs principally refer to economic costs due to reduced employment, workdays lost because of illness, reduced household income, higher disability payments, adult day or formal care, and household expenditures (Kowal et al. 2013, Huse et al. 2005, Zhao et al. 2013, O'Brien et al. 2009). According to Kowal et al (2013), the national economic burden of PD in the United States exceeded $14.4 billion in 2010 (approximately $22,800 per patient), $8.1 billion higher ($12,800 per capita) than expected for a population without PD. Indirect costs were estimated at $6.3 billion (approximately $10,000 per patient).Nursing home care was found to be a major medical cost, whereas reduced employment a major indirect cost of PD. Disease prevalence and economic burden are projected to increase considerably over the next decades (Dorsey et al. 2007, Kowal et al. 2013). Therefore, there is an urgent need for continuous refinement of treatment interventions to slow or disrupt the progression of motor and nonmotor disabilities in PD (Chen J J 2010).

2.8. Nonsurgical Management

Despite steady advances, no neuroprotective or disease-modifying therapy has yet been established (Rascol et al. 2011, Meissner et al. 2011).The revolutionary introduction of dopamine precursor levodopa (L-dopa) for the treatment of parkinsonism, more than forty years ago (Cotzias et al. 1969), clearly set the stage for the use of this pro-drug as a gold standard for symptomatic treatment of PD. Nonetheless, since dopaminergic dysfunction is not an exclusive underlying pathophysiologic mechanism of PD, certain motor manifestations, including gait impairment and postural instability, as well as the majority of non-motor manifestations (table 3.1) cannot be effectively treated with levodopa monotherapy (Post et al. 2011, Gallagher and Schrag 2012). Essentially, these symptoms constitute the most disabling long-term problems in PD (Hely et al. 2005). Moreover, levodopa-related motor complications, particularly motor fluctuations (wearing-off episodes) and dyskinesias, are experienced by approximately 40% of the patients within 4-6 years after starting levodopa therapy (Fahn 1999, Rascol et al. 2011,

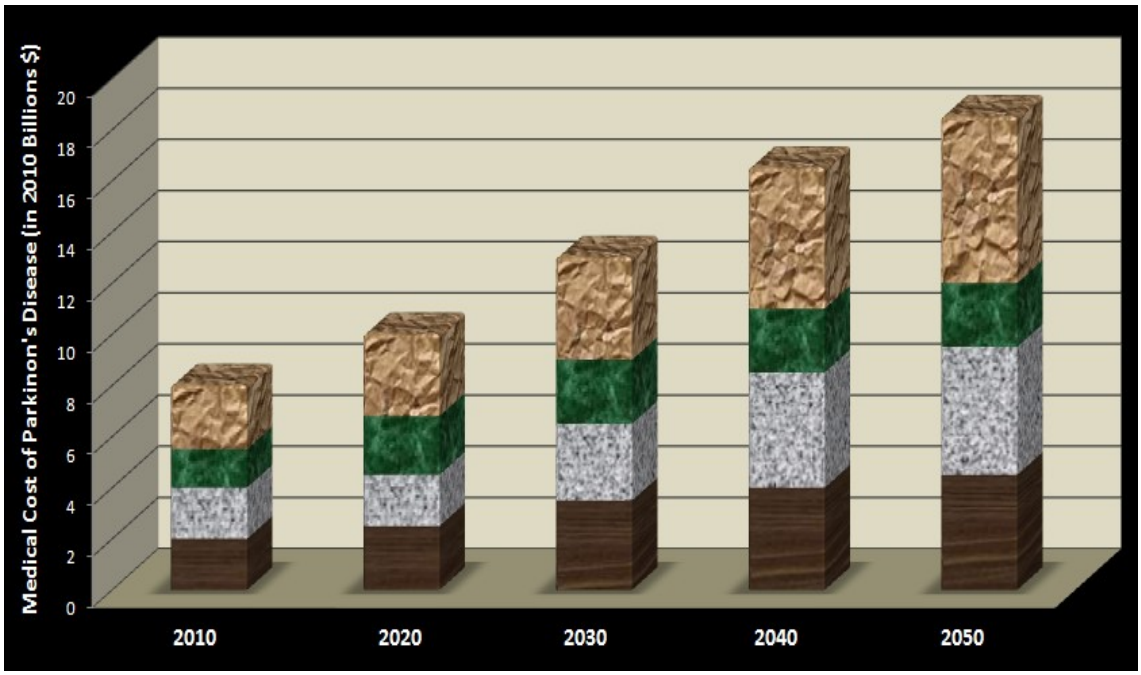
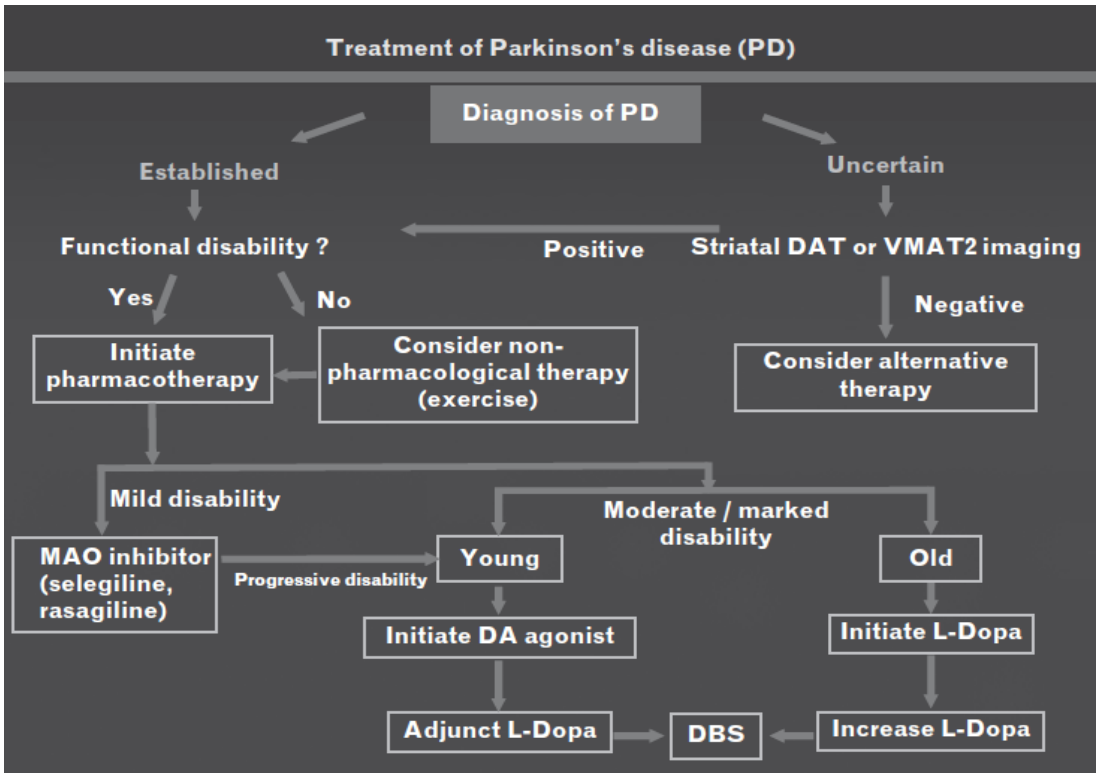


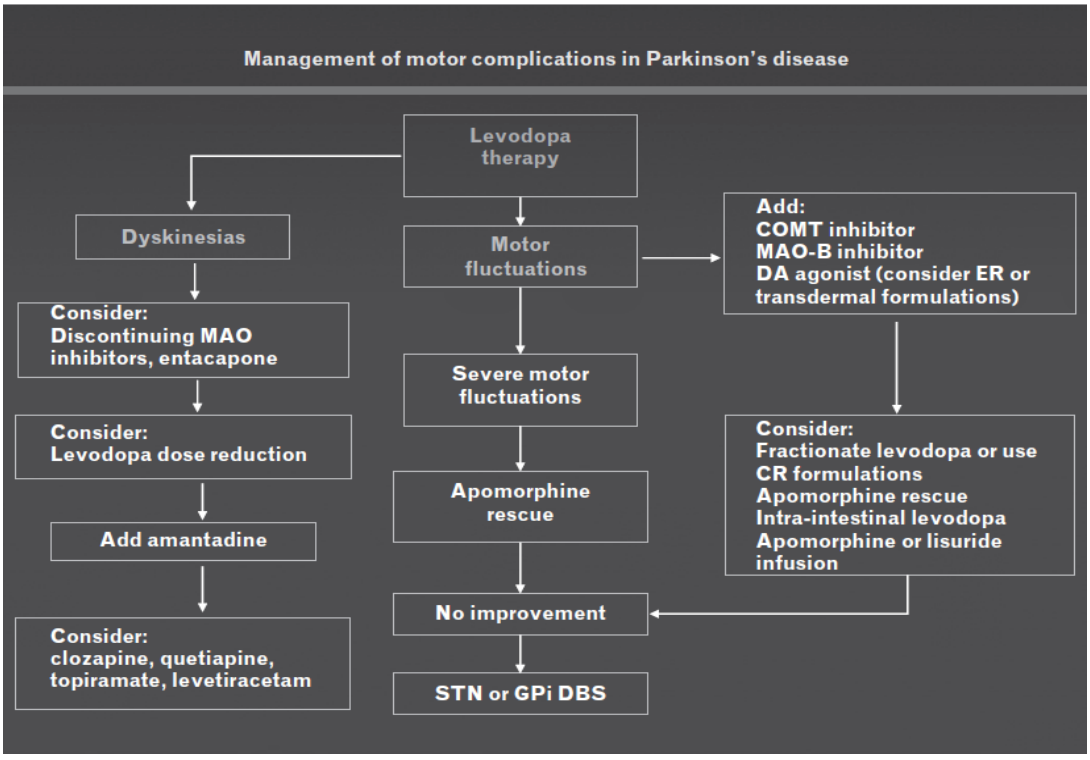
Figure 2.6. Medical costs of PD over time, including self/family (dark brown), commercial (grey), public (green) and Medicaid (light brown) costs (adapted with permission from Kowal et al. 2013).

Ahlskog and Muenter 2001). Several lines of evidence indicate that younger patients have a higher risk of levodopa-induced dyskinesias (Warren Olanow 2013, Jankovic and Poewe 2012). The above limitations emphasize the need for improved pharmacologic options and therapeutic strategies individualized to the patient's particular needs, age and other characteristics (Brichta et al. 2013, Jankovic and Poewe 2012, Fox et al. 2011, Seppi et al. 2011).

Inhibitors of monoamine oxidase type B (MAO-b) have received renewed attention over the last decade, based on a possible neuroprotective and disease-modifying effect of rasagiline and its implication in numerous mitochondrial mechanisms (Jenner and Langston 2011). Symptomatic therapy with MAO-b inhibitors is considered necessary for the treatment of PD in early stages (Jankovic and Poewe 2012) (figure 3.1(a)). Early monotherapy with dopamine receptor agonists, like pramipexole, ropinirole and rotigotine, provides sufficient symptomatic benefit over periods of up to 5 years and a significantly reduced risk of motor complications compared with levodopa (Fox et al. 2011, Brichta et al. 2013, Antonini et al. 2009). This fact suggests that dopamine agonists could be used in order to delay levodopa therapy in young patients with PD (Jankovic and Poewe 2012). However, compared with levodopa, dopamine agonists are associated with a higher incidence of dopaminergic adverse effects such as edema, somnolence, hallucinations and impulse control disorder (Antonini et al. 2009). Therefore, levodopa may be appropriate as an early symptomatic therapy in elderly patients who are more susceptible to neuropsychiatric side effects of dopamine agonists



(a)



(b)

Figure 2.7. Suggested guidelines for the treatment of (a) early to advanced staged PD and (b) levodopa-related motor fluctuations and dyskinesias. DA, dopamine; DAT,dopamine transporter; DBS, deep brain stimulation; MAO, monoamine oxidase; VMAT2, vesicular monoamine transporter type 2. COMT, catechol-Omethyl transferase; CR, controlled release; DA, dopamine; ER, extended release; GPi, globus pallidus interna; MAO, monoamine oxidase; STN, subthalamic nucleus (reproduced with permission from Jankovic and Poewe 2012).

(Jankovic and Poewe 2012). With disease progression, however, dopamine diffusion extracellularly and its catabolism by MAO and catechol-O-methyl transferase (COMT) might trigger the manifestation of motor complications (Troiano et al. 2009). Adjunctive therapy for the control of motor fluctuations in levodopa-treated patients with advanced PD is principally based on COMT or MAO-b inhibitors, dopamine agonists, duodenal infusions of levodopa, and apomorphine (Brichta et al. 2013, Jankovic and Poewe 2012, Fox et al. 2011, Talati et al. 2009), while amantadine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is so far the only approved compound providing a durable, yet modest, antidyskinetic benefit (Gottwald and Aminoff 2011) (figure 3.1 (b)). Notably, clinical efficacy of amantadine is being evaluated for the therapy of gait abnormalities (Chan et al. 2013, Lee et al. 2013).

Non-motor symptoms of PD, although frequently under-reported, are highly debilitating in advanced PD and exert significant impact on health-related quality of life (Politis et al. 2010, Rahman et al. 2008). The pathogenesis of some non-motor symptoms in PD is likely to differ substantially from non-PD patients (Gallagher and Schrag 2012). Therefore the development of disorder-specific management strategies is highly important (table 3.1). To date, efficacy of dopamine agonist pramipexole for the treatment of depressive symptoms, clozapine for the treatment of psychosis and rivastigmine for the treatment of dementia in PD has been well-established (Seppi et al. 2011). Evidence for the efficacy of repetitive transcranial magnetic stimulation (rTMS) for the treatment of depression or depressive symptoms in PD remains inconclusive (Seppi et al. 2011, Gallagher and Schrag 2012).

Gene therapy refers to the delivery of therapeutic proteins to a target region. The safety and efficacy of bilateral, intrastriatal delivery of ProSavin®, a lentiviral vector-based gene therapy aiming at restoring dopamine production in patients with advanced PD, has been recently corroborated by an open-label study, but further confirmation of these results in double-blind trials is required (Palfi et al. 2014).

2.9. Neurosurgery for Parkinson's Disease

We need to refocus our efforts by exploring new targets, stimulation parameters and paradigms, and technology that takes into account the anatomic variations of different targets and begin to explore the possibility of targeting locomotor centers and fiber tracts for gait and balance problems associated with PD.

J. L. Vitek (2012)

2.9.1. Deep Brain Stimulation for Parkinson's Disease

High frequency deep brain stimulation, as an adjunct to medical management, is an established and cost-effective treatment for advanced PD (Fox et al. 2011, Hickey and Stacy 2011, Williams et al. 2003, Eggington et al. 2014). Particularly, eligible for this procedure are patients with idiopathic, advanced PD who have medically intractable motor fluctuations, intractable tremor, or intolerance to medication -related adverse effects and no significant active cognitive or psychiatric problems. Surgery should be conducted by experienced multidisciplinary teams (Bronstein et al. 2011, Lozano 2012). The STN is generally the preferred target for stimulation (Benabid et al. 2009, Schuurman and Bosch 2007, Lozano 2012, Albanese and Romito 2011, Oderkerken et al. 2013, Foltynie and Hariz 2010).Significantly higher efficiency of STN-DBS for advanced PD versus medical management alone has been documented by large randomized controlled studies (Williams et al. 2013, Deuschl et al. 2006, Weaver et al 2009, Okun et al. 2012). Particularly, STN-DBS has been proven to induce remarkable and long-lasting improvement on levodopa-responsive symptoms and tremor, but also to significantly suppress dyskinesia and motor fluctuations in patients with advanced PD (Bronstein et al.2011, Castrioto et al. 2011 (a), Zibetti et al. 2011, Fasano et al. 2010, Rizzone et al. 2014, Moro et al. 2010, Vitek 2012 (a), Sturman et al. 2004, Hamani et al. 2011, Krack et al. 2003). In contrast to appendicular signs, however, progression of axial motor signs including levodopa-resistant gait impairment and postural-instability remains uncontrolled after STN-DBS surgery (Castrioto et al. 2011 (a), Zibetti et al. 2011, Fasano et al. 2010, Rizzone et al. 2014, Moro et al. 2010, Krack et al. 2003, Rodriguez-Oroz 2012). Development of non-motor symptoms including a significant cognitive decline, incidence of depression or anxiety, and a remarkable decline in speech intelligibility, over a long period after STN-DBS, has also been reported (Rizzone et al. 2014, Zibetti et al. 2011, Tripoliti et al. 2011, Moro et al. 2010, Klostermann et al. 2008, Temel et al. 2006 (a), Voon et al. 2006, 2008, Guehl et al. 2006, Krack et al. 2003, Rodriguez-Oroz et al. 2012). Rizzone et al (2014) reported that advanced age at disease onset, a high axial subscore in the off-condition and the presence of RBD at baseline are associated with a higher risk of developing disability over time under STN-DBS. Nevertheless, STN-DBS has proven to be a more effective treatment compared with pallidotomy (Esselink et al. 2009). In general, it is estimated that less than 5% of patients with PD meet eligibility criteria for STN-DBS, with an early stage of disease severity accounting for the largest part of exclusions (Morgante et al. 2007). Currently, however, two prospective, randomized clinical trials are evaluating the effect of STN-DBS at an early stage of PD (Deuschl et al. 2013, Kahn E et al. 2012). The first defines patients with early PD as those with recent onset of levodopa-induced motor complications (<3 years) (Deuschl et al. 2013), while the second includes patients treated with antiparkinsonian medications (levodopa or dopamine agonists) for a period greater than 6 months and less than 4

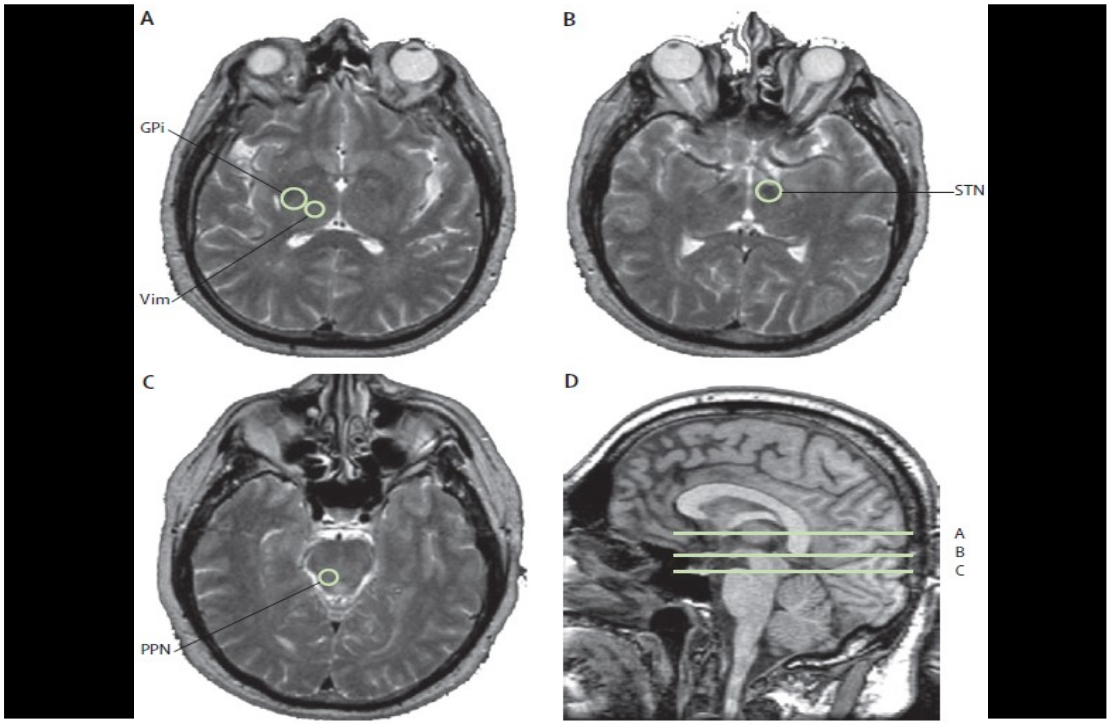


Figure 2.8. Main anatomical structures targeted by deep brain stimulation on T2-weighted brain MRI (reproduced with permission from Fasano et al. 2012).

years, without initiation of levodopa-induced motor complications (Kahn E et al. 2012). Key endpoints of these studies are, on the one hand, the determination of the safety and tolerability of STN-DBS in early stage PD and, on the other hand, the corroboration of a possible disease-modifying effect of stimulation, in light of evidence pointing to a neuroprotective effect of STN-DBS (Temel et al. 2006 (b), Harnack et al. 2008, Wallace et al. 2007, Spieles-Engemann et al. 2010, deSouza et al. 2013, Albanese and Romito 2011). Furthermore, unilateral STN-DBS has been suggested to improve contralateral motor symptoms in PD and provide an alternative to bilateral stimulation, specifically for patients with pronounced asymmetry (Alberts et al. 2008 (a), Alberts et al. 2008 (b), Castrioto et al. 2011(b), Walker et al. 2009, Brun et al. 2012) and for elderly patients, since it seems to be associated with a lower degree of cognitive complications (Slowinski et al. 2007).

With respect to alternative targeting options (figure 3.2), bilateral stimulation of the GPi has also been established as an adjunctive treatment to medical therapy for advanced PD (Fox et al. 2011), and proven to be equally efficacious for the control of motor symptoms, dyskinesia and motor fluctuations as STN-DBS (Anderson et al. 2005, Oyama et al. 2012, Follet et al. 2010, Moro et al. 2010, Oderkerken et al. 2013, Bronstein et al. 2011). However, GPi-DBS seems to be associated with a lower long-term decline in postural instability and gait

disability (George et al. 2010, Burchiel et al. 1999) and a lower degree of speech impairment than STN-DBS (Robertson et al. 2011). On the other hand, in contrast to pallidal stimulation, dopaminergic medication is substantially reduced after STN-DBS, albeit this is correlated with a higher incidence of treatment-related adverse effects (Moro et al. 2010, Follet et al. 2010). Eventually, target selection should be tailored to an individual patient's needs (Williams et al. 2014). There is also some evidence pointing to GPe as a potential therapeutic target for DBS in the treatment of PD (Vitek et al. 2004, Vitek et al. 2012 (b)). Medication-resistant tremor in PD can be equally effectively treated with unilateral thalamotomy or DBS of the thalamic ventrointermediate nucleus (Vim) (Schuurman et al. 2008, Fox et al. 2011). Besides, DBS of the posterior subthalamic area or the caudal zona incerta (cZi) is generally safe and effective for the treatment of tremor-dominant PD (Blomsted et al. 2010, 2012, Plaha et al. 2006, Fytagoridis and Blomstedt 2010). Stimulation of the pedunculopontine tegmental nucleus (PPTg) at low stimulation frequencies (10-70 Hz) has been consistently stated to significantly improve levodopa-resistant gait disturbances, including freezing of gait, and postural instability, as well as oromotor movements in patients with PD (Mazzone et al. 2005, 2012, 2014, Plaha and Gill 2005, Stefani et al. 2007, Moro et al. 2010, Thevathasan et al. 2010, Hamani et al. 2011, Benabid and Torres 2012, Pereira et al. 2011) (figure 3.3). However, criteria for patient selection and subtle differences in target location may in some cases have accounted for a less favorable evaluation (Ferraye et al. 2010, Mazzone et al. 2011). Interestingly, Stefani and colleagues have reported on an ameliorative effect of 25 Hz PPTg-DBS on RBD and cognitive symptoms of PD (Stefani et al. 2009, 2010). On the other hand, however, the same surgery has been recently associated with a marked deterioration of speech intelligibility (Pinto et al. 2014).

Given the incomplete effectiveness and risks of unifocal DBS as a treatment option of advanced PD, new strategies, related to combined multifocal DBS targeting, are emerging as promising alternative options (Vingerhoets et al. 1997). Within this framework, PPN-DBS in combination with either STN-DBS,cZi-DBS or pallidal DBS has been shown to induce significant cumulative improvement of axial and appendicular motor symptoms of PD (Stefani et al. 2007, Schrader et al. 2013, Kahn S et al. 2012) (figure 3.4). In addition, recent studies suggest a possible significant effect of concomitant STN/SNr stimulation on freezing of gait (Weiss et al. 2011, 2013). Furthermore, the possible improvement of both motor and cognitive symptoms of PD based on tandem DBS, involving, in addition to STN (or GPi)-DBS, stimulation of the fornix /hypothalamus, has been recently suggested (Uitti 2012). Several years before, Freund et al (2009) reported on a case of concomitant STN-DBS and stimulation of the nucleus basalis of Meynert in a patient with PDD, whereby marked amelioration of cognitive impairment was observed.

In relation to other types and symptoms of parkinsonism, STN-DBS for spinocerebellar ataxia type 3 (Freund et al. 2007), unilateral thalamic DBS for benign tremulous parkinsonism (Savica et al. 2011) and PPN-DBS for primary progressive freezing of gait (Wilcox et al. 2010) have also been reported, while the optimal target for the treatment of camptocormia in PD has yet to be defined (Capelle et al. 2011, Lyons et al. 2012).

2.9.2. Surgical and Hardware Complications of Deep Brain Stimulation

Despite the continuous development of DBS systems, rates of surgical procedure - and hardware - related adverse effects are still relatively high, constituting a major shortcoming of this therapy option (Shih and Tarsy 2011, Burdick et al. 2010, Lozano 2012, Morishita et al. 2013, Vergani et al. 2010, Chan et al. 2009, Rezai et al. 2006) (figure 3.5). Surgical-procedure related complications most frequently include intracranial hemorrhage, permanent neurological deficit or death (Zrinzo et al. 2011, 2012, Voges et al. 2007, Favre et al. 2002), while cases of intraoperative agitation, epileptic seizure, respiratory distress, postoperative psychosis and neuroleptic malignant syndrome (NMS) have also been reported (Boviatsis et al. 2010). Hardware-related complications are defined as those related to the implanted leads, the extension wire or the IPG, i.e. infection and/ or skin erosion, electrode breakage, electrode impendance increment, lead migration or displacement and stricture formation (Boviatsis et al. 2010, Pepper et al. 2013, Oh et al. 2002, Guridi et al. 2012, Linchares et al. 2013). Surgical procedure- and hardware-related adverse effects are observed in about 5.6% and 9% of patients, respectively (Vergani et al. 2010, Hamani et al. 2004). In addition, in about 19% of patients stimulation-related adverse effects, such as paraesthesias, dysarthria, and motor contractions are documented (Hamani et al. 2004). Nonetheless, these are mild and may be reversed by properly adjusting stimulation settings. The specific case of post-operative brain edema around DBS leads is considered a transient adverse effect with obscure underlying etiopathophysiology (Deogaonkar et al. 2011, Morishita et al. 2010). Still, there is evidence pointing to brain tissue penetration during hardware insertion as the most conspicuous risk factor (Holloway et al. 2014).

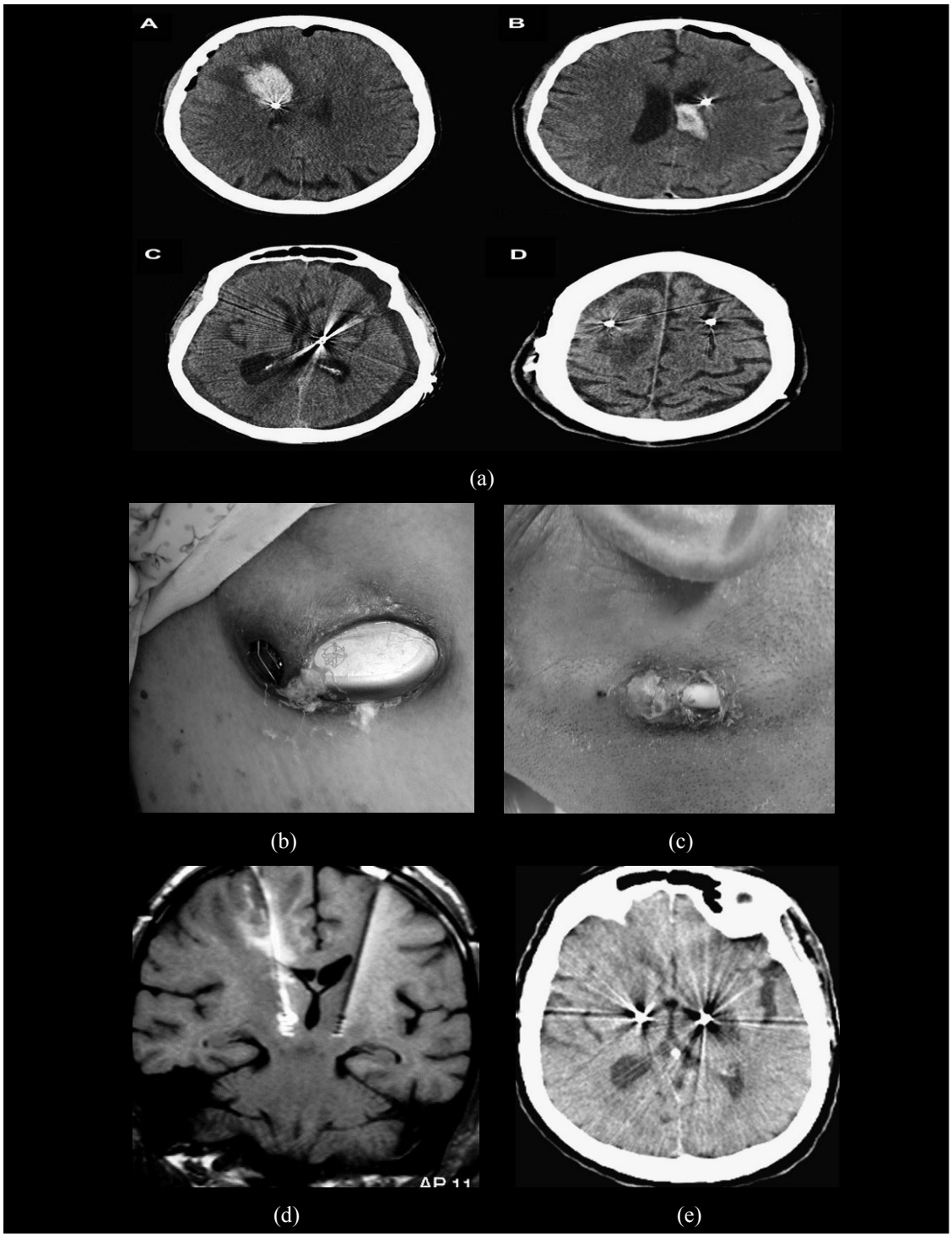


Figure 2.9. (a) CT scan images depicting examples of intracerebral hemorrhage following DBS lead implantation : intracerebral hemorrhage (A) intraventricular hemorrhage (B) subdural hemorrhage (C) and venous infarction (D) (reproduced with permission from Morishita et al. 2010) (b) IPG implantation site infection (reproduced with permission from Boviatsis et al. 2010) (c) Erosion of retroauricular skin due to implanted DBS system (reproduced with permission from Linhares et al. 2013) (d) Postoperative T1-weighted MRI showing hyperintense signal due to infection of the right electrode (reproduced with permission fromVergani et al. 2010) (e) Axial CT scan without contrast on post-operative day 4 at (a) the tip of the electrode showing a large hypodense area (edema) around the left deep brain stimulation electrode (reproduced with permission from Deogaonkar et al. 2011).

3

Obsessive-Compulsive Disorder

A 33-year-old woman presents with a seven-year history of hand washing for two to six hours a day, as well as urges to check doors and stoves extensively before leaving her home…

M. A. Jenike (2004)

3.1. Definition, Classification and Epidemiology

Obsessive-compulsive disorder (OCD) is an heterogeneous, generally chronic psychiatric condition with an estimated prevalence of 1- 2.5 % in the general population (Rasmussen and Eisen 1992, Sasson et al. 1997, Ruscio et al. 2010, Kessler et al. 2005, Hollander et al. 2005, Skoog G and Skoog I 1999, Karno et al. 1998, American Psychiatric Association [APA] 2013). Prevalence rates are characterized by a low cross-national variability (Weissman et al. 1994) and are almost twice those reported for schizophrenia (Goodman and Wayne 1999). OCD has been suggested as the fourth most common mental disorder following substance abuse, phobias and major depression (Kaplan et al. 1994), associated with a significant impairment in health-related quality of life (Hollander et al. 2010), and is considered one of the leading causes of years lived with disability in 15-44-year-old individuals (WHO 2001, Murray and Lopez 1996).

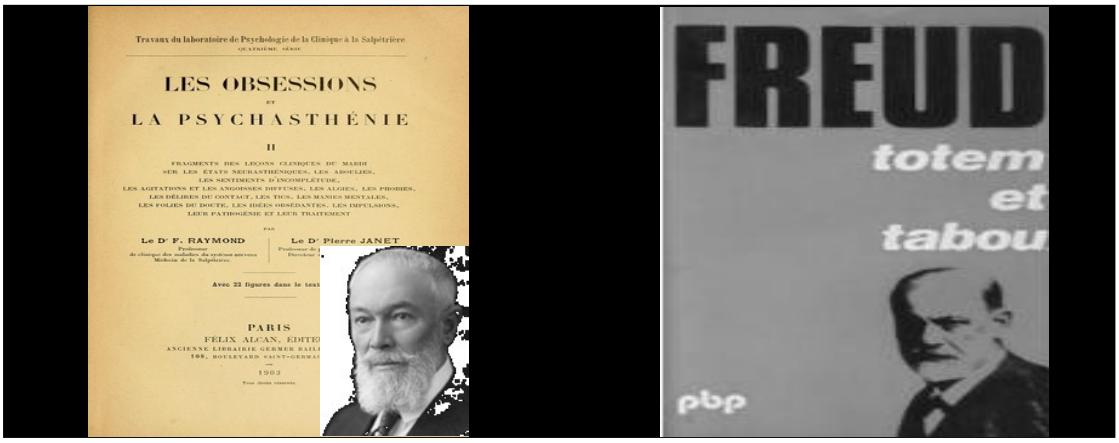
Although previously classified as an anxiety disorder, the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V) has categorized OCD within a new category of Obsessive-Compulsive and Related Disorders (OCRDs) (APA 2013). The mean age of onset of OCD is 20 years (Ruscio et al. 2010, Anholt et al. 2014), while onset after the early 30s is very rare (Rasmussen and Eisen 1992). Despite an almost even sex distribution, males tend to have an earlier age of onset than females. Particularly, nearly one quarter of males with OCD display the condition before age 10 (Ruscio et al. 2010). Juvenile-onset OCD appears to be genetically related to tic disorders (Eichstedt and Arnold 2001). Most commonly, onset is gradual, but acute onset has also been reported. The majority of patients have a chronic waxing and waning course (Rasmussen and Eisen 1992), while about 35% of patients experience an episodic course of the disorder with partial or complete remission (Demal et al. 1993).

3.2. Clinical Signs and Symptoms

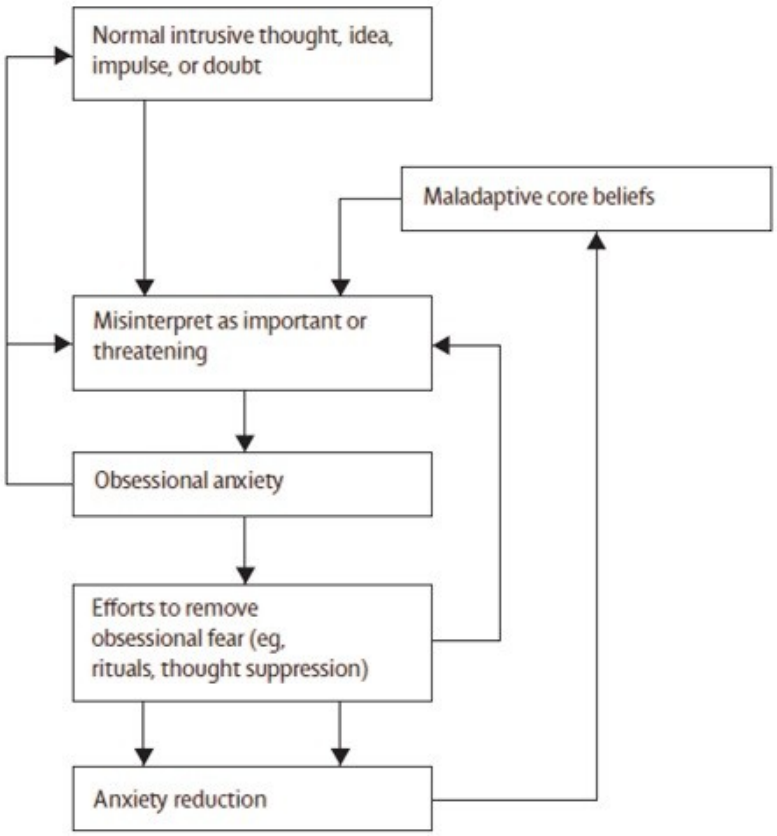
Obsessional prohibitions involve just as extensive renunciations and restrictions in the lives of those who are subject to them as do taboo prohibitions; but some of them can be lifted if certain actions are performed. Thereafter, these actions must be performed: they become compulsive or obsessive acts, and there can be no doubt that they are in the nature of expiation, penance, defensive measures and purification. The commonest of these obsessive acts is washing in water…

S. Freud (1913)

Principal clinical symptoms of OCD are obsessions that cause marked distress or anxiety, and compulsions, the outcome of which is interpreted by patients with OCD as a necessary condition for anxiety reduction. Thereby, there exists a dynamic functional relationship between obsessions and compulsions that form part of a self-perpetuating cycle (Abramowitz and Deacon 2005, Stein 2002, Okasha 2002) (figure 3.1). Obsessions are recurrent mental events, like persistent ideas, thoughts, impulses, or images that are experienced as intrusive, and are essentially anxiety-evoking (APA 2013). Obsessions have been characterized as egodystonic, i.e. in conflict with the patient's self-image, contrary to the egosyntonic nature of delusions (Denys 2011). In addition, they are unlikely to be related to a real-life problem. Differently, most commonly they involve contamination concerns, repeated doubts, an excessive need for symmetry or exactness, unwarranted fear about aggressive behavior toward self or others, sexual imagery and obsessions related to moral rightness or religion (APA 2013, Heyman et al. 2006, Leckman et al. 2005). About 80 to 90% of the general population experiences unreasonable intrusive thoughts identical to those reported by patients with OCD. Notwithstanding, whereas in healthy controls these events can be easily bypassed, in the



(a)



(b)

Figure 3.1. (a) Seminal work of Janet P, '*Les obsessions et la psychasthénie*' 1903 (Janet 1903) and Freud S, '*Totem and taboo: some points of agreement between the mental lives of savages and neurotics'* 1913 (Freud 1913) (b) Cognitive-behavioural model of OCD (adapted with permission from Abramowitz 2009).

pathological condition intrusive thoughts are evaluated as highly significant (Rachman and deSilva 1978, Salkovskis et al. 1997, Abramowitz et al. 2003 (a), Abramowitz 2009). Patients with OCD often consider a thought about a negative event synonymous with its occurrence in reality (Rachman and deSilva 1978, Amir et al. 2001, Abramowitz and Deacon 2005). Compulsions (rituals) are either overt, repetitive stereotyped behaviors or covert (mental) acts in which patients engage in order to be temporally relieved by anxiety or distress that accompanies an obsession. For example, contamination obsessions and obsessions related to moral rightness in OCD may be accompanied by washing and checking compulsions, respectively (APA 2013, Parrish and Radomsky 2010, Okasha 2002, Abramowitz and Houts 2005) (figure 3.2). Covert compulsions, also referred to as mental rituals or covert neutralizations, include strategies like avoidance, concealment, mentally reviewing, excessive reassurance seeking and thought suppression, and are considered functionally equivalent to overt compulsions. The occurrence of mental rituals invalidates the hypothesis of a 'pure obsessional' subtype (Williams et al. 2011).

3.3. The Diagnostic and Statistical Manual V (DSM-V) and the Yale Brown Obsessive-Compulsive Scale (Y-BOCS)

Superstitions and repetitive checking behaviors are commonly encountered in everyday life. A diagnosis of Obsessive-Compulsive Disorder should be considered only if they are particularly time consuming or result in clinically significant impairment or distress.

American Psychiatric Association (2013)

The Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association 2013) and the Yale–Brown obsessive compulsive scale (Y–BOCS) (Goodman et al. 1989 (a), (b)) are well established indices of the presence and severity of OCD symptoms.

According to the DSM, obsessions or compulsions have to provoke significant distress, be time consuming (more than 1 hour per day) and lead to functional disability and impairment of the patient's professional and socioeconomic status. This impairment may be intensified by the distracting impact of obsessive intrusions and the tendency of patients to systematically avoid objects or situations that provoke obsessions or compulsions. It has been argued that still in the newest edition of the DSM (DSM-V; APA 2013) the definition of compulsions focuses on their repetitive form instead of their functionality, thereby disregarding the high incidence rate of covert compulsive acts or neutralizing strategies (Abramowitz and Jacoby 2014, Shavitt et al. 2014, Gillan et al. 2014) (figure 3.2). On the other hand, the transition from the DSM-IV to the DMS -V has allowed for the introduction

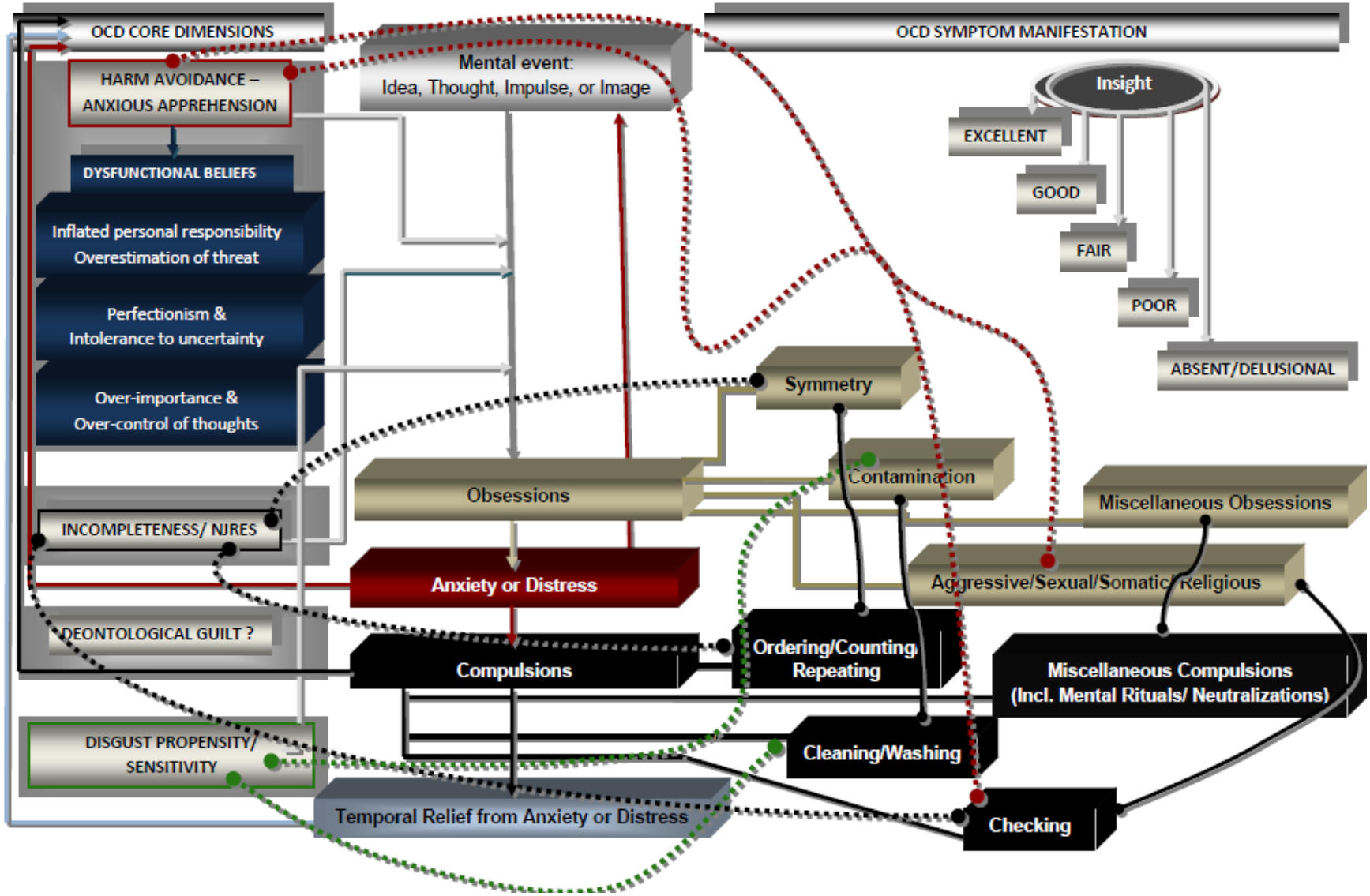


Figure 3.2. Symptom dimensions and suggested core affective-motivational dimensions underlying obsessive-compulsive symptom manifestation. Solid curves indicate symptom dimensions, while dotted curves indicate the association of affective-motivational dimensions with obsessive-compulsive symptom manifestation.

of a distinct dimensional specifier, i.e. a refined definition of global insight into the irrationality of obsessions and compulsions, under the rationale to improve the differential diagnosis of the clinical presentation of OCD. In particular, this construct facilitates a distinction between individuals with excellent, good, fair, poor, and absent/delusional insight (APA 2013). The two latter categories are identified with the lowest frequency rates across patients with OCD, yet they are associated with a greater symptom severity (Shavitt et al. 2014, Philips et al. 2012, Catapano et al. 2010). Particularly, the specifier 'with poor insight' refers to patients that maintain that obsessive thoughts or compulsive behaviors are not unreasonable or excessive (American Psychiatric Association 2013).

The Y-BOCS was originally designed by Goodman et al (1989 (a), (b)) in order to provide a reliable measure of the severity of symptoms of OCD according to the DSM-III, unbiased towards the number and the type of obsessions and compulsions present (Frost et al1995, Kim et al. 1990, Woody et al. 1995). Nevertheless, it soon became intensely evident that though OCD had been diagnostically classified as a unitary nosological entity, symptom manifestation of the disorder might be essentially heterogeneous varying within and across patients over time, thereby suggesting a multidimensional model of OCD (Mataix-Cols et al. 2005). This evolution combined with numerous requests for revision of the original Y-BOCS in terms of the symptom checklist content, the content of the item severity scale and the scoring framework (Deacon and Abramowitz 2005, Steketee et al. 1996, Federici et al. 2010) led to the formulation of the Dimensional Y-BOCS (DY-BOCS) (Rosario-Campos et al. 2006) and eventually the Y-BOCS-II (Storch et al. 2010). The Y-BOCS-II is intended for use as a semi-structured interview, wherein the items depend on the patient's report, but the final rating is based on the clinical judgment. More than sixty items are included in the symptom checklist, while the severity scale evaluates the degree of impairment in terms of time occupied, functional impairment, mental distress, degree of resistance, degree of control, insight, avoidance, indecisiveness, pathologic responsibility, slowness and pathologic doubting. Storch et al (2010) have attributed excellent psychometric properties to the Y-BOCS-II with respect to the assessment of the presence and severity of OCD symptoms. Except Y-BOCS, other scales employed for the diagnosis of OCD include the comprehensive psychopathological rating scale (CPRS), the national institute of mental health (NIMH)-global obsessive-compulsive scale (GOCS), the clinical global impression (CGI) scales, the Brown assessment of beliefs scale, the overvalued ideas scale (OVIS) (Okasha 2002) and the global assessment of functioning (GAF) scale. Remarkably, however, despite the variety of available diagnostic tools, the level of recognition of outpatients with OCD remains substantially low (Wahl et al. 2010).

3.4. Potential Dimensions Underlying Heterogeneity of Obsessive-Compulsive Disorder

In the framework of the symptom-based subtyping of OCD (Baer 1994, Khanna and Mukherjee D 1992, Calamari et al. 1999, Abramowitz et al. 2003 (b), Leckman et al. 1997, Mataix-Coils et al. 1999, Summerfeldt et al. 1999, 2004; Tek and Ulug 2001, Hantouche and Lancrenon 1996, McKay et al. 2004, Abramowitz and Houts 2005, Bjorgvinsson et al. 1997, Murphy et al. 2010) and following the classification of hoarding as a distinct diagnostic entity in the DSM-V, at least three symptom dimensions may be eventually considered on grounds of factor analysis: symmetry obsessions/ ordering, repeating or counting compulsions, contamination obsessions/ cleaning or washing compulsions, and (aggressive, sexual, somatic and religious) obsessions/checking compulsions. Miscellaneous obsessions (e.g. the need to know/remember details or the fear of not saying just the right thing) have been linked to miscellaneous compulsions including cognitive rituals and neutralizing (Summerfeldt et al. 2004). Importantly, however, the aforementioned symptom dimensions may exhibit a high degree of overlap, while symptom associations may vary significantly (Summerfeldt et al. 1999, 2004). Likewise, symptom dimensions are rooted in both distinct and overlapping neural correlates (van den Heuvel et al. 2009, Harrison et al. 2012). This implies that the characterization of OCD as a phenotypically and etiologically heterogeneous condition cannot be exclusively based on symptom-classification schemes.

Toward an alternative approach, *harm avoidance* and *incompleteness* have been suggested as core affective-motivational dimensions that underlie obsessive-compulsive symptom manifestation (Rasmussen and Eisen 1992, Summerfeldt et al. 2014, Ecker et al. 2014(a), Taylor et al. 2014) (figure 3.2). Though this refined and structurally validated (Summerfeldt et al. 2014) dimensional perspective is not addressed in the DSM-V, it might be employed as a key etiological substrate for the classification of OCD into the new category of OCRDs, but still adjacent to the chapter of Anxiety Disorders (APA 2013). Harm avoidance is associated with three-factor analytically types of dysfunctional beliefs including excessive personal responsibility and amplified threat estimation, perfectionism and fear of uncertainty, in addition to over-control of thoughts (Taylor et al. 2006). Fundamentally, this profile is dominated by anxious apprehension and may therefore constitute a common motivational underpinning of OCD and anxiety disorders (Summerfeldt et al. 2014, Ecker et al. 2014(a)). Nonetheless, specific obsessive-compulsive symptom expressions may not be attributable to harm avoidance *per se*, rather to an inner sense of dissatisfaction and imperfection with respect to perceptions or performed actions, an experience pertaining to the broader concept of incompleteness (Janet

1903) and commonly characterized by the notion of 'Not Just Right' (NJRE) (Coles et al. 2005). Remarkably, there is preliminary evidence for a unique association between incompleteness - but not harm avoidance - and symptom severity in OCD (Ecker and Gönner 2008), a fact reinforcing the conceptualization of OCD as a non-anxiety disorder in the DSM-V. Based upon analysis of a large clinical sample, Ecker and Gönner (Ecker and Gönner 2008) highlighted the motivational heterogeneity of checking, which predicted both core dimensions, and further pointed to the need for an in-depth assessment of the interplay between the two underlying vulnerabilities in compulsive checking behavior. On the other hand, unique correlations were identified between incompleteness and symmetry/ordering, and between harm avoidance and (aggressive, sexual, somatic and religious) obsessions. They could not, however, provide strong support for any association between either harm avoidance or incompleteness and neutralizing or the contamination/washing dimension.

With respect to the contamination/washing dimension, disgust propensity (the tendency to respond with disgust) is emerging as a distinct core dimension significantly and uniquely predicting washing compulsions, as opposed to disgust sensitivity (emotional sensitivity towards the experience of disgust) that is inclusively linked to anxiety sensitivity (Olatunji et al. 2011, Goetz et al. 2013). Further evidence in favor of the existence of this dimension would corroborate the prominent role of disgust in the psychobiology of OCD (Stein et al. 2001). Last, a fourth affective component is related to deontological guilt, a type of guilt descending from the violation of an inner moral rule, as opposed to altruistic guilt. This component appears to play a significant role in obsessive-compulsive symptom manifestation, but robust associations have yet to be established in the clinical population (Basile et al. 2013, D'Olimpio and Mancini 2014).

3.5. Comorbidity in Obsessive-Compulsive Disorder

Severity of OCD has been associated with a highly complex lifetime comorbidity of Axis I and II disorders (Hofmeijer-Sevinik et al. 2013, Ruscio et al. 2010, Hollander et al. 2005, Hollander et al. 2009, Miguel et al. 2005, O'Brien and Vincent 2003, Eisen et al. 2004, Masi et al. 2004, Angst et al. 2004, Merikangas et al. 2007) (figure 3.3), whereas diagnosis of lifetime 'pure' OCD is limited to a rate ranging from approximately 8 to 22 % (Torres et al. 2013, Hofmeijer-Sevinik et al. 2013, Ruscio et al. 2010, Pinto et al. 2006). Lifetime comorbid Axis I disorders include obsessive-compulsive spectrum disorders (OCSDs), in addition to mood, anxiety, substance use and psychotic disorders (Lochner et al. 2014, Hofmeijer-Sevinik et al. 2013, Ivarsson et al. 2008, Ruscio et al. 2010, Pinto et al. 2006). Within the obsessive-compulsive

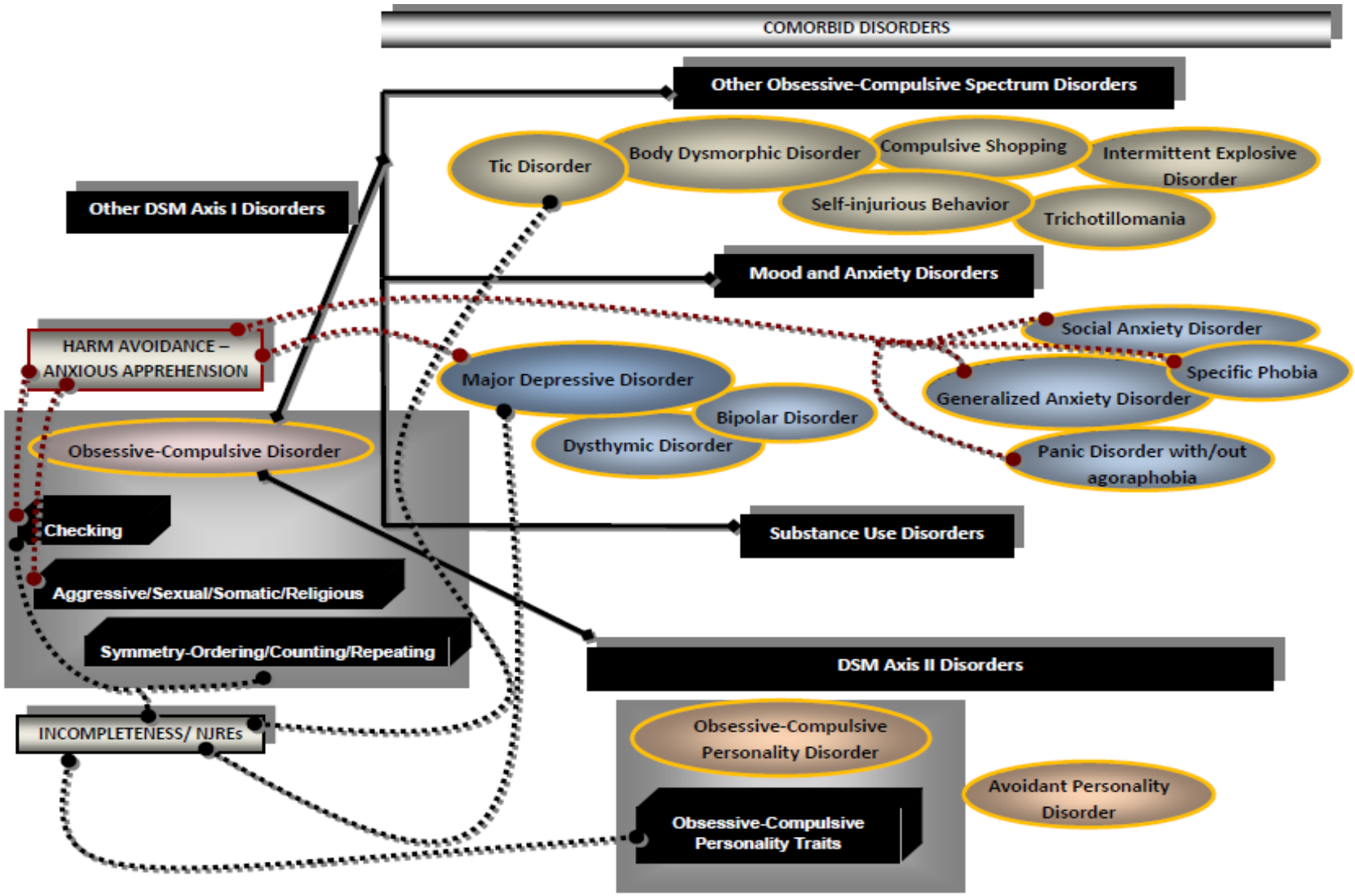


Figure 3.3. Comorbidity in obsessive-compulsive disorder and the role of affective-motivational dimensions.

spectrum, highest comorbidity rates have been reported for tic disorder, body dismorphic disorder (BDD), self-injurious behavior (e.g. excoriation disorder), compulsive shopping, intermittent explosive disorder and trichotillomania (TTM) (Lochner et al. 2014, Nestadt et al. 2009, du Toit et al. 2001). Noteworthily, among the aforementioned disorders, BDD, excoriation disorder and TTM are included in the category of OCRDs (APA 2013). Major depressive disorder (MDD), generalized anxiety disorder, social anxiety disorder, specific phobia, dysthymic disorder, panic disorder (with/out agoraphobia) and bipolar disorder are most commonly diagnosed as lifetime comorbid mood or anxiety disorders (Lochner et al. 2014, Fineberg et al. 2013, Hofmeijer-Sevinik et al. 2013, Ruscio et al. 2010, Nestadt et al. 2009, Pinto et al. 2006, LaSalle et al. 2004). There is also some evidence for high rates of comorbid substance use disorders (alcohol abuse or dependence/drug abuse or dependence) (Mancebo et al. 2009, Adam et al. 2012, Ruscio et al. 2010, Pinto et al. 2006). Further, the most commonly diagnosed comorbid Axis II disorder appears to be obsessive-compulsive personality disorder (OCPD) (Nestadt et al. 2009, Pinto et al. 2006, Denys et al. 2004(b), Starcevic et al. 2012, Garyfallos et al. 2010, Coles et al. 2008).

In light of the described comorbidity patterns, as well as of specific clinical characteristics, the existence of at least two subtypes of OCD has been suggested, i.e. tic-related OCD (de Alvarenga et al. 2012, Lochner et al. 2014, Nestadt et al. 2009) and the OCD-OCPD subtype (Coles et al. 2008, Garyfallos et al. 2010, Diedrich and Voderholzer 2015). Tic-related OCD principally involves comorbidity of OCD and either chronic motor tic disorder, chronic vocal tic disorder or Tourette syndrome (de Alvarenga et al. 2012). In the context of tic-related OCD, the core dimension of NJREs and feelings of incompleteness appears to be more frequently present than in the context of tic disorders without comorbid OCD (Ferrão et al. 2012, Neal and Cavanna 2013, Reese et al. 2014). In particular, these robust *sensory phenomena* plausibly account for the presence of ordering symptoms in tic-related OCD (Ferrão et al. 2012), but they do not concurrently reinforce some limited evidence for the presence of the contamination/washing symptom dimension or a higher severity of (aggressive, sexual, somatic and religious) obsessions (Ferrão et al. 2012, de Alvarenga et al. 2012). This implies that some additional affective-motivational dimensions may partially underlie symptom manifestation in tic-related OCD. Furthermore, it has been argued that NJREs and feelings of incompleteness may serve as an explanatory basis for the association observed between obsessive-compulsive personality traits (rigid perfectionism, perseveration, intimacy avoidance and restricted affectivity) and the checking or, more robustly, the symmetry/ordering symptom dimension (Ecker et al. 2014(b), Wetterneck et al. 2011, Lee et al. 2009, Coles et al. 2008). However, contrary to the case of tic-related OCD, there exists no association between obsessive-compulsive personality traits and the contamination/washing dimension or (aggressive, sexual,

somatic and religious) obsessions (Ecker et al. 2014(b)). These facts highlight the key role of the sensory-affective component in the framework of the OCD-OCPD subtype. Finally, though evidence for an OCD-MDD subtype is substantially limited (Nestadt et al. 2009), there is some indication for a correlation between a diagnosis of MDD and both incompleteness and harm avoidance severity (Ecker et al. 2014(a)). This fact may account for the lack of any observation of a weighted association between MDD and a specific OCD symptom dimension in a large-scale Brazilian clinical study (Quarantini et al. 2011).

3.6. Pathophysiology of Obsessive-Compulsive Disorder

Dysfunctions of the serotonergic, GABAergic and dopaminergic neurotransmitter systems have been implicated in the pathophysiology of OCD (Westenberg et al. 2007, Nikolaus et al. 2010, Pauls et al. 2010, Berlin et al. 2008, Bloch et al. 2006, Greenberg et al. 2010 (a)). The fundamental role of serotonin (5-HT) in the pathogenesis of OCD was first acknowledged based on observations that the tryciclic antidepressant clomipramine and selective serotonin reuptake inhibitors (SSRIs) exerted a significant antiobsessional and anticompulsive effect (Yaryura-Tobias et al. 1977, Goodman et al. 1989 (c), Jenike et al. 1989, Clomipramine Collaborative Study Group 1991). Nonetheless, even after the introduction of SRIs for the treatment of OCD in the mid-1980s, increasing documentation that a considerable number (40-60%) of patients failed to respond to SSRI treatment, partially or completely, or even demonstrated acute exacerbation of symptom severity, was pointing to the possible role of other neurotransmitter systems in the pathogenesis of OCD (Stein et al. 1999, Stein 2002, Goodman et al. 1989 (c), Goodman et al. 1990, Skoog G and Skoog I 1999). Indeed, it soon became evident that addition of antipsychotic augmentation agents, namely low-dose dopamine antagonists for treatment-refractory OCD resulted in remarkable clinical efficiency. This fact suggested that the dopaminergic neurotransmitter system was also involved in the pathophysiology of OCD (Stein et al. 1997, McDougle et al. 1995, Jacobsen 1995, Denys et al. 2003, Dougherty et al. 2004). The presence of obsessive-compulsive symptoms in the clinical presentation of disorders associated with dysregulation of the dopaminergic system, including TS, has further pointed to the role of dopamine in OCD (Lochner et al. 2005). Eventually, direct evidence that serotonergic, dopaminergic and even GABAergic perturbations are implicated in the pathophysiology of OCD has been provided by neuroimaging and neurochemical studies (van der Wee et al. 2004, Denys et al. 2004(a), Nikolaus et al. 2010, Koo et al. 2010). Importantly, Nikolaus et al. (2010) suggested that decreased inhibition of dopaminergic neurotransmission by GABAA and 5-HT may underlie the pathogenesis of the disorder.

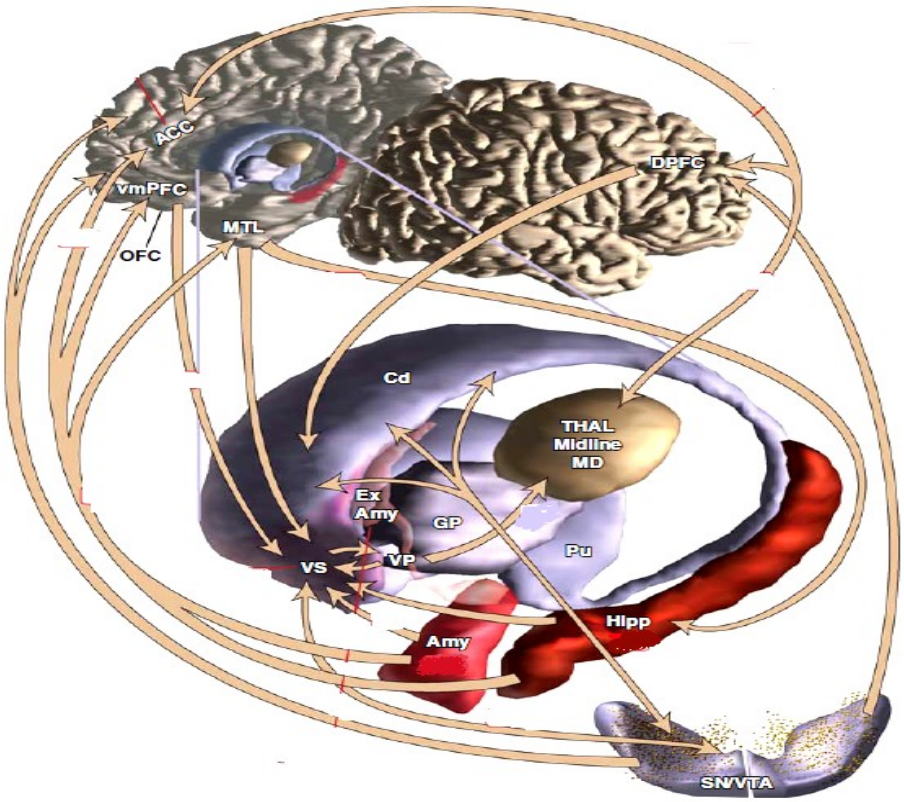
3.7. Neurocircuitry of Obsessive-Compulsive Disorder

Given the focus of psychiatry on the interface of motivation, emotion, and cognition, psychiatric neuroscience has progressively highlighted brain networks that subserve these functional domains and their interactions.

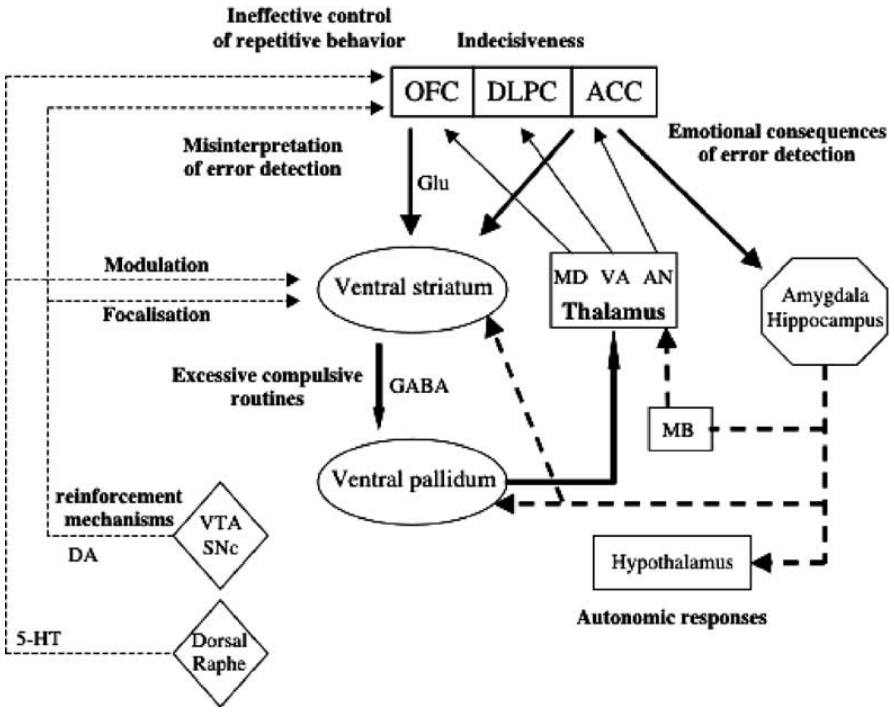
S. Haber and S. Rauch (2010)

Converging lines of evidence have underscored the pivotal role of cortico-striato-thalamo-cortical (CSTC) circuits in the pathology and pathophysiology of OCD. Specifically, the associative and limbic CSTC circuits, known to subserve executive (attentional control, cognitive flexibility and goal-directed behavior) and modulatory functioning, respectively (Friedlander), appear to be at the core of symptom manifestation (Alexander et al. 1989, Saxena et al. 1998, Kopell and Greenberg 2008, Greenberg et al. 2006, Berlin et al. 2008, Stathis et al. 2007, Aouizerate et al. 2004, Chamberlain et al. 2005, Velikova et al. 2010, Harrison et al. 2009, Rotge et al. 2009, Beucke et al. 2013, Sgambato-Faure et al. 2014, Lapidus et al. 2013, Haber and Greenberg 2012) (figure 3.4).

The associative or dorsolateral prefrontal CSTC loop involves the dorsolateral prefrontal cortex (DLPC) and the lateral orbitofrontal cortex (LOFC) projecting either directly, via the anterior IC and the inferior thalamic peduncle (ITP), or indirectly, via the basal ganglia, to the thalamus (ventral anterior parvocellularis and magnocellularis (VApc and mc) and dorsomedial (DM) thalamic nuclei). The basal ganglia structures involved in the indirect connection include the central striatum, i.e. the head of the caudate and the central/rostral areas of the putamen, as well as the dorsomedial GPi and the rostrolateral SNr. The limbic CSTC loop involves the anterior cingulate cortex (ACC), the medial orbitofrontal cortex (MOFC), and the agranular insular cortex (Brodmann areas 10, 11, 12, 13, 24, 25, 32), projecting either directly, via the anterior IC and the inferior thalamic peduncle, or indirectly, via the basal ganglia, to the DM thalamic nucleus. The indirect connection in this circuit involves the ventromedial striatum, i.e. either the ventromedial caudate and the NAcc core component that receive all the above - mentioned cortical projections, or the NAcc shell that receives projections predominantly from the subgenual cingulate (Brodmann area 25). In turn, the ventromedial caudate and the NAcc core component project to the dorsal SNr, the ventral tegmental area (VTA) and the ventromedial GPi, while the NAcc shell projects to the dorsal SNr, the VTA and a separate branch of the pallidum, the ventral pallidum (VeP). All of these output structures eventually project to the DM thalamus (Kopell and Greenberg 2008). Notably, similar to the motor CSTC loop, the indirect connections within both the associative and limbic CSTC loops involve a



(a)



(b)

Figure 3.4. (a) Key structures and pathways involved in neuropsychiatric disorders. Arrows illustrate projections (adapted from Haber and Rauch 2010) (b) General diagram of the disruption in the different types of information processing involved in the pathogenesis of OCD on grounds of the anatomical and neurochemical interconnections within distinct cortico-subcortical networks (reproduced with permission form Aouizerate et al. 2004)

further subdivision into a monosynaptic ‘direct’ and a polysynaptic ‘indirect’ pathway through the GPe and the STN, detailed in section 2.6.

It has been proposed that different subtypes of OCD have distinct neorocognitive basis and neural correlates (McKay and Storch 2013, Phillips and Mataix-Cols 2004). A deeper insight to this suggestion has been gained on the basis of fMRI, whereby abnormal activity in the LOFC and DLPC has been related to cognitive dysfunction (Page et al. 2009, Chamberlain et al. 2008), while abnormal patterns of connectivity from the dorsal ACC to left DLPC have been documented to suppress responses during decision making in patients with OCD (Schlösser et al. 2010). Hyperactivity in the ACC or the DLPC may also account for dysfunctional working memory, associated with checking rituals in OCD (Nakao et al. 2009, Zhang et al. 2008, van der Wee et al. 2003). Furthermore, dysfunctional reward processing, behavioral addiction, as well as enhanced action monitoring in OCD have been correlated with altered activation of the NAcc (Figee et al. 2011, Münte et al. 2007). In general, regional cerebral blood flow in ventral striatum, ACC, and bilateral OFC appears to be significantly increased in patients with OCD (Baxter et al. 1987, 1988, Rauch et al. 1994, Kwon et al. 2003). These structures have been further implicated in the pathophysiology of OCD on the grounds of indirect evidence including neurosurgical lesions (Maia et al. 2008), electrostimulation (Van Laere et al. 2006, Le Jeune et al. 2010, Aouizerate et al. 2009), or SSRI and behavior modification treatment (Baxter et al. 1992, Schwartz et al. 1996, Bolwing et al. 2007, Benkelfat et al. 1990). Differently, in patients with OCD and comorbid MDD significantly lower metabolism in the thalamus, caudate and hippocampus than in patients with primary OCD has been reported (Saxena et al. 2001).

Special reference should be made to a distinct subcortical area outside the traditional CTSC circuits, but strongly implicated in the psychopathology of OCD, the amygdala (McLean 1952). This structure is divided into a basolateral and a centromedial component, the former projecting to the NAcc core and related cortical regions, whereas the later projecting in tandem with the bed nucleus of the stria terminalis to the NAcc shell, area 25 and hypothalamic areas (Kopell and Greenberg 2008). Decreased frontostriatal control of the amygdala has been implicated in anxiety-driven symptoms and inadequate fear responses in OCD (van den Heuvel et al. 2004, Simon et al. 2014, Via et al. 2014, Milad and Rauch 2012), while the reciprocal connections of this structure with the NAcc point to its possible role in dysfunctional reward and motivational control observed in patients with OCD (Baxter and Murray 2002, Aouizerate et al. 2004).

Similar to the research on pathological patterns of neuronal activity in the basal ganglia nuclei of patients with PD, the presence of abnormal neuronal activity in the STN and the bed nucleus

of the stria terminalis of patients with OCD is being intensively explored over the last years (Piallat et al. 2011, Welter et al. 2011, Bastin et al. 2014 (a), (b) ; Neumann et al. 2014) based on electrophysiological recordings acquired during or after DBS surgery of the respective target regions (Cohen 2012). Particularly, Piallat et al (2011) and Welter et al (2011) reported on the high incidence of burst discharges in neuronal activity of the limbic-associative functional territory of the STN in patients with OCD, with a similar proportion to burst activity in the STN of patients with PD. On the other hand, according to the same studies, firing rate in the STN of patients with OCD appears to be significantly lower than firing rate in the STN of patients with PD. Furthermore, Welter et al (2011) described the presence of abnormal oscillatory activity in the limbic-associative functional territory of the STN in patients with OCD and highlighted the clinical relevance of increased delta and alpha oscillatory activity. Some evidence for the presence of abnormal oscillatory activity in the STN of patients with OCD has also been provided by Bastin et al (2014 (a), (b)). Notably, there are also indications for the clinical relevance of reduced coupling across the delta and beta frequency bands reflecting a frontal–subcortical functional disconnection (Velikova et al. 2010), and for the clinical relevance of increased coupling between beta or low-gamma and broadband gamma-frequency activity (Bahramisharif et al. 2015). Last, there is some evidence that abnormal neuronal activity in the STN of patients with OCD may be hemisphere-specific (Piallat et al. 2011, Bastin et al. 2014 (a), Eitan et al. 2013).

3.8. Nonsurgical Management

First-line treatment options usually involve either cognitive-behavioral therapy (CBT) or pharmacological therapy for mild to moderate severity of illness (Y-BOCS score of 8 to 23), or a combination of both for patients with severe OCD (National Collaborating Centre for Mental Health 2006, Schruers et al. 2005, Seibell and Hollander 2014, Koran et al. 2007) (figure 3.5).

Exposure and response prevention (ERP) is a behavioral therapy with well-established effectiveness in reducing OCD symptoms, reflected in response rates of up to 85% in patients who complete the therapy (Meyer 1996, The Expert Consensus Panel for obsessive-compulsive disorder 1997, Abramowitz et al. 2003(c), Foa and Goldstein 1978, Foa et al. 2005, Koran et al. 2007). This first-line treatment is a time-limited therapy of 13 to 20 sessions performed over a weekly or even daily basis (Abramowitz et al. 2003(c), Koran et al. 2007) and involves systematic exposure to anxiety-eliciting stimuli or situations, i.e. patient-specific symptom triggers that have been previously hierarchized on a scale from 0 to 100. Two types of exposure are commonly used: situational (*in vivo*) and imaginal exposure. Situational exposure refers to a confrontation with actual anxiety-provoking stimuli, while imaginal exposure refers to a

confrontation with anxiety-provoking thoughts, images or doubts, until substantial reduction of anxiety is achieved. Response prevention is a further essential component of this treatment wherein the patient desists from yielding to the performance of a compulsion or an avoidance behavior. The core function of ERP is to teach the patient that provoked anxiety will gradually decrease without the urge of performing overt or covert compulsive rituals and without relying on avoidance or safety-seeking behavior (Seibell and Hollander 2014, Abramowitz 2006, Abramowitz et al. 2009, Bjorgvinsson et al. 2007, de Silva et al. 2003). This process is referred to as *habituation*. Remarkably, despite the well-documented and long-lasting efficiency of ERP, a substantial minority of patients (~25%) either refuses treatment or drops out prematurely (Abramowitz 2006). An equally effective psychoanalytical treatment that can be used alternatively or in order to facilitate compliance with ERP is cognitive therapy (CT) that is based on the concept of modification of dysfunctional cognitive reasoning pertaining to the overestimation of threat, overimportance of intrusive thoughts as well as inflated responsibility (Salkovskis 1999, Obsessive Compulsive Cognitions Working Group 1997, Abramowitz 1997, Wilhelm et al. 2005, Schruers et al. 2005, Emmelkamp et al. 1980, Nerizoglou et al. 2006). Furthermore, in the last few years, internet-based CBT with therapist support is emerging as a potentially more accessible treatment option (Andersson et al. 2012). Notably, despite the high effect size of CBT in the treatment of OCD (Abramowitz 1997), a considerable number of patients remains symptomatic after treatment (Abramowitz 2002). In this regard, initial symptom severity or initial depression severity seem to be implicated in the treatment outcome of CBT for OCD. However, the exact degree of correlation of these factors with the outcome of different CBT options remains controversial (Olatunji et al. 2013). On the other hand, in the framework of OCD symptom subtypes, it has been suggested that patients with cleaning and/or checking compulsions may respond better to CBT (McKay et al. 2004).

The FDA has approved five agents for the pharmacological treatment of OCD: clomipramine and four SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline). Due to a more troublesome side-effect profile of clomipramine, an SSRI is preferred as a first-line pharmacological treatment. However, the response to each SSRI may be patient-specific. Twelve weeks is the minimal duration of therapy necessary to correctly estimate the response to a drug, while it is often necessary to prescribe the maximal dose in order to obtain a good response in the acute phase of the disorder (Koran et al. 2007). There is also sufficient evidence that supports the efficacy of citalopram and escitalopram (Pallanti et al. 2011), though these compounds are not FDA-approved. For patients with partial response to first-line treatment, augmentation of SRIs with CBT or with an antipsychotic agent (dopamine antagonist) including

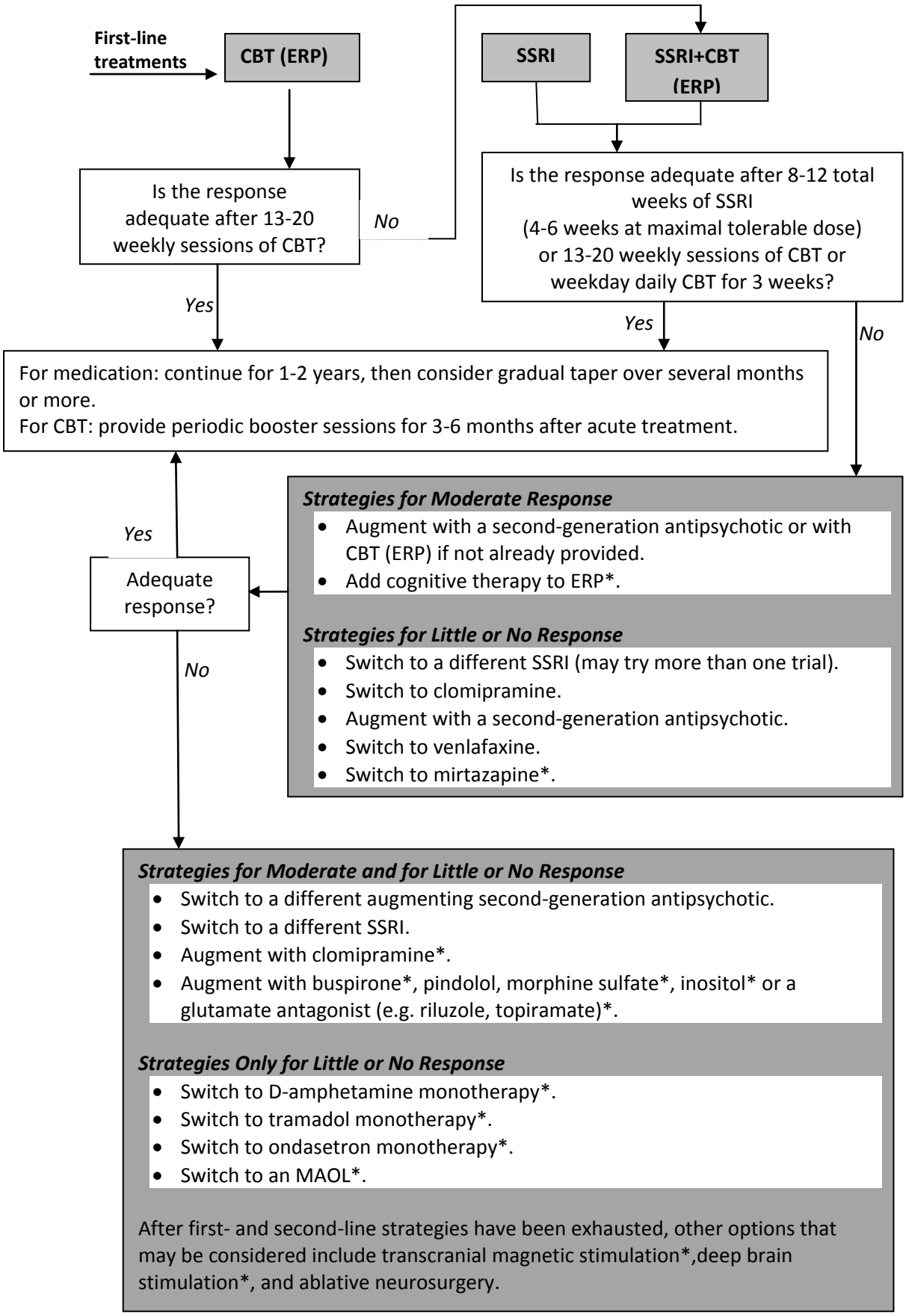


Figure 3.5. Algorithm for the Treatment of Obsessive-Compulsive Disorder (OCD).

*Treatment with little supporting evidence (Koran et al. 2007)

haloperidol, risperidone, or aripiprazole, may be considered. Patients with little (<25% reduction in Y-BOCS score) or no response to the initial SSRI may have their medication switched to a different SSRI or clomipramine, or to a serotonin–norepinephrine reuptake inhibitor (SNRI) including venlafaxine or mirtazapine. Augmentation strategies with an antipsychotic agent may be considered for these patients as well. Less supported second-line strategies include augmentation of SSRIs with clomipramine, buspirone, pindolol, riluzole (a glutamate modulating agent), or morphine sulfate. Exlusively for non-responders to second-line treatment, monotherapies with d-amphetamine, tramadol, monoamine oxidase inhibitors (MAOIs), or ondansetron may be considered (Koran et al. 2007, Seibell and Hollander 2014, Schruers et al. 2005, Bloch et al. 2008, Pittenger et al. 2006) (figure 3.5).

Pallanti et al (2002) have introduced operational criteria for discriminating between seven stages of response to treatment (Pallanti et al. 2002, Pallanti and Quercioli 2006) (table 3.1). The authors suggest use of the characterization ‘refractory’ only after at least three trials with SRI agents (including clomipramine), two augmentation trials with atypical antipsychotics, and at least 20-30 hours of CBT, while the term ‘recovery’ should be applied to indicate an almost complete absence of symptoms corresponding to an Y-BOCS value of 8 or below. Notably, recovery occurs only in an episodic course. Thus, the term ‘remission’ characterizes the most successful outcome in a non-episodic course. In an adequate trial of an SSRI, a 35% or greater Y-BOCS reduction could be considered a ‘full response’, between 25% and 35% a ‘partial response’, and less than 25% a ‘non-response’. Off note, the term ‘resistant’ should be used after fail of one trial of therapy with a first-line treatment (Pallanti et al. 2011).

Electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS) constitute non-surgical approaches for treatment-refractory OCD (National Collaborating Centre for Mental Health 2006). Particularly, ECT has been recommended by the Expert Consensus Guideline for treatment-refractory OCD and comorbid depression. Nevertheless, its efficiency exclusively for treatment-refractory OCD has not been established due to lack of convincing evidence. It has been reported that ECT may act by reducing comorbidity of depression, TS or schizophrenia, rather by treating OCD symptoms directly (Berlin et al. 2008, Lins-Martins et al. 2014). TMS for OCD involves the use of a pulsed magnetic field to induce changes in prefrontal cortical activity and thereby to ameliorate obsessive-compulsive symptoms. However, similar to ECT, there is inconclusive evidence upon which to base a recommendation for the use of TMS for treatment-refractory OCD. Future studies should be oriented towards the optimization of treatment duration and stimulation parameters as well as the determination of standardized stimulation sites (Berlin et al. 2008, Seibell and Hollander 2014).

Table 3.1. Stages of response (adapted form Pallanti et al. 2011)

Stage of response	Stage	Description
I	Recovery	Not at all ill; less than 8 on Y-BOCS
II	Remission	Less than 16 on Y-BOCS
III	Full response	35% or greater reduction of YBOCS and CGI 1 or 2
IV	Partial response	Greater than 25% but less than 35% YBOCS reduction
V	Non-response	Less than 25% YBOCS reduction, CGI 4
VI	Relapse	Symptoms return (CGI 6 or 25% increase in Y-BOCS from remission score) after 3+ months of 'adequate' treatment
VII	Refractory	No change or wosening with all available therapies

3.9. Neurosurgery for Treatment-Refractory Obsessive Compulsive Disorder

It is estimated that about 10% of patients with OCD demonstrate severe treatment-refractory symptoms (Denys 2006). For a select group of these patients, neurosurgical treatment may represent an effective alternative. Notably, in the current practice of psychiatric surgery treatment-refractory OCD is the condition most commonly referred (Lipsman et al. 2011). However, factors like cultural stigma surrounding psychiatric disease, reluctance of psychiatrists to refer patients and the historical misuse of psychosurgery have prevented widespread use of neurosurgery for treatment-refractory psychiatric indications. The safety and efficiency of traditional stereotactic ablative procedures, including anterior capsulotomy, anterior cingulotomy, subcaudate tractotomy and limbic leucotomy, for severe, treatment-refractory OCD, are supported just by level II evidence and remain at a 'proof-of-principle' investigational stage, while gamma knife and stereotactic-focused ultrasound lack evidence completely (Nuttin et al. 2014, National Collaborating Centre for Mental Health 2006). Furthermore, application of DBS for treatment-refractory OCD and validation of appropriate targets still remain at an experimental stage (Blomstedt et al. 2013, Kohl et al. 2014, Morishita et al. 2014, Figee et al. 2010, de Koning et al. 2011, Lapidus et al. 2013, Williams and Okun 2013, Krack et al. 2010). For the generation of level I clinical evidence with respect to neurosurgical procedures for psychiatric disorders, design of randomized and blinded controlled trials is required ensuring ethical conduct and giving priority to individual patient's safety and treatment. Accordingly, independent experts are needed for a comprehensive preoperative assessment using standardized

rating scales, including evaluation of treatment refractoriness, and carefully considering suicidality. Proper consent procedures have to be ensured. Equally important is the application of the neurosurgical procedure by an experienced multidisciplinary team, including trained neurosurgeons, psychiatrists, neurologists and neuropsychologists. Finally, a comprehensive postoperative assessment should be definitely warranted (Nuttin et al. 2014).

Since 1999, DBS has been evaluated in a total of approximately 100 individual patients as an advantageous treatment option over ablative procedures for severe, treatment-refractory OCD, by virtue of its reversibility and adjustability (Sakas et al. 2007 (b)). Due to limited knowledge of the pathophysiology of the disorder, target selection has been principally based on experience from traditional stereotactic lesioning procedures or on observations during DBS surgery for other disorders (Blomstedt et al. 2013, Benabid and Torres 2012). In the first published report of bilateral DBS for treatment-refractory OCD, the selected target was situated in the IC, immediately rostral to the anterior commissure extending into adjacent ventral capsule/ventral striatum (VC/VS) (Nuttin et al. 1999) (figure 3.6). The selected target was identical to the target region in capsulotomy. According to this report, in three of four patients beneficial acute effects were observed in the stimulation-on condition. Subsequently, long-term efficiency of anterior capsular and ventral striatal stimulation was being corroborated by a further series of small-scale studies (Nuttin et al. 2003, Gabriels et al. 2003, Abelson et al. 2005, Greenberg et al. 2006, Goodman et al. 2010). In a comprehensive evaluation of the clinical outcome of these studies Greenberg et al. (2010 (b)) reported during the last follow-up full responsiveness (72% >35% reduction in YBOC-S score) to VC/VS-DBS and remarkable improvements in depression, anxiety and global functioning in about two thirds (17/26) of patients, attributable to the gradual refinement of the implantation site within and across centers. Particularly, the optimal target was situated in the junction of the anterior capsule, anterior commissure and posterior ventral striatum. Adverse events reported included two intracranial hemorrhages, one seizure, one wound infection, two hardware-related complications, and stimulation-induced reversible effects, such as hypomania. Yet, cognitive decline is not induced by VC/VS-DBS (Kubu et al. 2013). In 2003, selecting the shell region of the right NAcc as a target for DBS was reported to induce significant improvement in OCD symptomatology (Sturm et al. 2003). This specific target choice was based on clinical observations about the possible role of the ventral-caudal part of the IC adjacent to the NAcc in the clinical outcome of anterior capsulotomy, but also on pathophysiological evidence pointing to the role of the NAcc as a central-relay structure between the amygdaloid complex and the subgenual cingulate (de Koning et al. 2012). Thereafter, application of unilateral DBS of the right NAcc for treatment-refractory OCD,

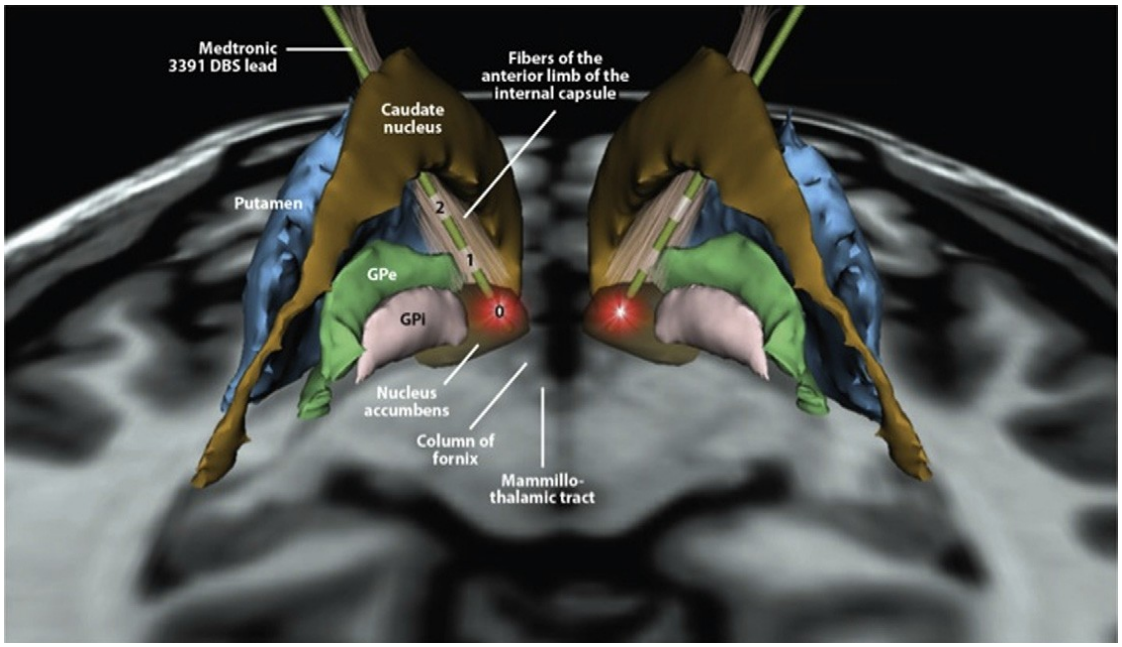


Figure 3.6. Three-dimensional illustration of DBS in ventral capsule/ventral striatum. Leads and brain structures are located on the axial plane 5 mm below the intercommisural plane as viewed posterior to anterior (reproduced with permission from Lapidus et al. 2013).

including a case of OCD with comorbid schizophrenia, resulted in moderate long-term beneficial effects (Huff et al. 2010, Plewnia et al. 2008), while bilateral DBS of the NAcc was associated with a significantly greater degree of long-term responsiveness yielding a level II evidence for the use of this procedure in clinical practice (Denys et al. 2010, Hamani et al. 2014, Franzini et al. 2010, Mantione et al. 2014). Notably, in all of the above-mentioned clinical trials high voltage amplitudes of stimulation (up to 10.5 V) have been required for significant clinical benefit.

With respect to a distinct target and according to a recent systematic review of Hamani et al (2014), there is level I evidence for the use of bilateral STN-DBS for treatment-refractory OCD. This evidence is based on the study of the French Stimulation dans le Trouble Obsessionnel Compulsif (STOC) Study Group (Mallet et al. 2008) that proposed this therapeutic option, after the observation that high frequency stimulation of the STN alleviated obsessive-compulsive symptoms in 2 patients with PD and a history of severe OCD (Mallet et al. 2002, Haynes and Mallet 2012). A further impetus to this specific selection was provided by multiple lines of evidence of the involvement of the STN, as a major node of the indirect pathway, in the pathophysiology of OCD and other behavioral disorders (Mallet et al. 2007, Winter et al. 2007, Winter et al. 2008(a), Haynes and Mallet 2012), as well as the proven efficiency of STN-HFS in the rat (Winter et al. 2008(b), Winter 2012, Klavir et al. 2009, Kupsch et al. 2004, Winter et al. 2007) and primate model of OCD (Baup et al. 2008) . According to the outcome of the study of

the French STOC Study Group, active contacts on postoperative MRI were placed in the anteromedial (associative-limbic) part of the STN, 2mm anterior and 1 mm medial to the target used during STN-DBS for PD. The YBOC-S score was reduced significantly (p=0.01) by 31% on average after 3 months of active stimulation. Chabardès et al (2013) evaluated the selection of the same target in four patients with severe OCD. In three of the four patients a 71-78% decrease in the YBOC-S score was reported at 6 months of stimulation, while in one case a lower clinical improvement (~34% decrease in the YBOC-S score) was achieved, even after adjustment of stimulation parameters, attributable to the functional misplacement of the electrodes. The authors remarked not only on the clinical effects of STN-DBS for treatment-refractory OCD, but also on the advantages associated with a well-known target region, as well as the lower energy requirements compared to the use of the aforementioned alternative targets.

Further target regions reported in the literature, in the framework of DBS for OCD, include the ITP, the bed nucleus of the stria terminalis and the anteromedial GPi (Jimenez-Ponce et al. 2009, Denys et al. 2003, Nair et al. 2014, Klavir et al. 2011, Gabriels et al. 2003). Jimenez-Ponce et al. (2009) observed a 49% reduction in the YBOC-S score of 5 patients after 12 months of stimulation of the ITP. Remarkably, however, ethical conduct in the framework of this study has been heavily criticized (Meyerson 2009). The bed nucleus of the stria terminalis as a clinical target for OCD is currently under evaluation by a multi-center study (Nuttin et al. 2013, Neumann et al. 2014). Thus far, surgical targeting of this nucleus has been associated with a significant posterior deviation from the original anatomical position.

4

Supporting Clinical Decision Making During Deep Brain Stimulation Surgery by means of a Stochastic Dynamical Model

Following the demonstration of the control of chaos in arrhythmic cardiac tissue, there are no longer any technical barriers to applying these techniques to neural tissue.

S J Schiff et al. (1994)

Abstract

Objective. The development of automatic methods for clinical decision making during deep brain stimulation (DBS) surgery for the treatment of advanced Parkinson's disease (PD) has to date been characterized by the absence of a robust single-biomarker approach. Moreover, it has only been restricted to the framework of microelectrode recording (MER) without encompassing intraoperative macrostimulation. Here, an integrated series of novel single-biomarker approaches is proposed applicable to the entire electrophysiological procedure by means of a stochastic dynamical model. *Approach.* The methods are applied to MER data pertinent to 10 DBS procedures. Considering the presence of measurement noise, a multivariate phase synchronization index is initially employed for automatic delineation of the functional boundaries of the subthalamic nucleus (STN) and determination of the acceptable MER trajectories. By introducing the index into a nonlinear stochastic model, appropriately fitted to pre-selected MERs, the neuronal response to periodic stimuli (130 Hz) is simulated, and the

Lyapunov exponent is examined as an indirect indicator of the clinical effectiveness yielded by stimulation at the corresponding sites. *Main results.* Compared with the gold-standard dataset of annotations made intraoperatively by clinical experts, the STN detection methodology demonstrates a false negative rate of 4.8% and a false positive rate of 0%, across all trajectories. Site eligibility for implantation of the DBS electrode, as implicitly determined through the Lyapunov exponent of the proposed stochastic model, displays a sensitivity of 71.43%. *Significance*. The suggested comprehensive method exhibits remarkable performance in automatically determining both the acceptable MER trajectories and the optimal stimulation sites, thereby having the potential to accelerate precise target finalization during DBS surgery for PD.

4.1. Targeting Modalities in Deep Brain Stimulation Surgery for Parkinson's Disease

In addition to appropriate patient selection and optimal postoperative management, the quality of the clinical outcome of DBS surgery is strongly correlated with appropriate anatomical target determination and accurate electrode placement in the targeted nucleus (Lozano et al. 2010 (a), Volkmann et al. 2006). In that vein, upon application of the stereotactic frame, pre-operative direct targeting modalities, namely CT, 1.5 T-MRI, and ventriculography have all been shown to be stereotactically accurate in the millimeter range (Rezai et al. 2006). However, while some surgical teams exclusively opt for these image-guided approaches, in the majority of clinical centers the additional use of microelectrode recording (MER) as an indirect targeting modality has been adopted in order to optimize accurate electrode localization (Abosch et al. 2013, Weaver et al. 2009). The latter option is justified on the grounds of specific drawbacks related to direct targeting, including brain shift: the target location determined during MRI, when the patient lies in the supine position, is not the same as the target location determined intra-operatively, when the patient lies in a more upright position (Abosch et al. 2010). Nevertheless, prospective randomized studies comparing the long-term efficiency of MER vs. the aforementioned image-guided approaches are still lacking (Rezai et al. 2006, Senatus et al. 2006, Mc-Clelland III 2011, Gross and McDougal M E 2013). In either case, final electrode placement is ultimately determined on the basis of the patient's response to intraoperative macrostimulation (Lozano 2012, Bour et al. 2010).

Intraoperative MER is considered a relatively safe and robust tool for reducing the risk of suboptimal localization of the targeted nucleus (Rezai et al. 2006, Reck et al. 2012, Lanotte et al. 2002, Chen et al. 2006, Schlaier et al. 2013). After burr holes are made anterior to the

coronal suture, one to five microelectrodes are (concurrently) advanced towards the targeted nucleus using a microdrive. During this process, the physiological 'signature' of each penetrated nuclear structure can be visualized thereby assisting clinical decision with respect to the optimal recording trajectory, i.e. the trajectory traversing the broadest extent of the nucleus (Lozano et al. 2010 (a), Marceglia et al. 2010). With respect to the subthalamic nucleus (STN) (see section 4.2), an increased background noise level, a high discharge rate and an irregular or bursting pattern of activity, are distinguishing features of this target structure compared with surrounding brain structures (Bour et al 2010). Following delineation of the functional boundaries of the STN, its total length for each recording track can be defined. An acceptable track should pass through >= 3 mm of the nucleus (Marceglia et al 2010). Framebased DBS surgery including MER has a similar outcome when compared with frameless stereotaxy (Tai et al. 2010, Holloway et al. 2005, Bronte-Stewart et al. 2010, Rezai et al. 2006). However, there is currently no compelling evidence for a positive correlation between the number of recording electrodes used and the degree of improvement of motor symptoms or the risk of intracranial hemorrhage (Temel et al. 2007, Gross et al. 2006, Chang et al. 2011, Zibetti et al. 2014). In addition, firm conclusions about the effects of anesthesia on microelectrode mapping have not been yet drawn (Lettieri et al. 2012, Maltete et al. 2004, Rezai et al. 2006).

Meanwhile, direct visualization techniques for preoperative or intraoperative use are being optimized with the ultimate goal of improving the accuracy of anatomic target localization or even excluding a possible hemorrhage risk associated with microelectrode penetrations (Zrinzo et al 2012). Within this framework, the accuracy achieved using susceptibility-weighted imaging at 3 (3.0T-MRI) or 7 Tesla (7.0T-MRI), high-field interventional MRI (iMRI), intra-operative CT ,O-arm images, or diffusion tensor imaging (DTI) tractography appears to be at least comparable to the accuracy reported when using standard MER stereotactic methods (Patil et al. 2012, Abosch et al. 2010, Cho et al. 2010, Toda et al. 2009, Liu et al. 2013, Larson et al. 2012, Starr et al. 2010, Ostrem et al. 2013, Burchiel et al. 2013, Fiegele et al. 2008, Coenen et al. 2011, Holloway and Docef 2013, Henderson 2012, D'Albis et al. 2014, Sudhyadom et al. 2009). Notwithstanding, for the emerging targets the exclusive use of direct visualization techniques may be less appropriate than electrophysiologically guided neurosurgery (Starr et al. 2010).

Importantly, irrespectively of the targeting modality used, intraoperative clinical testing of macrostimulation is a strong prerequisite for optimal lead finalization, ensuring that maximal therapeutic effects of stimulation at a specific site are achieved along with minimal side-effects (Rezai et al. 2006, Abosch et al. 2010, Starr et al. 2010, Pollak et al. 2002. Kinfe andVesper 2013). Macrostimulation is most commonly applied through the low-impendance shaft of the

microelectrode (Sakas et al. 2007 (a)), a macroelectrode (Coenen et al. 2011), or the DBS electrode (Chen C C et al. 2006) at multiple sites, in order to assess the optimal ratio between the intensity threshold for the appearance of side-effects and the intensity threshold for clinical effectiveness, i.e. the optimal *therapeutic window* (Marceglia et al. 2010). Thus, intraoperative stimulation provides a neurophysiological refinement of the targeted nucleus for lead finalization. The intuitive justification behind this approach lies in the fact that intraoperative macrostimulation-induced effects are similar to the postoperative effects induced by the chronic DBS electrode. Therefore, stimulation parameters utilized intraoperatively simulate the respective parameters applied postoperatively, i.e., most commonly, a frequency of 130 Hz, a pulse width of 60 μ s and amplitudes up to 5 V (Pollak et al. 2002). Intraoperative clinical testing is currently being performed by neurosurgeons, neurologists, and clinical neurophysiologists (Rezai et al. 2006). A reliable assessment of the clinical benefits during STN-DBS, most frequently involves evaluation of rigidity improvement, improvement of segmental akinesia and/or stimulation-induced dyskinesias, which should be noticeable at low electrical intensities (Houeto et al. 2003, Pollak et al. 2002, Gross et al. 2006). Regarding certain motor and oculomotor side-effects (motor contractions in the contralateral labial commissure, face, or hand, and monocular eye deviation or unilateral change in the pupil diameter), these should be induced at high intensity levels, whereas for sensory and vegetative adverse effects a narrow therapeutic window is acceptable (Pollak et al. 2002, Tommasi et al. 2008). During surgery, improvements in motor symptoms of PD and/or onset of dyskinesias have been observed by simply implanting the DBS electrode at the STN, the so-called *microlesion effect* (Chen C C et al. 2006, Yoshida et al. 2010). Though this effect seems to be of positive prognostic significance, no definite conclusions have been reached (Rezai et al. 2006).

Within the general framework of targeting modalities used during DBS surgery, there exists a variety of algorithms and advanced software systems designed to support or even automate clinical decision making intraoperatively. Specifically, biomarkers and modeling approaches based on electrophysiological data or oriented to the development of patient-specific 3-dimensional models of the target area significantly facilitate optimal trajectory identification (Wong et al. 2009, Cagnan et al. 2011, Falkenberg et al. 2006, Chan et al. 2010, Novak et al. 2011, Pesenti et al. 2004, Pinzon-Morales et al. 2011, Holdefer et al. 2010, Danish et al. 2008, Snellings et al. 2009, Zaidel et al. 2009, 2010, Chen C C et al. 2006, Taghva et al. 2011, Abosh et al. 2013, Beriault et al. 2012). In addition, patient-specific modeling approaches being inclusively applicable to clinical macrostimulation testing encompass the potential to optimize and accelerate lead finalization (Miocinovic et al. 2007, Butson et al. 2011, D'Haese et al. 2012, Maedler and Coenen 2012).

4.2. The Subthalamic Nucleus Target: Topographic Organization and Functionality

The STN, also known as the *corpus Luysii*, is a biconvex-shaped structure situated at the diencephalo-mesencephalic junction (Luys 1865, Yelnik and Percheron 1979). The borders of the STN are defined by the zona incerta, a portion of the fasciculus lenticularis, fibers of the IC, the field H of Forel, the postero-lateral hypothalamus, the cerebral peduncle, the substantia nigra pars reticulata and the red nucleus (Schaltenbrand and Wahren 1977). Fiber tracts coursing near the border of the STN include the subthalamic fasciculus, the ansa lenticularis, the lenticular fasciculus, the thalamic fasciculus, dopaminergic nigrostriatal fibers, the medial lemniscus, the spinothalamic tract, the trigeminothalamic tract and the reticulothalamic tract (Hamani et al. 2004). The volume of human STN has been reported to range between 175mm^3 and 240 mm^3 and to include an average of 240.000-560.000 neurons (Hardman et al. 2002, Levesque and Parent 2005). Its length, width, and height are 9.8 ± 1.6, 11.5 ± 1.6, and 3.7 ±0.7 mm, respectively (Patil et al. 2012). Notably, there is some evidence of a significant inter-individual variability in anatomical position and dimensions of the STN (Daniluk et al. 2010, Reese et al. 2012). The vascular supply to the STN is mediated by branches of the anterior choroidal artery, the posterior communicating artery and posteromedial choroidal arteries (Hamani et al. 2004).

The STN is the only nucleus within the basal ganglia network principally composed of projection neurons exerting an intense glutamate-mediated excitatory effect upon other structures. Particularly, these neurons project mainly to the pallidum, striatum, substantia nigra, PPN and cortex. Notwithstanding, GABAergic interneurons also appear to play a role in the intrinsic organization of the STN. The STN receives its afferents from the cerebral cortex, the thalamus, the GPe, the substantia nigra, the PPTg and the dorsal raphe nucleus (Parent and Hazrati 1995, Hamani et al. 2004, Marani et al. 2008, Nambu et al. 2002, Levesque and Parent 2005). As stated in section 2.6, the pallidosubthalamic projection constitutes an essential component of the indirect pathway (Parent and Hazrati 1995, Karachi et al. 2005). Importantly, the structural and functional subdivision of the basal ganglia into the sensorimotor, associative and limbic regions is reflected in the existence of three corresponding functional zones in the STN, i.e. the sensorimotor, the associative and the limbic zone residing in the posterior (dorsolateral), mid (ventromedial) and anterior (medial) part of the nucleus, respectively (Alexander and Crutcher 1990, Lambert et al. 2012, Hamani et al. 2004, Karachi et al. 2005, Parent and Hazrati 1995, Brunenberg et al. 2012, Tan et al. 2006, Sudhyadhom et al. 2007, Stathis et al. 2007). Accordingly, the STN is not only actively involved in the regulation of

movement, but also in cognitive and emotional processing (Péron et al. 2013, Le Jeune et al. 2010, Benedetti et al. 2004, Greenhouse et al. 2011, Drapier et al. 2008, Baláž et al. 2011, Bockova et al. 2011, Buot et al. 2013, Kopell and Greenberg 2008, Baunez et al. 2011, Burbaud et al. 1994). Interestingly, however, these three functional modalities may not be processed in a strictly topographically segregated manner, but may be integrated within the small volume of the STN (Mallet et al. 2007, Hershey et al. 2010, Baláž et al. 2011, Haynes and Haber 2013, Lalys et al. 2013). The existence of this functional connectivity pattern within the borders of the STN may explain the absence of an academic consensus in support of a strictly tripartite functional subdivision of this core structure (Alkemade and Forstmann 2014).

While pathological patterns of neuronal activity in the STN of patients with PD have been extensively described in section 2.6, special reference should be made to the topographic organization of these patterns. In this respect, single-cell and LFP recordings have revealed a higher incidence of burst discharges, of movement-related neuronal activity, of beta and tremor-related oscillatory activity, and of pathological synchronization in the dorsal compared with the ventral part of the STN of patients with PD, although this difference has not always reached statistical significance (Kühn et al. 2005, Weinberger et al. 2006, Seifried et al. 2012, Contarino et al. 2011, Rodriguez-Oroz et al. 2001, Hamani et al. 2004, Guo et al. 2013, Lourens et al. 2013). In accordance with this topographic organization but also with the functional connectivity pattern of the STN stays the fact that DBS electrodes positioned at the ventral or medial part of the STN of patients with PD may improve motor symptoms, but at the expense of inducing speech, cognitive or emotional impairment (Hershey et al. 2010, Astrom et al. 2010, Mikos et al. 2011, Mallet et al. 2007, Paek et al. 2008). On the other hand, the dorsolateral margin of the STN has consistently been characterized as the stereotactic position correlated to the greatest improvement of the UPDRS-III-on score (Herzog et al. 2004, Guo et al. 2013, Johnsen et al. 2010, Godihno et al. 2006, Lanotte et al. 2002, Maks et al. 2009, Zaidel et al. 2010), though there is also some evidence that stimulation in that area may negatively affect speech intelligibility (Lalys et al. 2013). Moreover, stimulation of the lateral STN has been associated with a lower therapeutic effect on bradykinesia as opposed to rigidity (Cooper et al. 2011), a phenomenon possibly invoked by activation of pyramidal tract fibers in the adjacent IC (Xu e al. 2011). Besides, stimulation-induced activation of pyramidal tract fibers, including corticobulbar and corticospinal pathways, has been reported to induce cranial motor contractions that constitute one of the most common side effects observed during STN-DBS for PD (Tommasi et al. 2008, 2012).

4.3 Mechanisms of Action of Deep Brain Stimulation

'The mechanism of action is not well understood' - no phrase is repeated more often in reports on deep brain stimulation in psychiatry and neurology.

M. G. P. Feenstra and D. Denys (2012)

The elucidation of the mechanism associated with clinically effective DBS is crucial to a deeper understanding of the functional underpinnings of this technology, as well as to the determination of its full therapeutic potential, that may in turn favor the development and advancement of novel and clinically more efficient stimulation patterns. Variations in the approach used (imaging, neurophysiology, microdialysis), in the mode of stimulation (using the standard multicontact DBS electrode versus using a microelectrode or the guide-tube as the active electrode) and stimulation parameters, or in the latencies (short versus long-term) of the observed effects are the main synergetic factors towards relatively contradictory hypothetical mechanisms of action of DBS (Lozano and Lipsman 2013). The 'functional lesion' hypothesis, i.e. the hypothesis that stimulation evokes silencing of pathologically hyperactive neurons, originated in the observation of a comparable effect of stimulation to ablation in the thalamus, STN and GPi (Benabid et al. 2000, Benazzouz et al. 1995, Beurrier et al. 2001). This initially postulated mechanism of action has been further corroborated by more recent studies methodologically based upon concomitant intraoperative recording of neuronal activity and application of high frequency stimulation (Welter et al. 2004, Meissner et al. 2005, Filali et al. 2004, Toleikis et al. 2012). Overall, inhibition of the activity of subthalamic or pallidal target neurons may be due to depolarization blockade (K, Na effects), synaptic failure, excitatory neurotransmitter depletion (glutamate), hyperpolarization of neuronal cell bodies and dendrites, release of inhibitory neurotransmitters (gamma-aminobutyric acid (GABA), adenosine) or synaptic inhibition of afferent projections (Lozano and Lipsman 2013). On the other hand, experimental, computational modeling and functional imaging studies have highlighted a predominantly excitatory effect of subthalamic high-frequency stimulation (STN-HFS) on the output of the target nucleus (Garcia et al. 2005, Hilker et al. 2008, Garraux et al. 2011, Novak et al. 2009, So et al. 2012) or, most importantly, a decoupling effect of stimulation on somatic and axonal activity, i.e. somatic inhibition and deactivation of afferents, and axonal excitation and activation of efferents (McIntyre and Grill 2000, 2002, McIntyre et al. 2004 (a),(b),(c), McIntyre and Hahn 2010, Vitek 2002, Deniau et al. 2010, Johnson et al. 2013, Kringelbach et al. 2007, Grill and McIntyre 2001). At a fiber-pathway level, antidromic activation or synaptic effects on neuronal structures connected to the STN, including the SNr, the globus pallidus, the SNc, the contralateral STN, the PPN, the cerebral cortex, the thalamus and the superior colliculus are well-documented (Burbaud et al. 1994, Benazzouz et al. 1995, 2000, Windels et al. 2005, Maurice et al. 2003, Tai et al. 2003, Degos et al. 2005, Shi et al. 2006, Maltete et al. 2007, Hashimoto et al. 2003, Dorval et al. 2010, Hahn et al. 2008, Hahn and McIntyre 2010,

Hilker et al. 2008, 2004, Reese et al. 2008, 2011, Meissner et al. 2002, Lee et al. 2004, 2006 , Li et al. 2012, Gubellini et al.2006, Novak et al. 2009, Florio et al. 2007, Jech et al. 2006, Li et al. 2006, Pötter-Nerger et al. 2008, Eusebio et al. 2009, Kuriakose et al. 2010, Lehmkuhle et al. 2009, Xu et al. 2008, Bressand et al. 2002, Garraux et al. 2011, Geday et al. 2009, Guo et al. 2008, Moran et al. 2012, Rubin and Terman 2004, Santaniello et al. 2010, Sotiropoulos and Steinmetz 2007, Volonte et al. 2012, Walker et al. 2011, Whitmer et al. 2012, Zheng et al. 2011, Lafreniere-Roula et al. 2012).

Ultimately, the combinatorial effect of stimulation on a sub-cellular, neuronal, and fiber-pathway level (synaptic inhibition, excitation and antidromic activation) may underlie the observed modulation of pathophysiological patterns of neuronal activity within both the stimulated nucleus and the basal ganglia-thalamo-cortical circuit (McIntyre and Hahn 2010, Grill et al. 2004, Montgomery and Gale 2008, Rosenbaum et al. 2014, Carlson et al. 2010, Deniau et al. 2010). In particular, the mechanism of action of DBS for PD, may be primarily attributed to the reinforcement-driven regularization of neural firing patterns and the creation of an 'informational lesion' in the vicinity of the stimulated nucleus (McConnell et al. 2012, Santaniello et al. 2015, Grill et al. 2004), while there are also new indications emphasizing the disruptive effect of stimulation on abnormal cortical neural activity (de Hemptinne 2015). Noteworthily, using standard therapeutic stimulus parameters, Carlson et al (2010) observed that a subset of STN neurons, originally exhibiting bursting or tonic firing, shifted to a more random pattern after stimulation. This result is closely linked to the observed alterations in the discharge pattern of STN neurons in response to contralateral STN-DBS (Walker et al. 2011) and the reported desynchronizing effect of standard HFS (Hauptmann et al. 2007, Rubin et al. 2012), but also to the concept that STN- DBS modulates pathological patterns of synchronized oscillations in the STN (Bronte-Stewart et al. 2009, Eusebio et al. 2011, 2012, Meissner et al. 2002, Whitmer et al. 2012, Wingeier et al. 2006), thereby controlling motor output (Kuhn et al. 2008). Most importantly, computational modeling and clinical studies indicate that temporally alternative patterns of stimulation hold the potential to drive the neuronal dynamics within the basal ganglia back to the normal desynchronized state (Feng et al. 2007(a),(b), Adamchic et al. 2014). Meanwhile, a possible disease-modifying and neuroprotective effect of STN-DBS (Temel et al. 2006 (b), Harnack et al. 2008, Wallace et al. 2007, Spieles-Engemann et al. 2010, deSouza et al. 2013, Albanese and Romito 2011, Shon et al. 2010, Van Gompel et al. 2010, Grahn et al. 2014) is currently under investigation by a prospective clinical trial (Kahn et al. 2012).

In relation to the mechanisms associated with the neuropsychiatric side effects of STN-DBS, hypotheses vary to a great extent. There is evidence suggesting the alteration of valence-related

emotional information processing within the STN as an underlying mechanism of stimulation leading to behavioral complications. This alteration can be quantified by means of the event-related desynchronization of subthalamic alpha activity (Brücke et al. 2007, Huebl et al. 2011). Other studies have emphasized the destabilization of the 5-hydroxytryptamine (5-HT) system induced by STN-HFS, as a contributing factor to the development of psychiatric side-effects (Hartung et al. 2011, Tan et al. 2012 (a), (b)). From an alternative but equally plausible view, spread of current to non-motor pathways within and around the STN may be responsible for the cognitive and emotional impairment following bilateral STN-DBS (Frankemolle et al. 2010, Alberts et al. 2010, Hershey et al. 2010, Mallet et al. 2007, Daniels et al. 2012). The latter mechanism may also underlie the stimulation-induced decrease of verbal fluency performance (Mikos et al. 2011).

Regarding stimulation effects on alternative targets, evidence is relatively limited. GPi stimulation has been proven to abolish low-frequency synchronized oscillations and to rather entrain (Cleary et al. 2013, Mc-Cairn and Turner 2009, Bar-Gad et al. 2004, Agnesi et al. 2013) than to silence neuronal activity (Dostrovsky et al. 2000, Pirini et al. 2009). On the other hand, thalamic DBS may lead to tremor arrest through masking and/or blocking rhythmic firing of tremor cells (Kiss et al. 2002). Finally, in relation to the underlying mechanism of action of PPTg-DBS, imaging studies have suggested that neuromodulation of the PPN activity may induce functional changes in areas of the cerebello-thalamo-cortical circuit involved in the control of lower limb movements (Ballanger et al. 2009).

4.4. Rationale and Objective of the Current Analysis

As stated in section 4.1, in the context of microelectrode mapping, automated methods aiming at enhanced objectivity and reduced operation time have been extensively investigated (Falkenberg et al 2006, Danish et al 2008, Zaidel et al 2009, Wong et al 2009, Novak et al 2011, Cagnan et al 2011, Pinzon-Morales et al 2011). In that respect, combinatorial application of quantitative features related to the local field potential (LFP) and/or the high-pass filtered signal (i.e. the high-frequency background activity or the spiking activity), has been evaluated. Whereas multi-feature approaches provide increased accuracy and reliability for STN targeting, the use of an unique robust biomarker would substantially simplify and accelerate intraoperative nucleus detection. In addition to the aforementioned perspective, a complementary single-biomarker approach applicable to the process of intraoperative stimulation would lead to significant improvement of the entire electrophysiological procedure, by optimizing clinical decision making and decreasing total surgical time.

There is emerging evidence suggesting correlation of subthalamic oscillatory synchronization with clinical impairment in PD (Kühn et al 2009, Pogosyan et al 2010), and, conversely, desynchronization of the neuronal activity as a possible mechanism of action of STN-DBS (Carlson et al 2010, Walker et al 2011, Hauptmann et al 2007, Modolo and Beuter 2009, Wilson et al 2011, Johnson et al 2013). In light of this evidence, the main objective of this study was to evaluate collective dynamical and response properties of the subthalamic oscillatory activity as crucial hallmarks for the selection of the optimal stimulation site during DBS for PD. Specifically, the goal was to assess the applicability of two complementary single-biomarker approaches within the principal mapping techniques that are commonly used intraoperatively: MER and macrostimulation testing. Within this frame of reference, based upon MERs acquired during 10 surgical interventions, a multivariate phase synchronization index (Carmeli et al 2005, Allefeld et al 2007, Polychronaki 2011) was initially assessed as a combined measure of local and spatially extended oscillatory synchronization (Moran and Bar-Gad 2010), keeping susceptibility to measurement noise to a minimum (Rossberg et al 2004, Sun et al 2008). Implementation of the proposed index was intended to point to the acceptable trajectories, i.e. the trajectories that would be the best candidates for macrostimulation (Marceglia et al 2010). This feature was subsequently employed as one of the constituent parameters of a stochastic phase model appropriately fitted to pre-selected MERs. Based on this model, the Lyapunov exponent (Pikovsky et al 2001) was assessed as a quantity reflecting subthalamic synchronization dynamics in response to periodic inputs (130 Hz) and further evaluated its predictability in identification of the sites where stimulation yielded the best clinical benefit. The entire automatic methodology was evaluated based on the decisions made intraoperatively by clinical experts.

4.5. Patients and Methods

4.5.1. Patients and Surgery

During a 1-year period, 10 patients underwent implantation of DBS electrodes in the STN, at the Department of Neurosurgery at Evangelismos General Hospital of Athens. Three women and seven men participated with informed consent and the permission of the local ethics committee. Their ages ranged from 50 to 70 years, with a mean of 60 years. The clinical criteria included idiopathic PD (as documented by a positive response to levodopa) with motor fluctuations and/or dyskinesias. The mean disease duration was 14.5 years (range: 10–19 years). The mean motor Unified Parkinson's Disease Rating Scale (UPDRS) score preoperatively in the off-medication state was 61.5 (range: 40–75) and 22.9 (range: 12-32) in the on-medication state.

Anti-parkinsonian medication was withdrawn at least 12 hours before surgery. Table 4.1 summarizes patient clinical characteristics.Stereotactic surgery was based on pre-operative anatomical targeting of the STN, MER and high frequency test stimulation (Sakas et al 2007(a), Boviatsis et al 2010). Patients underwent application of a CRW stereotactic frame (Cosman–Roberts–Wells – Radionics Inc., Burlington, MA, USA) under local anesthesia and in a way that the anterior commissure/posterior commissure (AC-PC) plane was approximately parallel to the base plane of the frame. Anatomical targeting of the STN was achieved via both indirect visualization according to a stereotactic atlas (Schaltenbrand and Wahren 1977) and direct visualization according to an image fusion technique. This technique involved a combination of frameless T2-weighted magnetic resonance imaging (MRI) and framebased computed tomography (CT) and was developed on a Radionics hardware/ software system (StereoPlan, Integra Radionics, Burlington, MA, USA). The coordinates obtained with both indirect and direct methods were combined for determination of the anatomical target point used during microelectrode mapping. The surgical procedure was performed under local anesthesia. Fourteen mm diameter, burr holes were centered over a point anterior to the coronal suture and 3.4 cm lateral to midline. Stereotactic arc settings ranged from 55^{o} to 70^{o} for declination, and slide settings were 10^{o}-15^{o}. Microelectrodes were placed on a five-channel holder with central, lateral, medial, anterior and posterior positions, 2 mm apart (Ben's gun). The initial point of MER was typically within the white matter, superior and rostral to the thalamic reticular shell. A micropositioner system (Microtargeting Drive –Medtronic Inc., Minneapolis, MN) was used to advance the microelectrode in submillimeter steps. At each site, signals were recorded for $\leq 10s$. Visual and auditory analyses were performed on-line by two clinical experts. The electrophysiological criteria used to distinguish the STN were an increased background noise level and neuronal firing rate, an irregular pattern of activity and/or cellular responses to passive movements of the patients' extremities. At the end of MER mapping, the total penetrated length of the STN was noted for each recording track. Following determination of the trajectories traversing the broadest extent of the nucleus, macrostimulation was performed usually at 3 selected depth positions with an external pulse generator (Medtronic Screener Model 3625; Medtronic, Inc., Minneapolis, MN). The stimulation parameters utilized were a frequency of 130 Hz, a pulse width of 60 μs and amplitudes up to 5V. Rigidity improvement was judged on passive movements of the contralateral wrist, whereas the assessment of side-effects was mainly based on observation of certain motor contractions and/or of tonic eye deviation and/or blurred vision. Once the site with the best therapeutic window was identified, the DBS lead (Medtronic electrodes 3389 and 3387) was advanced 2 mm, in order for the contacts to 'encompass' the optimal target point, and finally anchored with a Navigus cap (Image Guided Neurologics, FL, USA). Final lead placement was confirmed with fluoroscopy. The same procedure was then repeated for the other side, in cases of bilateral surgery. Post-operative MRI was performed

Table 4.1. Clinical details of patients with advanced PD

Case	Age (years) and sex	Disease duration (years)	Hemisphere(s) tested	Motor UPDRS ON/OFF drugs pre-op	Motor UPDRS ON/OFF drugs post-op	Lev. equiv. pre-op/post-op	Site with the best therapeutic window[a]	Clinical Outcome
1	59,f	11	Right STN/Left STN	12/40	14/38	850/750	C 0/A -0.5	Moderate
2	53,f	16	Right STN	16/52	8/18	1450/600	A -1.0	Excellent
3	66,m	19	Left STN	28/72	24/62	1000/600	P -2.0	Moderate
4	53,m	10	Right STN/Left STN	16/53	18/24	1100/300	P 0/ L -2.0	Excellent
5	62,m	18	Right STN/Left STN	23/68	18/38	1400/500	M -1.0/P 0	Excellent
6	50,m	16	Right STN	26/66	24/28	1400/450	P 0/C 0	Excellent
7	70,m	13	Right STN	24/58	20/34	750/450	C -1.0	Excellent
8	62,m	15	Right STN/Left STN	32/70	30/41	1800/750	P -1.0/P +1.0	Excellent
9	64,m	14	Right STN	28/75	22/32	1600/600	L -1.5	Excellent
10	67,f	13	Left STN	24/61	26/54	1150/850	M -1.0	Moderate

m,male; f,female; pre-op, preoperatively; post-op, postoperatively; C,Central; L,Lateral; A,Anterior; P,Posterior; M,Medial.
[a] -, mm above anatomical target point (0 mm); +, mm below anatomical target point (0 mm).

within 2 days to confirm the location of the DBS electrodes before they were connected to the internal pulse generator (IPG) (Kinetra, Medtronic Inc., Minneapolis, MN).

4.5.2. Data Description

A commercially available microrecording system (Leadpoint TM Neural Activity Monitoring System, Medtronic Inc., Minneapolis, MN) was used to acquire and store data. Five tungsten microelectrodes (2mm apart, tip diameter < 25 μm, Medtronic Inc., Minneapolis, MN) were used for recording. The recorded signal was pre-amplified, band-pass filtered between 0.1 Hz and 10 kHz and 1000× amplified (Nicolet Vicking IV; Nicolet Biomedical, Madison, USA).The signal was sampled at 24 kHz using a 16-bit A/D converter (CED Power1401, Cambridge Electronic Design, Cambridge, UK). In total, data from 70 MER trajectories obtained from 10 STN-DBS procedures were retrospectively analyzed in Matlab (Mathworks, Inc., Natick, MA), (table 4.1). Initially, the acquired signals were digitally band-pass filtered at 1-141 Hz and 0.5-10 kHz applying 4-pole Butterworth filters.

4.5.3. Signal Preprocessing

The extracellular signal recorded from the microelectrode (figure 4.1(a)) conveys the sum of two complementary signals acquired by the aforementioned frequency-band separation: the multi-unit activity reflected in the high frequency signal component and the local field potentials (LFPs) reflected in the low-frequency signal component (Logothetis 2002). The LFPs predominantly represent synaptic events in a neural population within a large radius (0.5-3mm) of the electrode tip (Mitzdorf 1987). By contrast, the multi-unit activity reflects the spiking activity of a neural population within a small radius (200-300μm) of the electrode tip (Logothetis 2002). The multi-unit activity actually consists of spiking activity of one or just a few large isolated cells and background unit activity, which represents the sub-noise level spiking activity of the surrounding neural population (Moran and Bar-Gad 2010).

Accordingly, the methods presented here were based on the assessment of multi-scale neuronal activity: a. spiking activity quantified through the spike detection process, b. activity of small neural populations quantified through the background unit activity extraction process (Moran et al 2008), and c. activity of large neural populations reflected in the LFPs (figures 4.1(b)-(d)) .

4.5.3.1. Mechanical Artifacts - Extraction of Spiking and Background Unit Activity

Occasional events, like vibrational effects, 50/60 Hz power-line interference and static discharge may result in high amplitude artifacts (Dolan et al 2009). Automatic detection and elimination of high amplitude artifacts was based on noise level estimation, as proposed by Dolan et al (2009). Low amplitude artifacts were also detected and excluded from further analysis as described by Cagnan et al (2011).

The spike detection process involved application of morphological criteria based on a five-point spike template (Wong et al 2009, Cagnan et al 2011). Specifically, an amplitude threshold set at *3.5* times the estimated noise level was employed, and hard-coded thresholds for the peak-to-peak spike width and the distance between zero crossings flanking the candidate spike.

Reconstruction of the background unit activity (figure 4.1(d)) was performed eliminating the bias of dominant spikes (Moran et al 2008).Thus, following identification of the spiking activity, the surrounding time windows (-0.5 to $+2.5$ ms around the spike identification point) were removed and the empty segments were replaced by randomly chosen 3-ms spike-free windows from the same recorded trace. Small inconsistencies between the real and the inserted spike-free segments were considered negligible for power alterations in the low-frequency range (Moran and Bar-Gad 2010).

4.5.4. MER - Automatic Detection of STN Borders and Identification of Acceptable Trajectories

For automatic delineation of the functional boundaries of the STN during MER based on a single-biomarker approach, dynamic interactions were quantified and integrated between pairs of the three distinct signals: (1) the spiking activity (2) the background unit activity and (3) the local field potentials (figures 4.1(b)-(d)). To this end, phase synchronization analysis was performed (Tass et al 1998, Carmeli et al 2005, Allefeld et al 2007, Polychronaki 2011), restricted to the beta frequency band, in light of strong evidence that beta oscillatory synchronization in the STN is dramatically increased in the pathological state (Kühn et al 2005, Weinberger et al 2006, Moran and Bar-Gad 2010).

4.5.4.1. Envelope Extraction

Importantly, in addition to the LFPs, the envelope of the high-frequency signal component may also yield power in the low-frequency range (1-141Hz) (Logothetis 2002, Moran and Bar-Gad 2010). In that respect, the low-frequency envelope of the background unit activity signal was extracted employing the full-wave rectification (FWR) method, before a 4-pole Butterworth filter was applied (passband 1-141Hz). This filter was also used in order to recover the low-

frequency amplitude modulation of the spiking activity. All signals were further down-sampled to 1 kHz.

4.5.4.2. Data-driven Optimal Filtering

On account of the presence of measurement noise (Hurtado et al 2004, Rossberg et al 2004, Sun et al 2008), a complex –valued, linear bandpass filter was applied, prior to the phase reconstruction procedure as described by Rossberg et al (2004). Particularly, optimization was performed under the constraint of a spectral window ranging within 10-33 Hz, taking into consideration that beta band activity may also be expressed at frequencies below 13 Hz or above 33 Hz (Tsirogiannis et al 2009). Exemplary trajectories of the filtered signals ($z(t)$) corresponding to the multi-scale neuronal activity are illustrated in figures 4.1(e)-(g).

4.5.4.3. Instantaneous Phase Reconstruction

In order to maximize reliability in the detection of phase synchronization, phase evolution ϕ was obtained from the complex magnitude of the filtered signal ($z(t)$) by means of the method of neighbourhood-based phase estimation (NPE) proposed by Sun *et al* (2008). Adoption of this method was motivated by its improved efficacy over application of the Hilbert transform (figure 4.2(b)). The principle of NPE is based on Takens' theorem (Takens 1981) and on the fact that in the phase space reconstructed by time-delay embedding, the state recurrences of a reference vector are represented by its nearest neighbours. Selection of embedding dimension d and number of neighbours N (figure 4.2(a)) is discussed in section 7.2.4.6.

4.5.4.4. Bivariate Phase Synchronization Index

An index based on the Shannon entropy (Tass et al 1998) was employed as a measure for bivariate phase synchronization. Specifically, due to the non-stationarity of the data, the analysis was performed over a sliding window of 1 s ($M = 1000$ samples) (Hurtado et al 2004) and for every sampling point t_k the distribution of the relative phase series $\Delta\phi$ of the interacting oscillators was computed, using $I = \exp(0.626 + 0.4\ln(M-1)) = 30$ bins (Gross et al 2000). The entropy of the distribution was calculated as

$$h(t_k) = -\sum_{i=1}^{I} p_i(k) \ln p_i(k), \qquad (4.1)$$

where p_i is the probability corresponding to the ith bin. The synchronization index used was equal to the normalized entropy of the distribution

$$\rho(t_k) = \frac{h_{\max} - h(t_k)}{h_{\max}} \quad , \tag{4.2}$$

where $h_{\max} = \ln I$. Obviously, $0 \le \rho(t_k) \le 1$, where the value $\rho(t_k) = 0$ corresponds to a uniform distribution (unsynchronized time series), whereas the value $\rho(t_k) = 1$ corresponds to perfect synchronization.

Eventually, at each recording site along a specific trajectory, a set of synchronization index time series $\rho_{1,2}(t)$, $\rho_{1,3}(t)$ and $\rho_{2,3}(t)$ corresponding to the pairs of the oscillatory signals (spiking activity - background unit activity, spiking activity - LFPs and background unit activity - LFPs) was assessed and their mean amplitudes $\rho_{1,2}$, $\rho_{1,3}$, $\rho_{2,3}$ were retrieved (figures 4.3(e) – (g)).

4.5.4.5. STN Detection and Determination of Acceptable MER Trajectories

For delineation of the STN borders based on a robust single biomarker, a multivariate phase synchronization measure was used (figure 4.3(h)) as a means to quantify dynamic interactions between the three scales ($K = 3$) of neuronal populations (Carmeli et al 2005) given by

$$Q = 1 + \frac{\sum_{i=1}^{K} \lambda_i' \log \lambda_i'}{\log(K)} \quad , \tag{4.3}$$

where λ_i' are the normalized eigenvalues $\left(\lambda_i' = \frac{\lambda_i}{K} \right)$ belonging to the $K \times K$ matrix of bivariate phase synchronization indices (Allefeld et al 2007, Polychronaki 2011). In particular, eigenvalue decomposition was applied on the following matrix:

$$P = \begin{bmatrix} 1 & \rho_{1,2} & \rho_{1,3} \\ \rho_{1,2} & 1 & \rho_{2,3} \\ \rho_{1,3} & \rho_{2,3} & 1 \end{bmatrix} \tag{4.4}$$

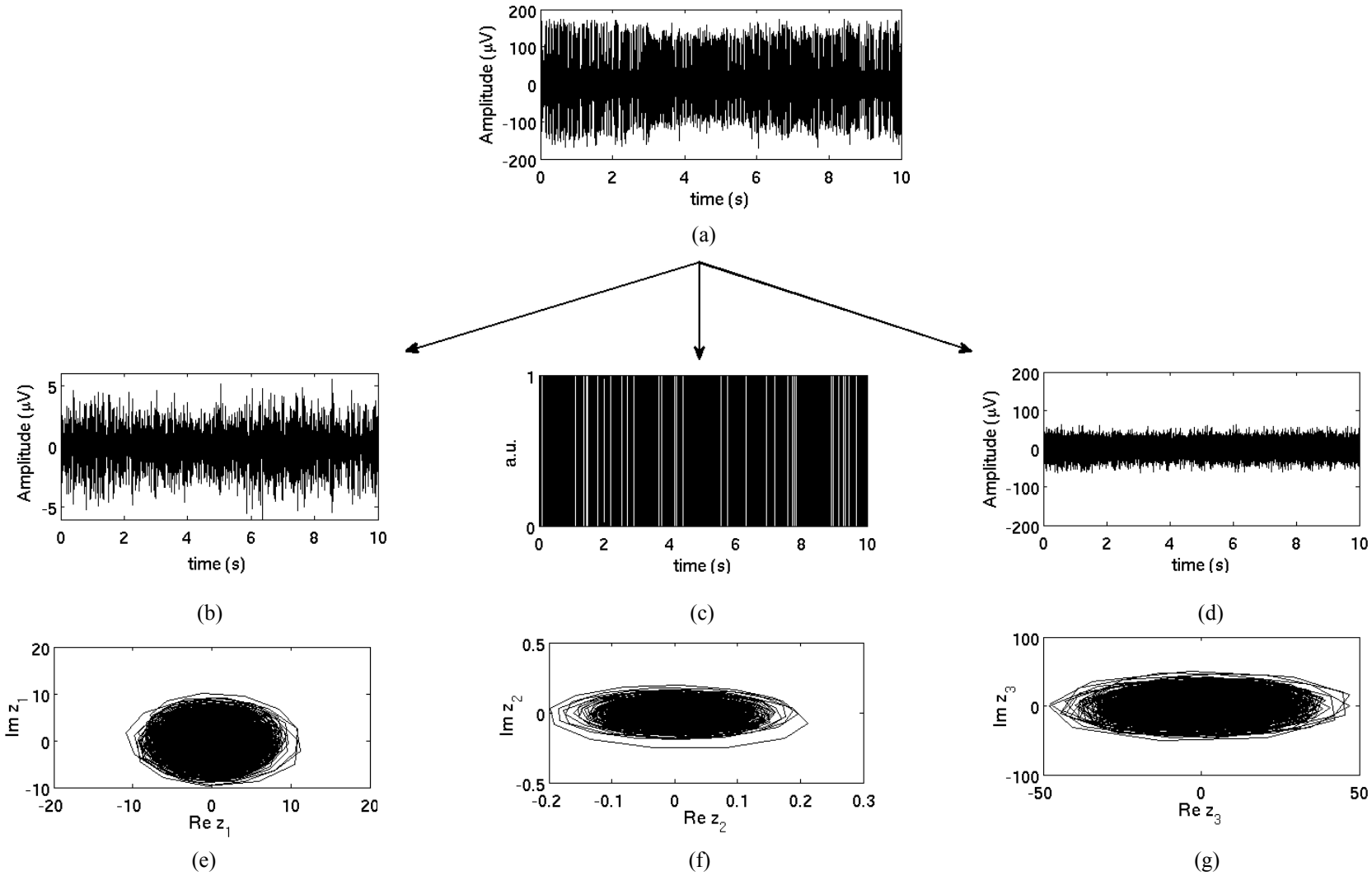


Figure 4.1. Multi-scale neuronal activity and optimal filtering. (a) Example of a raw extracellular signal recorded in the right STN, case 2 (recording site depth: A +0.5). (b)-(d) The three derived signals: LFPs, spiking activity (a.u.=arbitrary units) and background unit activity, respectively. (e)-(g) The trajectories of the filtered signals $z(t)$ (see section 7.2.4.2) obtained from series (b)-(d), respectively, after low-frequency amplitude modulation (of series (c) and (d)) and down-sampling to 1 kHz

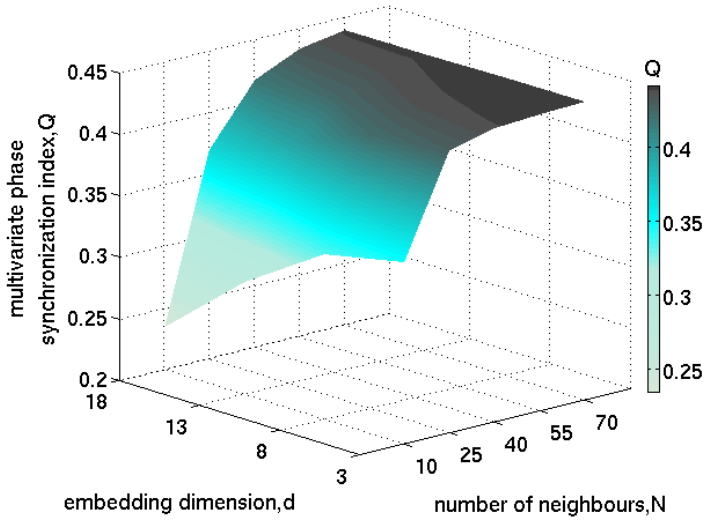
A MER trajectory was considered acceptable if there existed a distance $>= 3mm$(Marceglia *et* al 2010) along which Q remained above the synchronization index threshold Q_{thres} (evaluation of Q_{thres} is described in the next paragraph).The first site (located dorsally) along that distance was defined as the dorsal border of the STN, whereas the last site (located ventrally) was defined as the ventral border of the STN. The detection process described is evaluated in section 3 with respect to its efficacy to point to acceptable MER trajectories that are likely to be further considered during macrostimulation testing.

4.5.4.6. Optimal Embedding Parameters and Threshold Calculation

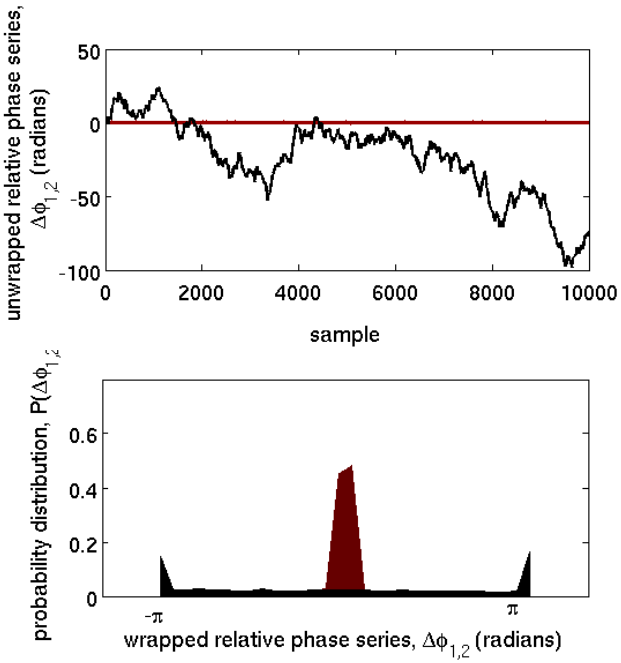
In order to determine the optimal embedding dimension and number of nearest neighbors for the NPE method, the evolution of the mean value of synchronization index Q within the STN boundaries as a function of these parameters was examined, in a total of 21 trajectories defined as acceptable by the clinical experts (figure 4.2(a)). Results showed that Q increased very slowly after N had reached particular values ($40 \le N \le 50$) even for small values of embedding dimension ($d = 3$). On the other hand, over-embedding ($d > 11$) reduced markedly the performance of the method. N was set at 70 and *d* at 3, since these values yielded the maximal estimate of synchronization index Q .Synchronization index threshold Q_{thres} was determined by optimizing the performance of the STN-detection method with respect to the annotations made intraoperatively. Specifically, Q_{thres} was defined as the maximum threshold whose application minimized the false negative and false positive rates in the 70 - MER - trajectories data set ($Q_{\text{thres}} = 0.37$).

4.5.5. Macrostimulation - Automatic Assessment of the Sites Related to the Most Beneficial Clinical Response

Automatic determination of the sites where intraoperative test macrostimulation conferred greater clinical effectiveness, was based on increasing evidence that the beneficial effects of STN-DBS are mediated by modification of the abnormal firing pattern in the STN and disruption of neural population synchrony (Carlson et al 2010, Walker et al 2011, Hauptmann et al 2007, Modolo and Beuter 2009, Wilson et al 2011, Johnson et al 2013). Thereupon, employing a stochastic phase model and using the multivariate phase synchronization index Q as one of its constituent parameters, the neuronal response to macrostimulation at selected recording sites was simulated. This response could be quantified by means of a distinct single biomarker, the Lyapunov exponent. In the context of nonlinear dynamics, the Lyapunov exponent characterizes the convergence/divergence properties of two nearby trajectories in the



(a)



(b)

Figure 4.2. Selection of optimal parameters for the NPE method and reconstruction of the relative phase series. (a) Mean value of synchronization index Q within the STN boundaries for a range of combinations of embedding dimension d and number of neighbours N, averaged over 21 MER trajectories to which a positive detection was ascribed by the clinical experts. (b) The top panel shows the unwrapped relative phase series $\Delta\phi_{1,2}$, corresponding to the pair of the oscillatory signals presented in figures 4.1. (c)-(d).The red line indicates the result obtained based on combinatorial application of data-driven optimal filtering and the NPE method. The black line indicates the result that would be obtained, in case a traditional linear band-pass filter in combination with the Hilbert transform were applied. In the lower panel, the respective distributions $P(\Delta\phi_{1,2})$ of the wrapped relative phase series are depicted

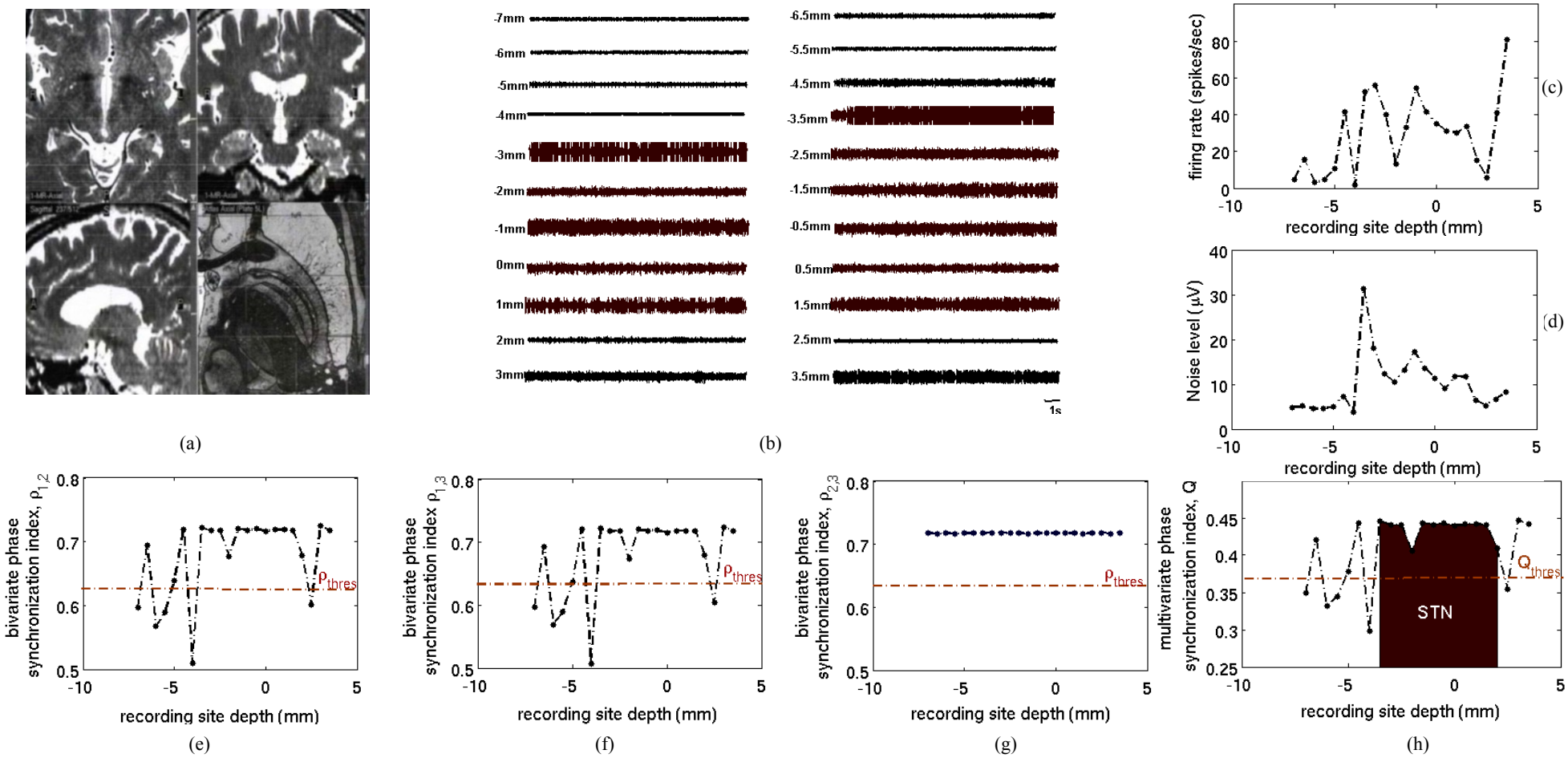


Figure 4.3. Assessment of the multivariate phase synchronization index Q along the lateral trajectory in the right hemisphere of case 1. (a) Planning of the target based on the image fusion hardware system (StereoPlan, Integra Radionics, Burlington, MA, USA). (b) 10s MER epochs obtained in sub-millimeter steps. Depth value 0 corresponds to the anatomical target point determined preoperatively. (c) – (d) Respective changes in firing rate and noise level. (e) – (g) The mean amplitudes $\rho_{1,2}$, $\rho_{1,3}$ and $\rho_{2,3}$ of the bivariate phase synchronization indices as a function of the recording site depth. (h) The multivariate phase synchronization index Q. The dashed horizontal line indicates the generic threshold $Q_{\text{thres}} = 0.37$. The dark region corresponds to the STN length determined intraoperatively by the clinical experts.

phase space (Pikovsky et al 2001). Positive values of the Lyapunov exponent indicate desynchronization. Based on the aforementioned facts, the Lyapunov exponent was examined as an implicit indicator of the clinical effectiveness of stimulation during DBS surgery.

4.5.6. Phase Reduction: Some Basic Concepts

In the context of phase reduction, neural oscillators can be described by a single phase variable, θ (Izhikevich 2007). In case of tonic spiking, the definition of the phase of an oscillation is associated with the parametrization of its limit-cycle attractor, i.e. the phase may be considered as a circular variable representing how far the oscillation has progressed along its limit cycle. The phase is usually dimensionless and defined on [0, 1) or [0, 2π) (Ermentrout et al. 2011).

Neural oscillators are characterized by an associated phase-resetting curve (PRC) (Kuramoto 1984, Winfree 2001), which is 'a vital entity for modeling the biophysical dynamics of oscillators' (Ly 2014). Particularly, it quantifies the magnitude of the phase shift of a spike train due to the implementation of an external perturbation. This magnitude, Δ, depends on the exact timing of the stimulus relative to the phase of oscillation (Izhikevich 2007) (figure 4.4):

$$\Delta(\theta) = \{\theta_{new} - \theta\} \tag{4.5}$$

The infinitesimal phase response curve (iPRC) gives the phase sensitivity to an *infinitesimal* perturbation.

Though PRCs are highly heterogeneous, since they crucially depend on the neuron's biophysical profile (ionic currents, firing rate etc.), they may be generally classified into two board categories in the context of *weak* resetting: type I (1+cos(2πθ)) and type II (-sin(2πθ)). These categories may be condensed by means of the following formula (Ly 2014) (figure 4.4):

$$\Delta(\theta) = k\left[-\sin(2\pi\theta + \gamma) + \sin\gamma\right], \quad \gamma \in [0, \pi/2] \tag{4.6}$$

and $k = \dfrac{1}{\sqrt{\sin^2(\gamma) + 1}}$ is a normalizing constant.

Strong resetting may result in a type 0 (discontinuous) PRC with mean slope 0.

It has been proven that oscillators with Type II PRCs receiving common noisy input sychronize more readily than those with Type I PRCs (Abouzeid and Ermentrout 2009). In addition to

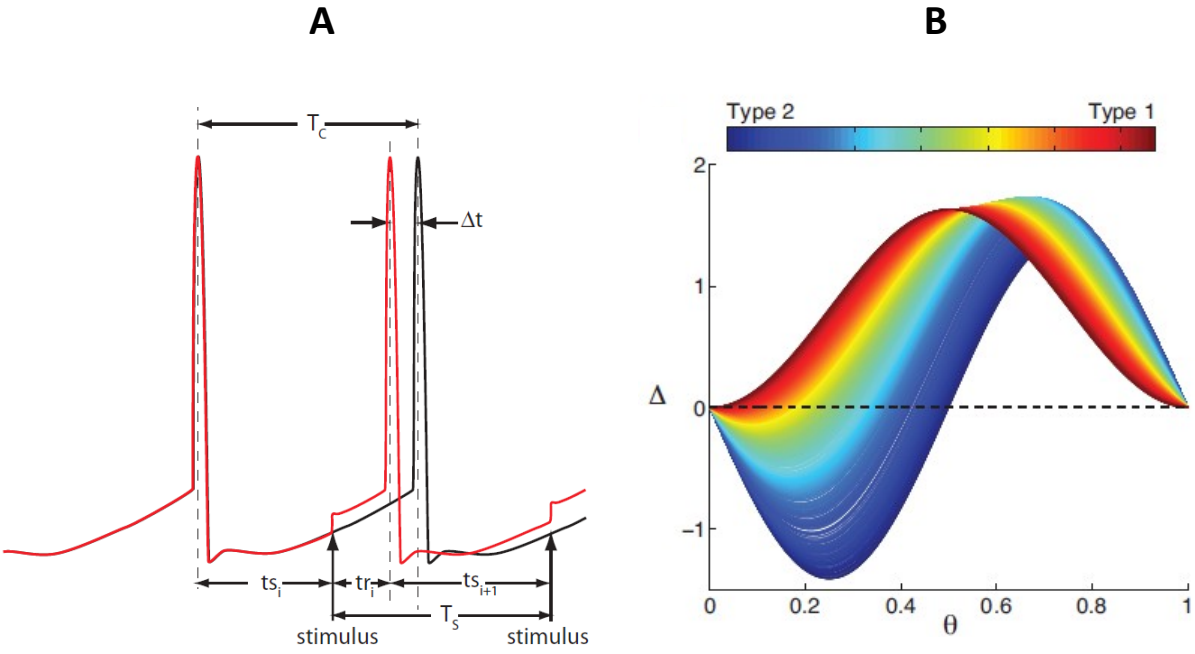


Figure 4.4. (A) Two trajectories of a spontaneously active neuron firing with period *T*c are shown, one unperturbed (black) and one perturbed by the stimulus presented at period *T*s. The phase-dependent change in the period caused by the stimulus is *Δt.* Stimulation latencies relative to cell firing are indicated by *t*s, and response latencies relative to the stimulus are labeled *t*r (Wilson et al. 2011) (B) Types of phase resetting curves (Ly 2014).

common noise, however, global coupling may also exert a significant effect on neuronal synchronization (Nagai and Kori 2010).

4.5.6.1. The Phase Model

The following Langevin equation (by virtue of the Stratonovich interpretation (Gardiner 1994)) describing an ensemble of N globally coupled identical phase oscillators, driven by intrinsic independent and extrinsic common noises, but also subject to periodic forcing is considered (figure 4.5):

$$\frac{\mathrm{d}\phi_i}{\mathrm{d}t} = \omega + \frac{K}{N}\sum_{j=1}^{N}\sin\left(2\pi\left(\phi_j - \phi_i\right)\right) + \sigma_{\mathrm{I}} R_{\mathrm{I}}(\phi_i)\xi_i(t) + \sigma_{\mathrm{C}} R_{\mathrm{C}}(\phi_i)\eta(t) + \Delta(\phi_i,\beta)\sum_k \delta(t - kT_{\mathrm{s}}) \qquad (4.7)$$

Here $\phi_i \in [0,1)$ is the phase variable of the ith oscillator, ω is its natural frequency and $K > 0$ is the coupling strength. $\xi_i(t)$ is assumed to be zero mean Gaussian white noise, added independently to each oscillator, with correlation specified by $\left\langle \xi_i(t)\xi_j(t')\right\rangle = \delta_{ij}\delta(t-t')$, where $\delta_{ij} = 1$ if $i = j$ and 0 if $i \neq j$. $\eta(t)$ is regarded as colored noise with zero mean and unitary

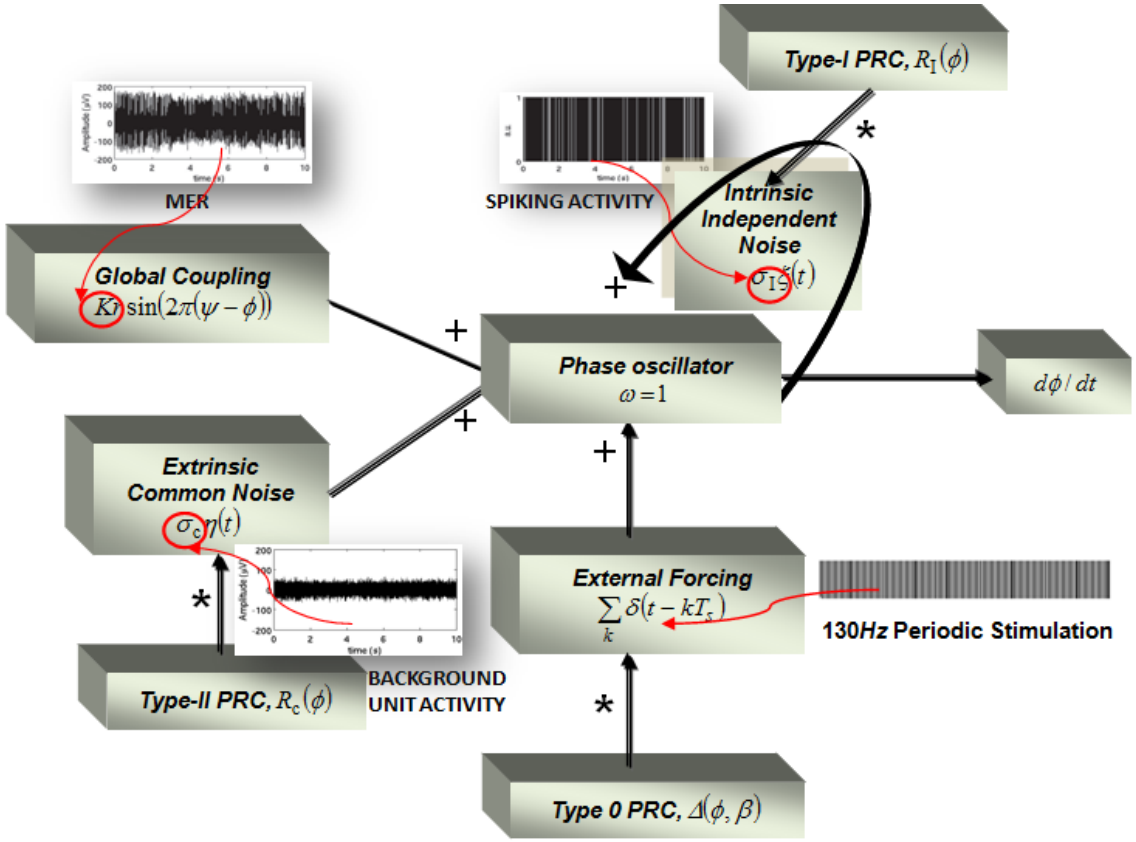


Figure 4.5. Block diagram of the stochastic phase model

variance, i.e. with autocorrelation function $C(t) = \langle \eta(t)\eta(0) \rangle = \frac{1}{2\tau_C} \mathrm{e}^{-\frac{|t|}{\tau_C}}$. Thus, $\eta(t)$ can be regarded as an Ornstein-Uhlenbeck process with correlation time τ_C (Gardiner 1994). σ_I and σ_C are small parameters representing the intensity of independent and common noise, respectively. $R_C(\phi_i)$ and $R_I(\phi_i)$ are phase sensitivity functions that represent the linear response of the phase variable ϕ_i to the respective infinitesimal noise perturbations, while $\Delta(\phi_i, \beta)$ is the phase response curve (PRC) to a single (DBS) impulse (Kuramoto 1984, Winfree 2001). β represents the stimulus amplitude, $T_s = 130\text{Hz}$ is the period of the stimulation and $0 \le k < \infty$.

Taking into consideration that for weak Gaussian common driving noise, a Type-II PRC is optimal for stochastic synchronization (Abouzeid and Ermentrout 2009), this shape is used for the phase sensitivity to common noise in order to simulate the state of pathological synchronization in PD. A Type-I PRC is selected for the phase sensitivity to independent noise. Both PRCs are normalized as $\sqrt{\int_0^1 R^2(\phi) \mathrm{d}\phi} = 1$.

Accordingly the following functions are considered:

$$R_{\mathrm{C}}(\phi)=\sqrt{2}\left(-\sin(2\pi\phi)\right) \tag{4.8}$$

$$R_{\mathrm{I}}(\phi)=\sqrt{\frac{2}{3}}\left(1-\cos(2\pi\phi)\right) \tag{4.9}$$

Differently, there is evidence that the type 0 PRC may be optimal for stochastic desynchronization (Hata et al 2011). Hence, in order to simulate the desynchronizing effect of DBS, $\Delta(\varphi,0)$ is considered equal to zero and

$$\Delta(\phi,\beta)=\begin{cases}\phi\,\mathrm{e}^{(10-\beta)(\phi-0.5)} & 0<\phi\le 0.5\\ (\phi-1)\mathrm{e}^{-(10-\beta)(\phi-0.5)} & 0.5\le\phi<1\end{cases}, \tag{4.10}$$

where $0<\beta\le 10$.

Introducing the (complex) Kuramoto order parameter defined by $r\mathrm{e}^{2\pi\mathrm{i}\psi}=\frac{1}{N}\sum_{j=1}^{N}\mathrm{e}^{2\pi\mathrm{i}\phi_j}$

(Kuramoto 1984), (4.7) can be rewritten as (Strogatz 2000):

$$\frac{\mathrm{d}\phi}{\mathrm{d}t}=\omega+Kr\sin(2\pi(\psi-\phi))+\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)\xi(t)+\sigma_{\mathrm{C}}R_{\mathrm{C}}(\phi)\eta(t)+\Delta(\phi,\beta)\sum_{k}\delta(t-kT_{\mathrm{s}}) \tag{4.11}$$

where r characterizes the degree of synchrony and ψ is the mean phase of the oscillators. Next, defining the effective drift and diffusion coefficients (Nakao et al 2010)

$$v\approx{\sigma_{\mathrm{C}}}^2\int_0^\infty ds\,C(s)\int_0^1 d\phi\,R_{\mathrm{C}}'(\phi)\,R_{\mathrm{C}}(\phi-\omega s)\quad\text{and}\quad D\approx{\sigma_{\mathrm{C}}}^2\int_{-\infty}^\infty ds\,C(s)\int_0^1 d\phi\,R_{\mathrm{C}}(\phi)R_{\mathrm{C}}(\phi-\omega s) \tag{4.12}$$

the following white-noise Langevin equation is obtained:

$$\frac{\mathrm{d}\phi}{\mathrm{d}t}=\omega+Kr\left(\sin 2\pi(\psi-\phi)\right)+\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)\xi(t)+v+\sqrt{D}\xi(t)+\Delta(\phi,\beta)\sum_{k}\delta(t-kT_{\mathrm{s}}) \tag{4.13}$$

or

$$\frac{\mathrm{d}\phi}{\mathrm{d}t}=\omega+Kr\sin(2\pi(\psi-\phi))+v+\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)+\sqrt{D}\right)\xi(t)+\Delta(\phi,\beta)\sum_{k}\delta(t-kT_{\mathrm{s}}) \tag{4.14}$$

The Stratonovich eq. (4.14) is converted to an equivalent Ito stochastic differential equation (Gardiner 1994):

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = \omega + Kr\sin\left(2\pi(\psi-\phi)\right) + v + \left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi) + \sqrt{D}\right)\xi(t) + \frac{\sigma_{\mathrm{I}}}{2}R_{\mathrm{I}}'(\phi)\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi) + \sqrt{D}\right) + \Delta(\phi,\beta)\sum_{k}\delta(t-kT_{\mathrm{s}}) \tag{4.15}$$

Phase eq. (4.15) is solved through the stochastic map from one stimulus cycle to the next (Nesse and Clark 2010). The phase dynamics during the inter-impulse interval T_{s} is described by

$$\phi_{n+1} = \phi_n + \left(\omega + Kr\sin\left(2\pi(\psi-\phi_n)\right) + v + \frac{\sigma_{\mathrm{I}}}{2}R_{\mathrm{I}}'(\phi_n)\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi_n) + \sqrt{D}\right)\right)T_{\mathrm{s}} + \left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi_n) + \sqrt{D}\right)\times W(T_{\mathrm{s}}) + \Delta(\phi_n,\beta) \tag{4.16}$$

where $W(t)$ is a Wiener process with probability density function f_{W_t}, which is a Gaussian with zero mean and variance T_{s}. The stochastic map is defined by the ("modulo-one") Perron-Frobenius operator F, that maps the density of phases at the time of the $(n+1)th$ impulse, $p_{n+1}(\phi)$, onto the density of phases at the time of the nth impulse, $p_n(\phi)$ (Ermentrout and Saunders 2006, Nesse et al 2007, Yamanobe and Pakdaman 2002):

$$p_{n+1}(\phi) = \int_0^1 \sum_{j\in Z} f_{W_t}\left(\frac{\phi-\phi'+j-\left(\omega + Kr\sin\left(2\pi(\psi-\phi')\right) + v + \frac{\sigma_{\mathrm{I}}}{2}R_{\mathrm{I}}'(\phi')\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi') + \sqrt{D}\right)\right)T_{\mathrm{s}} - \Delta(\phi',\beta)}{\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi') + \sqrt{D}\right)}\right) \cdot \frac{1}{\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi') + \sqrt{D}\right)}p_n(\phi')d\phi' \tag{4.17}$$

Setting

$$A(\phi,\phi') = \sum_{j\in Z} f_{W_t}\left(\frac{\phi-\phi'+j-\left(\omega + Kr\sin\left(2\pi(\psi-\phi')\right) + v + \frac{\sigma_{\mathrm{I}}}{2}R_{\mathrm{I}}'(\phi')\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi') + \sqrt{D}\right)\right)T_{\mathrm{s}} - \Delta(\phi',\beta)}{\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi') + \sqrt{D}\right)}\right) \times \frac{1}{\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi') + \sqrt{D}\right)} \tag{4.18}$$

and discretizing the density into $M = 500$bins of size $1/M$, we obtain:

$$\int_0^1 A(\phi,\phi')p(\phi')d\phi' \approx \frac{1}{\mathrm{M}}\sum_{j=0}^{M-1} A\left(\frac{i}{M},\frac{j}{M}\right)p^j . \tag{4.19}$$

Hence, the stochastic map is approximated using a 500×500 transition matrix (stochastic kernel) having all positive entries and a spectral radius of 1 (figure 4.6). This matrix possessed the strong Perron-Frobenius property (Noutsos and Tsatsomeros 2008). The iterated mapping (4.17) converges to the steady-state phase distribution (invariant density) after h number of stimuli:

$$p_{\mathrm{st}}(\phi) = \left[F^h p_0\right](\phi) \tag{4.20}$$

This distribution is represented by the eigenvector corresponding to the dominant (unit) eigenvalue of A (figures 4.6 (j) - (l)).To quantify the stability of the synchronized states the Lyapunov exponent is calculated (figure 4.7), using phase map (4.16), as (Pikovsky et al 2001, Teramae and Tanaka 2004):

$$\begin{aligned}
\lambda &= \frac{\left\langle \ln\left|\mathrm{d}\phi_{n+1}/\mathrm{d}\phi_n\right|\right\rangle}{T_s} \\
&= \frac{1}{T_{\mathrm{s}}}\left\langle \ln\left|\begin{aligned}&1+\left(-2\pi Kr\cos\left(2\pi(\psi-\phi)\right)+\frac{\sigma_{\mathrm{I}}}{2}R''(\phi)\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)+\sqrt{D}\right)+\frac{\sigma_{\mathrm{I}}^2}{2}\left(R'_{\mathrm{I}}(\phi)\right)^2\right)T_{\mathrm{s}}\\&+\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)+\sqrt{D}\right)'W(T_{\mathrm{s}})+\Delta'(\phi,\beta)\end{aligned}\right|\right\rangle_{W(T_{\mathrm{s}})} \\
&= \frac{1}{T_{\mathrm{s}}}\int_0^1 \mathrm{d}\phi \ln\left|1+\left(-2\pi Kr\cos\left(2\pi(\psi-\phi)\right)+\frac{\sigma_{\mathrm{I}}}{2}R''_{\mathrm{I}}(\phi)\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)+\sqrt{D}\right)\right)T_{\mathrm{s}}+\Delta'(\phi,\beta)\right|\cdot p_{\mathrm{st}}(\phi)
\end{aligned} \tag{4.21}$$

4.5.6.2. Determination of Model Parameters

For each depth position selected for macrostimulation, there are eight parameters that must be estimated in the phase model (4.13): $\omega, r, K, \psi, \sigma_{\mathrm{C}}, v, D$ and σ_{I}. We set $\omega = 1$ according to Wilson et al (2011). We also consider $\psi = 0$. The remaining parameters are estimated on the basis of the respective signal acquired during MER, which is considered to reflect a no-input stimulus epoch (figure 4.8). The modulus r of the order parameter is set equal to the value of the phase synchronization index Q, estimated in 4.2.4.5. Coupling strength K is estimated by (Allefeld and Kuhrts 2004, Allefeld et al 2007):

$$K = \lambda \mu^2 \tag{4.22}$$

where $\lambda > 1$ is the largest eigenvalue of matrix (4. 4) and μ is the first element of the corresponding eigenvector.

As indicated by (4.12), calculation of parameters v and D is dependent on estimation of σ_C and $C(t)$. The intensity of common noise σ_C is determined through evaluation of the power spectraldensity function of the background unit activity (Moran and Bar-Gad 2010) using Welch's method, while the autocorrelation function of this signal is used as an estimate of $C(t)$.

Once the above parameters were estimated, we proceed to evaluate the intensity of independent noise σ_I, through definition of the first passage time problem for the phase model (4.15) with no input; let $\rho(\phi, t)$ represent the probability density function of phases at time t. The corresponding Fokker-Planck equation is (Gardiner 1994)

$$\frac{\partial \rho}{\partial t} = -\frac{\partial}{\partial \phi}\left\{\left[\omega + Kr\sin(2\pi(\psi - \phi)) + v + \frac{\sigma_I}{2} R_I'(\phi)\left(\sigma_I R_I(\phi) + \sqrt{D}\right)\right]\rho\right\}$$

$$+ \frac{1}{2}\frac{\partial^2}{\partial \phi^2}\left\{\left(\sigma_I R_I(\phi) + \sqrt{D}\right)^2 \rho\right\}, \tag{4.23}$$

with periodic boundary condition

$$\rho(0, t) = \rho(1, t). \tag{4.24}$$

Extending the definition of the phase from $\phi \in [0,1)$ to $\phi \in \Re$ and considering $\sigma_I << 1$ we obtain the following approximations (Ly and Ermentrout 2011)

$$R_I(\phi) \approx R_I(t) \text{ and } Kr\sin(2\pi(\psi - \phi)) \approx Kr\sin(2\pi(\psi - t)) \tag{4.25}$$

The Fokker-Planck equation for the corresponding probability density function $\zeta(\phi, t)$ is

$$\frac{\partial \zeta}{\partial t} = -\left[\omega + Kr\sin(2\pi(\psi - t)) + v + \frac{\sigma_I}{2} R_I'(t)\left(\sigma_I R_I(t) + \sqrt{D}\right)\right]\frac{\partial \zeta}{\partial \phi} + \frac{\left(\sigma_I R_I(t) + \sqrt{D}\right)^2}{2}\frac{\partial^2 \zeta}{\partial \phi^2} \tag{4.26}$$

$$\zeta(\phi, 0) = \delta(\phi)\ ,\ \phi \in \Re \tag{4.27}$$

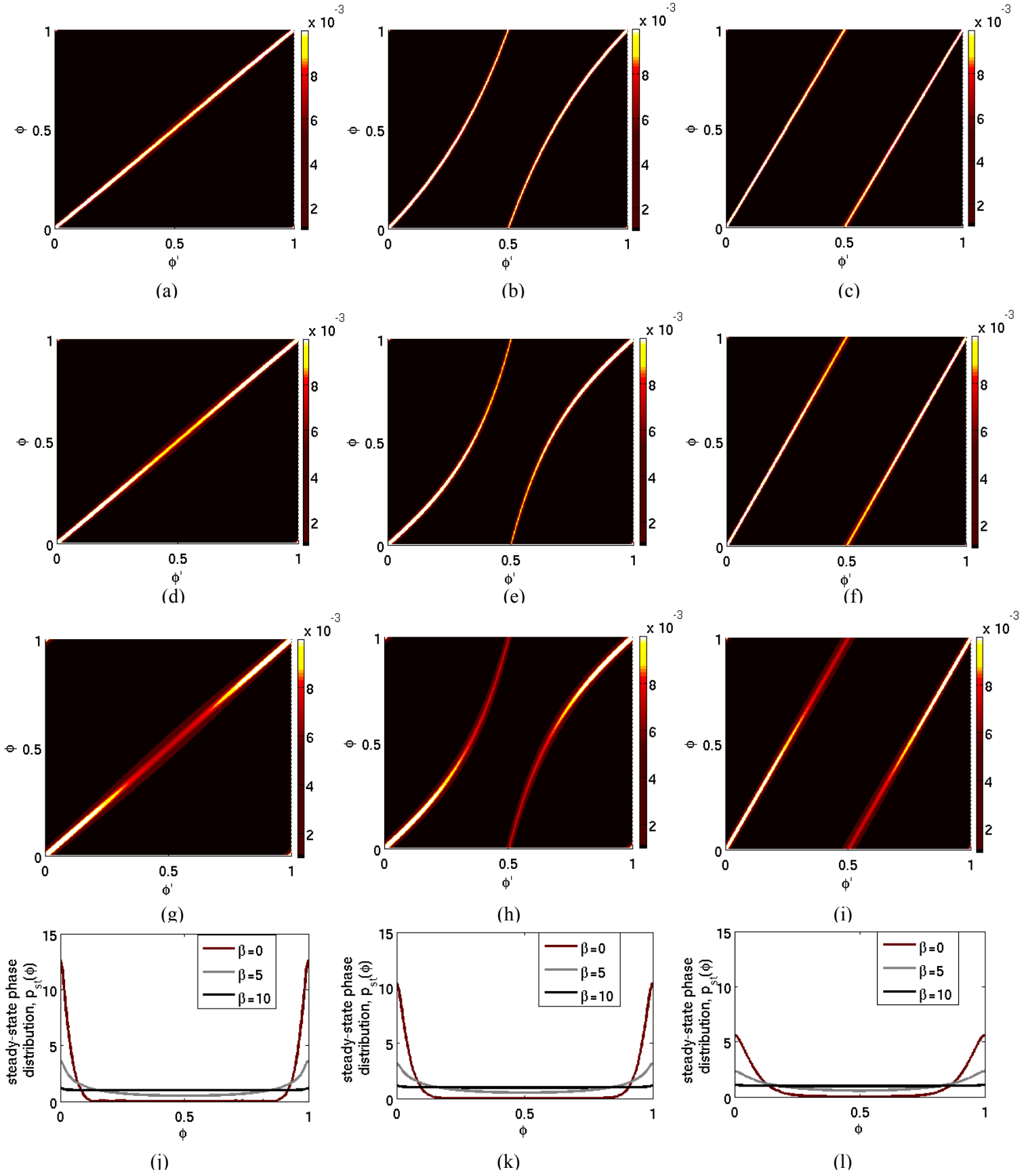
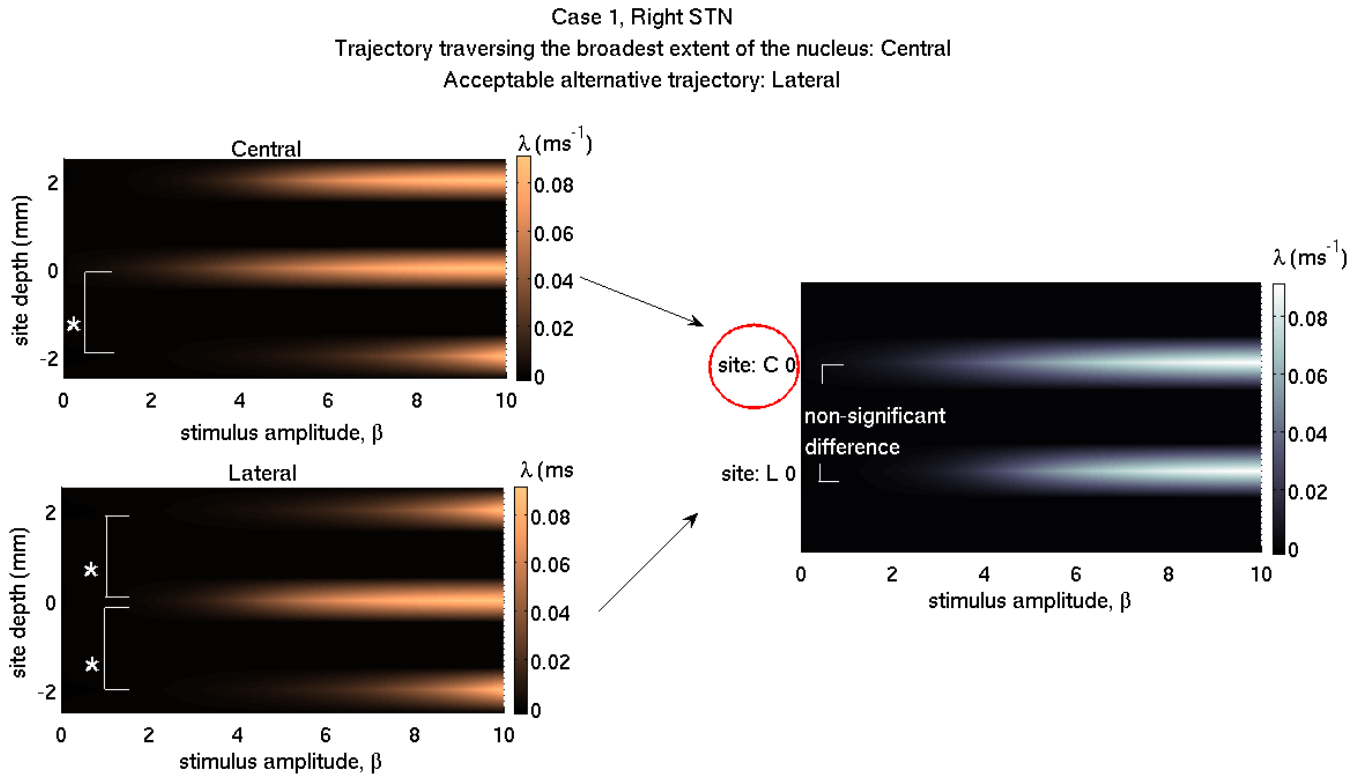
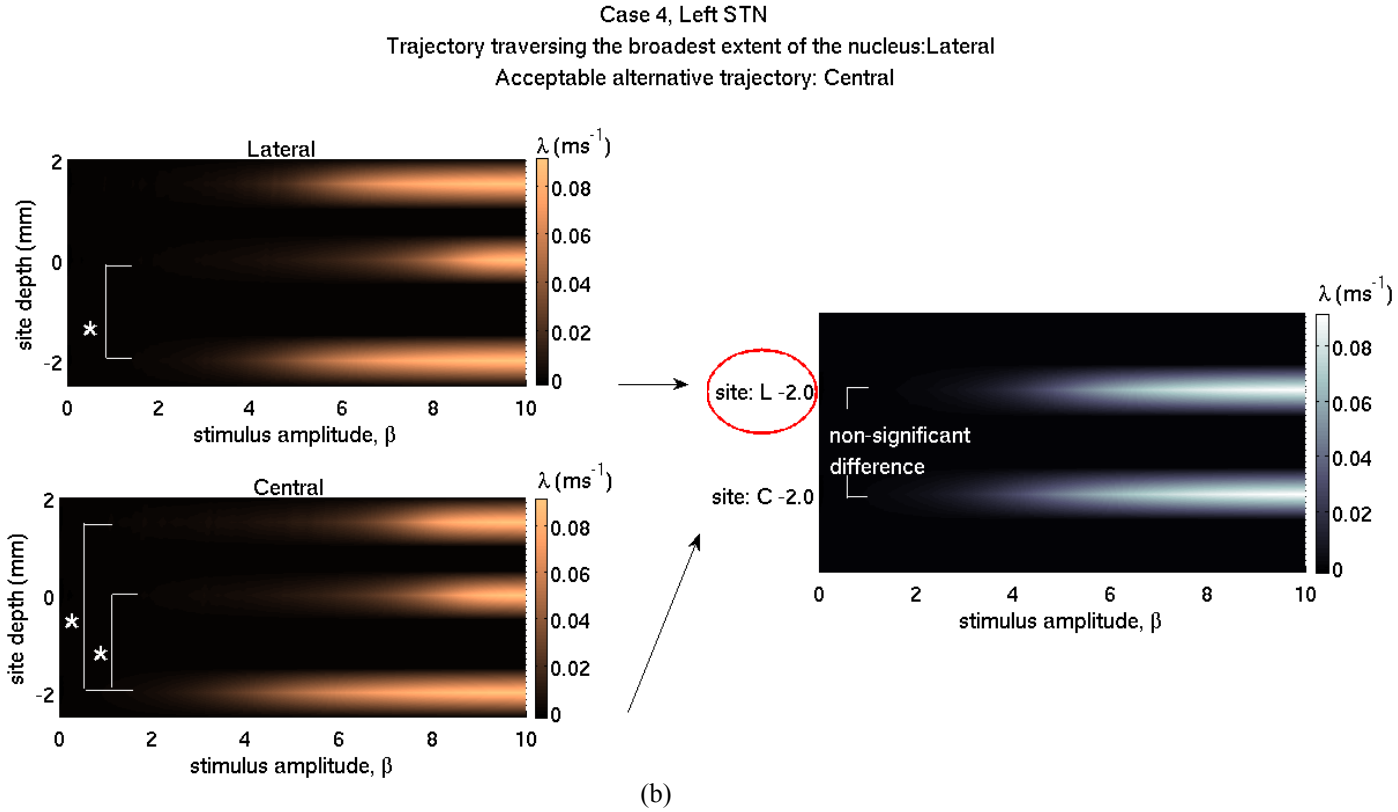


Figure 4.6. (a)-(i) Stochastic kernel functions $A(\phi,\phi')$ based on MERs at: (a)-(c) C 0, right STN, case 1, for $\beta=0$, $\beta=5$ and $\beta=10$, respectively, (d)-(f) P +2, right STN, case 5, for $\beta=0$, $\beta=5$ and $\beta=10$, respectively and (g)-(i) P +2, right STN, case 6, for $\beta=0$, $\beta=5$ and $\beta=10$, respectively. (j)-(l) Steady-state phase distributions for $\beta=0$ (red line), $\beta=5$ (gray line) and $\beta=10$ (black line), corresponding to the cases described in (a)-(c), (d)-(f) and (g)-(i).



(a)



(b)

Figure 4.7. The Lyapunov exponent, λ as a function of stimulus amplitude β for a pair of acceptable trajectories in two distinct cases. (a) Left panels: the Lyapunov exponent, λ at three pre-selected sites of central (upper) and lateral (lower) trajectory, right hemisphere, case 1. Asterisks denote significant differences. Right panel: sites where the highest values of λ were obtained for each of the acceptable trajectories. At these sites, values of λ between the 2 trajectories were not significantly different. Circled is the optimal target point according to clinical decision. (b) Left panels: the Lyapunov exponent, λ at three pre-selected sites of lateral (upper) and central (lower) trajectory, left hemisphere, case 4. Right panel: sites where the highest values of λ were obtained for each of the acceptable trajectories. At these sites, values of λ between the 2 trajectories were not significantly different.Circled is the optimal target point according to clinical decision.

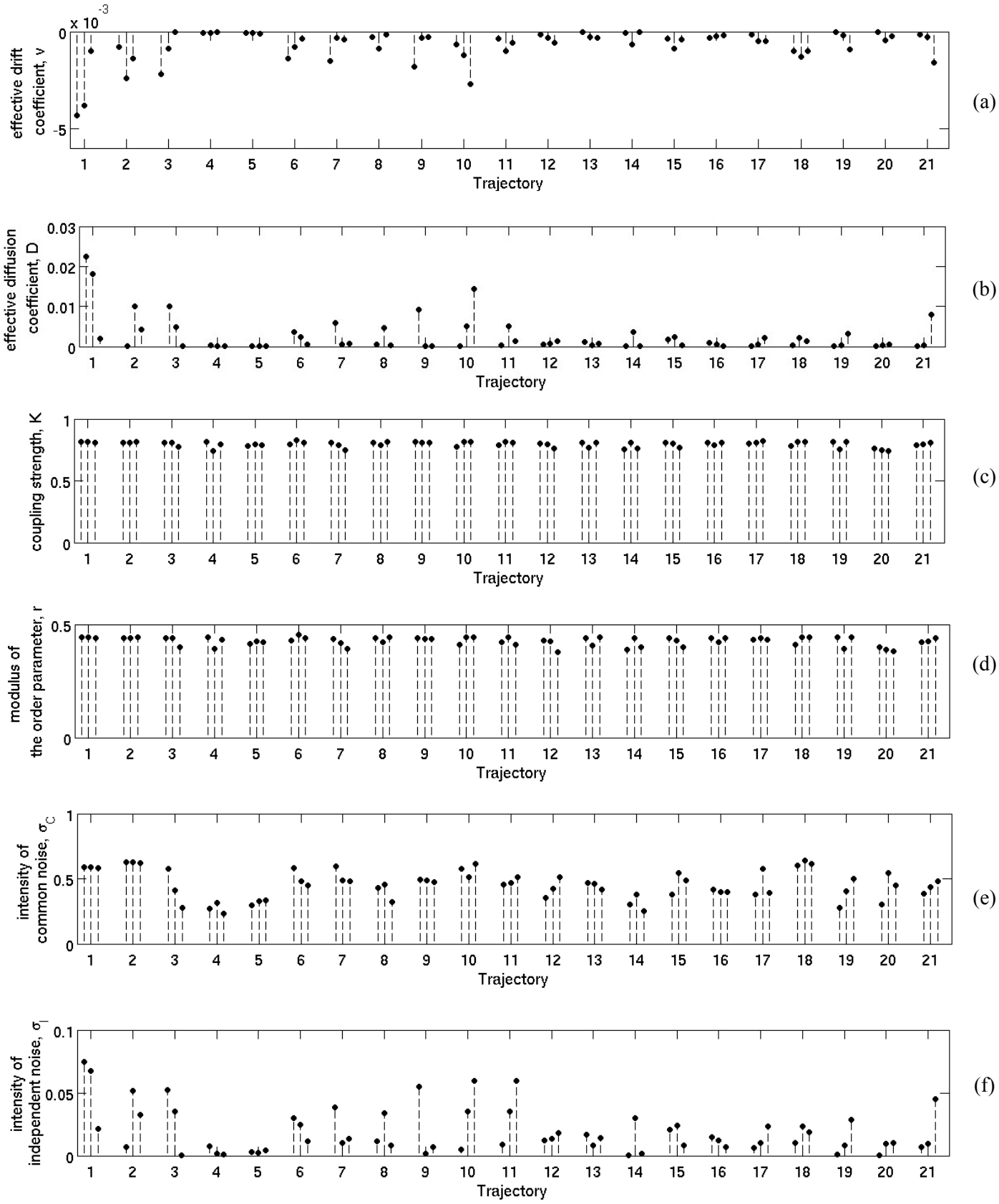


Figure 4.8. Parameter values based on MERs along 21 trajectories selected for macrostimulation testing by the clinical experts. For each trajectory, parameters are assessed at 3 site depths selected for intraoperative macrostimulation. Parameters depicted are (a) effective drift coefficient, v (b) effective diffusion coefficient, D (c) coupling strength, K (d) modulus of the order parameter, r (e) intensity of common noise, σ_C and (f) intensity of independent noise, σ_I.

An analytic solution to (4.26) is

$$\zeta(\phi,t)=\frac{1}{\left(2\pi\left(\sigma_{\mathrm{I}}{}^{2}\int_{0}^{t}R_{\mathrm{I}}^{2}(s)ds+2\sigma_{\mathrm{I}}\sqrt{D}\int_{0}^{t}R_{\mathrm{I}}(s)ds+Dt\right)\right)^{1/2}}$$

$$\times\exp\left(-\frac{\left((\omega+v)t+\frac{1}{2\pi}Kr\cos(2\pi(\psi-t))-\phi+\frac{\sigma_{\mathrm{I}}^{2}}{4}R_{\mathrm{I}}^{2}(t)+\frac{\sigma_{\mathrm{I}}\sqrt{D}}{2}R_{\mathrm{I}}(t)\right)^{2}}{2\left(\sigma_{\mathrm{I}}^{2}\int_{0}^{t}R_{\mathrm{I}}^{2}(s)ds+2\sigma_{\mathrm{I}}\sqrt{D}\int_{0}^{t}R_{\mathrm{I}}(s)ds+Dt\right)}\right) \tag{4.28}$$

Respectively, the first passage time distribution is simply

$$z(t)=\zeta(1,t). \tag{4.29}$$

Finally, maximization of the log likelihood function L over σ_{I}, yields an estimate for σ_{I} (Nesse and Clark 2010):

$$\frac{\mathrm{d}}{\mathrm{d}\sigma_{\mathrm{I}}}L(\sigma_{\mathrm{I}}|\{\Delta t_i\},v,K,r,D)=\frac{\mathrm{d}}{\mathrm{d}\sigma_{\mathrm{I}}}\sum_{i}\ln z(\Delta t_i|\sigma_{\mathrm{I}},v,K,r,D)=0, \tag{4.30}$$

where $\{\Delta t_i\}$ are the interspike interval (ISI) data.

4.5.7. Performance Evaluation

To assess the performance of the entire automatic methodology, the dataset of the decisions made intraoperatively by two clinical experts was used as the gold standard.

Significant changes in the multivariate phase synchronization index within the intraoperatively determined STN length were evaluated by applying a two-sample t-test (statistical significance was defined at $p<0.05$). Additionally, stability of the phase synchronization indices in the presence of measurement noise was assessed and compared with the stability of firing rate and noise level measures within the STN boundaries. Comparative assessment was based on evaluation of the standard deviation of the corresponding normalized measures (two-sample t-test, $p<0.05$). Normalization was performed by dividing each measure by its mean value within

the intraoperatively determined STN length. Finally the number of trajectories traversing the STN according to the automatic method and the clinical experts was comparatively assessed and the sensitivity of the method in detecting the dorsal and ventral borders of the STN was determined.

Performance of the stochastic dynamical model for designation of the sites where stimulation yielded the best clinical benefit was assessed evaluating the sensitivity of the corresponding method under two principal conditions (two-sample t-test, $p < 0.05$).

4.6. Results

4.6.1. Determination of Acceptable MER Trajectories

According to the annotations made intraoperatively by the clinical experts, 40 out of 70 trajectories penetrated a subthalamic dorsoventral extent greater than 3 mm. With reference to these positive detections Q displayed significantly higher average values within the STN compared to its average values within neighboring structures ($p = 10^{-11}$). Figure 4.3 displays an application example of the STN detection methodology, i.e. on the lateral trajectory, in the right STN of case 1. Importantly, there is a striking difference between the stability of firing rate and noise level values and the stability of phase synchronization index Q, observed within the STN. This result provides an indication for the robustness of phase synchronization index despite the presence of measurement noise. Overall, multivariate phase synchronization index Q displayed significantly higher stability within the STN compared with firing rate ($p = 10^{-17}$) and noise level measures ($p = 10^{-8}$) (figure 4.9).

Principally, the STN detection methodology demonstrated a false negative rate (FNR) of 4.8% and a false positive rate (FPR) of 0%. With reference to the true positive detections, the mean depth of the STN dorsal border according to the automatic algorithm was 0.0357 ± 0.1336 mm above the STN entry designated by the clinical experts. The mean depth of the STN ventral border was 0.0714 ± 0.3852 mm above the STN exit determined intraoperatively. Using a precision criterion of 0.5 mm within the current gold standard, the STN detection methodology yielded sensitivities of 100% and 92% for the STN dorsal and ventral border, respectively (table 4.2).

Interestingly, performance of the STN detection methodology based on the bivariate phase synchronization indices $\rho_{1,2}$ and $\rho_{1,3}$, was identical to the one based on synchronization index

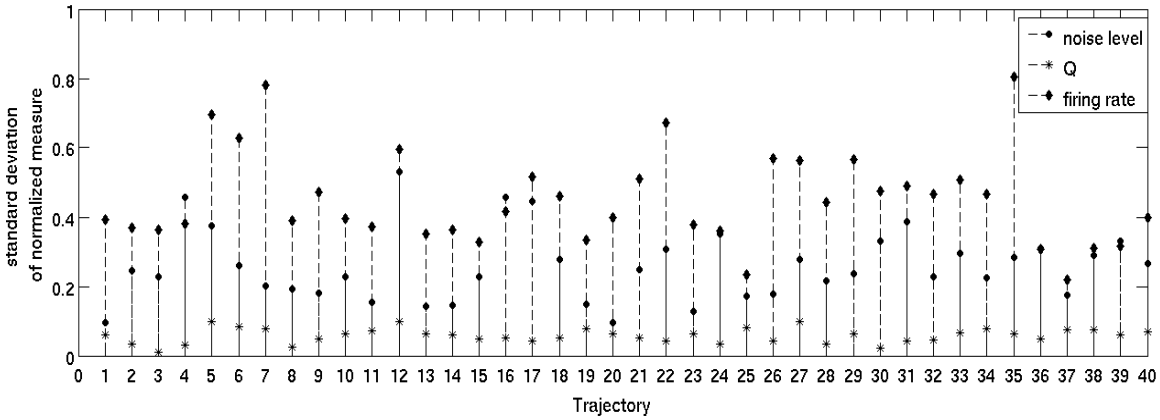


Figure 4.9. Standard deviation of the normalized firing rate, noise level and multivariate phase synchronization measures within the intraoperatively determined STN length, for 40 trajectories to which a positive detection was ascribed by the clinical experts. Principally, Q displayed significantly higher stability within the STN compared with firing rate and noise level measures ($p < 0.05$).

Q (table 4.2). However, it should be pointed out, that the specific value of the multivariate synchronization index Q lied in its particular utility as a model parameter (section 7.2.5.2).

On the other hand, phase synchronization index $\rho_{2,3}$ displayed no discriminating power, as its average values within the STN were not significantly different from the average values outside the STN ($p = 0.9893$). This observation may reflect the fact that there exists a sparse correlation within the surrounding neural population not only within but also across the STN boundaries (Moran and Bar-Gad 2010).

4.6.2. Predictability of the Lyapunov Exponent of the Stochastic Model in Identification of the Sites where Stimulation yielded the Best Clinical Benefit

Figure 4.6 depicts the stochastic kernel functions and invariant densities (obtained using (4.19)) for different values of stimulus amplitude β , derived based on MERs at three distinct site depths assessed for intraoperative macrostimulation. For $\beta = 0$, the proposed phase model the proposed phase model reproduces the pathological synchronized state ($\phi = \phi'$), which appears to be more intense in case 1 than in cases 5 and 6. With increasing β , the obtained states become gradually less synchronized in all cases. This observation was general across all site depths examined and strongly suggested that the desynchronizing effect of periodic stimulation was captured and validated by the current model. Figure 4.8 depicts a set of parameter values, derived based on 21 MER trajectories considered appropriate for macrostimulation testing by the clinical experts. The following observations are made: first and foremost, effective drift coefficient v was always negative, as indicated by Nakao *et al* 2010. Secondly, coupling strength K was positive, a

Table 4.2. Performance of the STN detection methodology.

Index	FPR	FNR	Sensitivity for the STN dorsal border[a]	Sensitivity for the STN ventral border[a]
Q	0%	4.8%	100%	92%
$\rho_{1,2}$	0%	4.8%	100%	92%
$\rho_{1,3}$	0%	4.8%	100%	92%
$\rho_{2,3}$	-	-	-	-

[a] within 0.5 mm accuracy of the current gold standard.

Table 4.3. Performance of the stochastic model under 2 principal conditions[a,b] for designation of the optimal stimulation site.

Measure	Sensitivity
λ [a]	78.57%
λ [b]	71.43%

[a] Values of λ within the optimal trajectory were for no other site significantly higher than the values derived for the optimal stimulation site (according to clinical decision) ($p < 0.05$).

[b] In addition to a, there was no site along the alternative trajectory for which the derived exponent was significantly higher than the one corresponding to the finally selected site ($p < 0.05$).

criterion imposed on phase model (4.7). Last, the condition $\sigma_I << 1$ was always satisfied, while for common noise, moderate intensities were obtained.

Figure 4.7 displays the Lyapunov exponent as a function of stimulus amplitude, derived based on the analysis of MERs, at different site depths and trajectories selected for intraoperative macrostimulation. Overall, the Lyapunov exponent gradually increased with increasing stimulus amplitude. This fact provided further corroboration that the proposed model held the ability to simulate the desynchronizing effect of stimulation. For each case in figure 4.7, 2 trajectories

traversing the broadest extent of the nucleus (i.e. defined as acceptable by the clinical experts) are examined. The optimal target points according to clinical decision are C 0 (case 1) and L -2.0 (case 4) (table 4.1). In the aforementioned cases, values of the Lyapunov exponent are for no other site significantly higher than values for the optimal stimulation site ($p < 0.05$), within the trajectory along which the best stimulation effects are obtained. Comparing results between trajectories, there is no site along the alternative trajectory for which the derived exponent is significantly higher than the one corresponding to the finally selected site ($p < 0.05$).

In general, considering as true positive the result obtained under the condition that the derived values of λ were not significantly higher for the nearby sites than the values derived for the optimal stimulation site ($p < 0.05$), the proposed method yielded a sensitivity of 78.57%. Strengthening the condition by including comparative assessment of the Lyapunov exponent between two MER trajectories, the method yielded a sensitivity of 71.43% (table 4.3).

Figure 4.10 provides an integrated visualization scheme of the procedure of clinical decision making during DBS surgery, based on the proposed stochastic model. Initially, synchronization index, Q was comparatively assessed for the five trajectories (central, anterior, posterior, medial and lateral). Accordingly, the acceptable trajectories could be determined as described in 4.6.4.5. Subsequently, values of biomarker Q at specific sites of the acceptable trajectories were employed as one of the inputs (parameters) to the stochastic phase model, while the respective values of biomarker λ actually reflected the output of the model. Eventually, sites where the highest positive values of λ were obtained, were considered as the sites where stimulation yielded the best clinical benefit.

Remarkably, the proposed stochastic model corroborated the increased effectiveness of high frequency stimulation compared with low frequency stimulation in PD (Rizzone et al 2001, Moro et al 2002), (figure 4.11). Importantly, however, stimulation at beta frequencies did not further synchronize oscillatory activity, as indicated by positive values of the Lyapunov exponent. This observation is in agreement with the study of Tsang et al (2012), who suggested that beta frequencies did not worsen PD motor signs.

4.7. Discussion

Physiologically guided neurosurgery has been adopted by the majority of DBS centers and will apparently continue to be a powerful practice in the field of stereotactic and functional neurosurgery for many years to come (Lozano et al 2010 (b), Abosch et al 2013). Development of related automatic methodologies having the potential to be intraoperatively incorporated, thereby

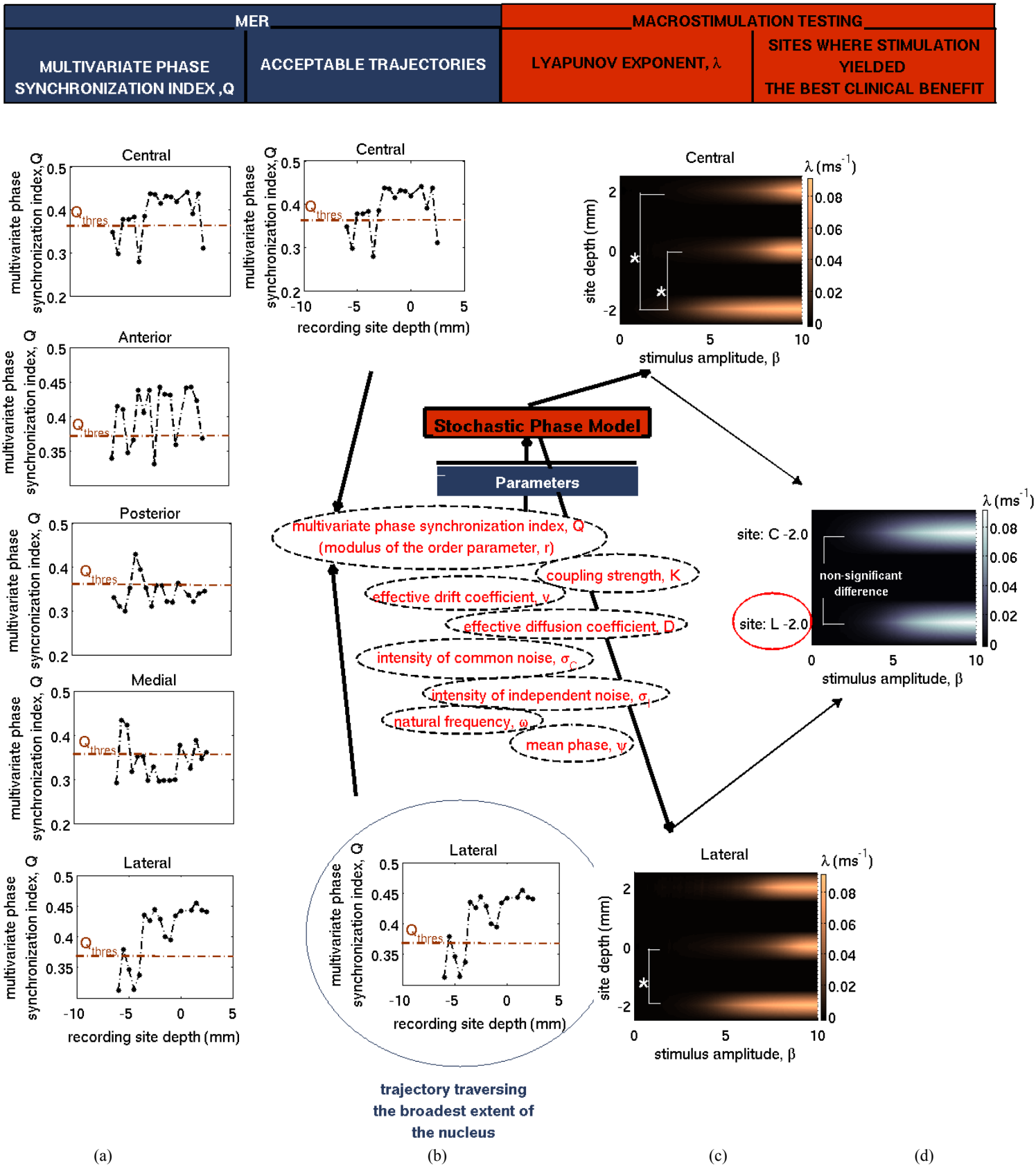
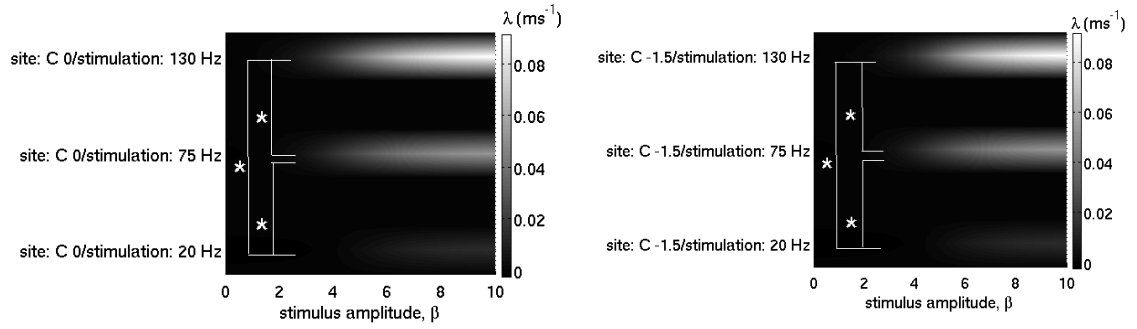


Figure 4.10. The proposed scheme for clinical decision making during DBS surgery for PD, based on the stochastic dynamical model. (a) Assessment of the multivariate phase synchronization index Q across 5 trajectories of left STN, case 4. (b) Determination of the 2 acceptable trajectories, including the one traversing the broadest extent of the nucleus. Biomarker Q was subsequently used as one of the constituent parameters of the stochastic phase model through which we defined (c) the Lyapunov exponent, λ as a function of stimulus amplitude β, at 3 pre-selected recording sites, for both acceptable trajectories. Asterisks denote significant differences. (d) Sites where the highest values of λ were obtained according to (c) for each of the acceptable trajectories. At these sites, values of λ between the 2 trajectories were not significantly different. Circled is the site finally selected by the clinical experts.



(a) (b)

Figure 4.11. Increased effectiveness of high frequency stimulation corroborated by the stochastic phase model. The Lyapunov exponent λ as a function of stimulus amplitude β, at sites (a) C 0, right STN, case 7 and (b) C -1.5, right STN, case 9, for three different stimulation frequencies (20 Hz, 75 Hz and 130 Hz).

leading to significant reduction of surgical time and optimization of clinical decision making, is therefore of practical importance. Several studies have suggested certain STN detection algorithms, based mainly on combinations of quantitative measures (Falkenberg et al 2006, Danish et al 2008, Zaidel et al 2009, Wong et al 2009, Cagnan et al 2011, Pinzon-Morales et al 2011). Nevertheless, application of a robust single-biomarker approach, having the inherent potential to simplify and accelerate intraoperative nucleus detection, has not been reported in the literature before. Most importantly, to the best of our knowledge, no extensive study has to date been published on an automatic algorithm applicable to the entire electrophysiological procedure, i.e. encompassing both MER and intraoperative stimulation, and pointing to the finally selected site for implantation of the DBS electrode.

Pathological synchronization is considered to be related to the severity of motor impairment in PD (Kühn et al 2009, Pogosyan et al 2010). Furthermore, there is recent electrophysiological evidence regarding patients with movement disorders but also modeling studies suggesting that alterations in the abnormal discharge pattern of STN neurons and disruption of neuronal synchronization probably explain the therapeutic mechanism of action of STN-DBS (Carlson et al 2010, Walker et al 2011, Hauptmann et al 2007, Modolo and Beuter 2009, Wilson et al 2011, Johnson et al 2013). Both of the above facts implicitly point to the possible usefulness of methods from stochastic nonlinear dynamics in the context of clinical decision making during surgical implantation of the DBS electrode. In that vein, in the present work, an attempt was made to develop a novel integrated approach based on two principal biomarkers, the multivariate phase synchronization index, Q and the Lyapunov exponent, λ of a stochastic phase model, for optimal target identification during DBS surgery. To address this goal, we relied on the assessment of multi-scale neuronal activity through MER. Essentially, the presence of noise constituted a key factor for the twofold objective of the current study: on the one hand, application of phase synchronization indices had to be robust against the impact of measurement noise, while on the

other hand, intrinsic and extrinsic components of the noise were of paramount importance in the phase model employed.

The results of this work signified the high discriminative power of multivariate phase synchronization index, Q (as well as of the bivariate phase synchronization indices $\rho_{1,2}$ and $\rho_{1,3}$) in the context of STN localization, a procedure forming the first part of electrophysiological monitoring (Marceglia et al 2010). Application of data-driven optimal filtering on the examined signal components (Rossberg et al 2004) in combination with neighbourhood-based phase estimation (Sun et al 2008) ensured remarkable stability of feature evolution inside the nucleus against the presence of noise. To the best of our knowledge a single-biomarker approach displaying similar stability for intraoperative nucleus detection has not been presented in the literature before. This biomarker was subsequently exploited as one of the constituent parameters of the stochastic phase model. Principally, the proposed model held the ability to reproduce the desynchronizing effect of periodic stimulation. This fact was validated through both the invariant measure and the Lyapunov exponent, λ of the stochastic phase map. There are two principal reasons that could have contributed to this result. Firstly, selection of a Type-II PRC as the phase sensitivity function to common (extrinsic) noise (Abouzeid and Ermentrout 2009), guaranteed to a great extent that the model would simulate the pathological synchronous state in the absence of any stimulus, yielding a negative Lyapunov exponent. On the contrary, a Type- I PRC would rather be linked to the normal desynchronized state (Farries and Wilson 2012). Secondly, application of a type 0 PRC, potentially optimal for stochastic desynchronization (Hata et al 2011), contributed to simulation of one of the hypothetical mechanisms of high frequency stimulation. Eventually, on the basis of the simulations proposed, a neurosurgeon may be able to determine the optimal stimulation sites with enhanced sensitivity.

The proposed phase model was developed incorporating multiple factors affecting neuronal dynamics: neuronal coupling, intrinsic independent and extrinsic common noise sources, and periodic forcing. Thus, the derived Lyapunov exponent, λ was combinatorially correlated with the set of the respective parameter values and not uniquely determined by multivariate phase synchronization index, Q. Some previous studies (Tass et al 2006, Nabi et al 2013) have suggested similar models in the framework of desynchronizing stimulation, yet only embodying the effect of intrinsic noise, disregarding extrinsic noise sources (Teramae and Tanaka 2004). Additionally, the above models did not consider the phase dependence of the noise (Ermentrout and Saunders 2006), thus noise forcing was not necessarily multiplicative (Ly and Ermentrout 2011). Most importantly, in this work, intending to implement a more realistic model, common noise has been considered as colored, namely as an Ornstein-Uhlenbeck process with specific correlation time (Galán 2009). For this reason, a transformation of the initial phase model to a

white noise Langevin equation has been required, introducing the effective drift and diffusion coefficients (Nakao et al 2010).

In what concerns the simplifications and limitations of the presented approach, first and foremost, application of the proposed method cannot be regarded as a complete substitute for functional stimulation techniques. Assessment of stimulation-induced side-effects is undoubtedly a significant factor in clinical decision making during intraoperative macrostimulation (Schlaier et al 2013) and was not quantitatively incorporated in the present study. However, it should be pointed out that intraoperative quantification of the therapeutic window (intensity threshold for side effects/intensity threshold for clinical effects) depends to a large extent on the assessment of the therapeutic effects of stimulation (Marceglia et al 2010). Besides, a relatively low threshold for the appearance of clinical effects is evidently associated with reduced probability that a side-effect will be evoked at the same intensity, since the most common side effects induced by STN-DBS, i.e. pyramidal tract side effects, occur at a median amplitude of 4.8V (Tommasi et al 2008). The above facts in combination with the good consistency of the proposed scheme with expert annotations, assign a specific value to the presented approach. Considering further the limitations of this work, the fact that single units are not isolated prior to feature evaluation would likely have influenced the results of our study. Still, similar approaches in the context of automatic algorithms for nucleus localization have been adopted by other studies as well (Wong et al 2009, Cagnan et al 2011). Last, it should be noted that the extent to which simulations of the stochastic model would be distinct for different types of phase response functions to the noise sources was not hereby characterized.

Further perspectives include assessment of the predictive value of the stochastic model considering data from more patients and other clinical implementations of DBS (Mallet et al 2008, Chabardès et al 2013, Fytagoridis et al 2012). Particularly, in patients with obsessive-compulsive disorder (OCD), evidence that the efficacy of STN-DBS probably lies in alteration of the abnormal bursty activity pattern observed in the associative-limbic part of the nucleus (Piallat et al 2010, Welter et al 2011) implicitly indicates possible suitability of the current approach for DBS electrode localization. At the same time, appropriate modification of the presented methodology to include quantitative measures reflecting the evaluation of stimulation-induced side effects is expected to enhance its practicability in the surgical procedure. Furthermore, in light of evidence pointing to a possible correlation between intra- and postoperative outcomes of clinical evaluation (Xie et al 2010), proper adaptation of the proposed scheme to DBS programming could potentially facilitate clinical decision making postoperatively. Finally, due to the considerably realistic nature of the stochastic phase model employed, model variations could prove useful for investigating the clinical efficacy induced by alternative patterns of DBS stimulation (Brocker et al 2012), as described in the following chapter.

5

Evaluating the Efficiency of Alternative Patterns of Subthalamic Nucleus Deep Brain Stimulation for Parkinson's Disease and Obsessive-Compulsive Disorder in a Data-Driven Computational Model

Temporal pattern of stimulation is a new dimension of therapeutic innovation.

W M Grill (2015)[1]

Abstract

Objective. Recent experimental and computational modeling evidence has signified the efficiency of alternative patterns of stimulation; however, no indications exist for treatment-refractory OCD. Here, we comparatively simulate the desynchronizing effect of standard (regular at 130Hz) versus temporally alternative (in terms of frequency, temporal variability and the existence of bursts or pauses) patterns of STN-DBS for PD and OCD, by means of a stochastic dynamical model and two microelectrode recording (MER) datasets. *Approach.* The stochastic model is fitted to subthalamic MERs acquired during eight surgical interventions for PD and eight surgical interventions for OCD. For each dynamical system simulated, we comparatively assess the invariant density (steady-state phase distribution), as a measure inversely related to the desynchronizing effect yielded by the applied patterns of stimulation. *Main results.* We

[1]7th International IEEE/EMBS Conference on Neural Engineering, Montpellier, France, 2015

demonstrate that high (130 Hz) - and low (80 Hz) - frequency irregular patterns of stimulation, and low-frequency periodic stimulation interrupted by bursts of pulses yield in both pathologic conditions a significantly stronger desynchronizing effect compared with standard STN-DBS and distinct alternative patterns of stimulation. In PD, values of the invariant density measure are proven to be optimal at the dorsolateral oscillatory region of the STN including sites with the optimal therapeutic window. *Significance*. In addition to providing novel insights into the efficiency of low-frequency non-regular patterns of STN-DBS for advanced PD and treatment-refractory OCD, this work points to a possible correlation of a model-based outcome measure with the clinical effectiveness of stimulation and may have significant implications for an energy- and therapeutically-efficient configuration of a closed-loop neuromodulation system.

5.1. Introduction

It is now increasingly being recognized that application of temporally alternative patterns of stimulation could potentially lead to a more effective symptom control, reduced side-effects, and lower energy requirements (Sarem-Aslani and Mullet 2011, Gross et al. 2013, Hess et al. 2013). Indeed, there is currently a growing body of experimental evidence pointing to an equivalent or even improved clinical efficacy of specific characteristics of temporally non-regular compared with regular patterns of stimulation. Accordingly, temporally non-regular thalamic DBS has been reported to suppress tremor equally effectively with regular stimulation, if there are no long pauses (Birdno et al. 2012, Swan et al. 2013). On the contrary, Kuncel et al. (2012) reported that thalamic stimulation characterized by pauses for a maximum duration of 40% of the total delivery time may be as effective as regular stimulation on tremor reduction. Very interestingly, high-frequency non-regular STN-DBS, if not highly irregular, has been documented to ameliorate bradykinesia in PD more effectively than regular stimulation (Brocker et al. 2013, Swan et al. 2013). Furthermore, clinical studies addressing the efficacy of high ($\geq$ 130 Hz) versus low-frequency ($\leq$ 80 Hz) STN-DBS for PD are pointing to a rather similar or patient-specific effect of low-frequency stimulation compared with high-frequency stimulation, in reference to axial symptoms (Sidiropoulos et al. 2013, Vallabhajosula et al. 2014, Ricchi et al. 2012), involuntary movements (Merola et al. 2013) or overall motor function (Tsang et al. 2012, Khoo et al. 2014).

Appropriately designed waveforms may be advantageous over the traditional rectangular pulse in terms of both clinical efficiency and energy consumption (Foutz and McIntyre 2010, Hofmann et al. 2011, Wongsarnpigoon and Grill 2010). As well, interleaving programming with two distinct amplitudes of stimulation may optimize the clinical outcome of STN-DBS for PD (Wojtecki et al. 2011). Finally, the protocol of coordinated reset stimulation constitutes a radical deviation from standard DBS patterns and has been designed to induce strong neuronal desynchronization and

long-term modulation of synaptic plasticity (Tass 2003, Tass et al. 2006, 2012, Tass and Hauptmann 2007, 2009, Tass and Majtanik 2006, Hauptmann et al. 2009, Hauptmann and Tass 2007, 2009, 2010, Hauptmann et al. 2007, Lucken et al. 2013, Lysyansky et al. 2011 (a), (b), Popovych and Tass 2012). Two proof-of-principle studies have pointed to the potential efficiency of this neuromodulation paradigm (Tass et al. 2012, Adamchic et al. 2014) that is receiving increasing attention in the field of DBS over the last years (Rubin et al. 2012, DeLong and Wichmann 2012, McIntyre et al. 2014, Lourens et al. 2015).

In view of the fact that temporally alternative patterns of stimulation may lie at the core of closed-loop DBS strategies (Feng et al. 2007 (b), Wilson and Moehlis 2014) that have been proven superior in ameliorating parkinsonism (Rosin et al. 2011), further investigations seem to be of importance, in order to gain additional insights into the specific characteristics that render these patterns effective for the treatment of movement and neuropsychiatric disorders.

Building upon the hypothesis that standard and temporally alternative patterns of STN-DBS exert their local-level effect through desynchronization of subthalamic neuronal activity, in this study, we employ methods from stochastic nonlinear dynamics (Gardiner 1985, Kuramoto 1984, Winfree 2001, Pikovsky et al. 2001) and two microelectrode recording (MER) datasets to comparatively assess the desynchronizing effect of standard (regular at 130Hz) versus eleven temporally alternative patterns of STN-DBS for PD and OCD, and to further determine the particular pattern characteristics correlated with a significantly stronger desynchronizing effect. Particularly, on grounds of the stochastic phase model developed in chapter 4, describing an ensemble of globally coupled chaotic oscillators driven by common, independent noises, and external forcing (figure 5.1), we evaluate, for a total of 2x96 subthalamic MERs (each dataset acquired during STN-DBS for PD and STN-DBS for OCD, respectively) the invariant density (steady-state phase distribution) (Hata et al. 2010, Yamanobe 2011), as a quantity herein reflecting the desynchronizing effect of the applied patterns of stimulation on the subthalamic neural population activity. We corroborate the robustness of this measure in discriminating desynchronization scenarios through comparisons with an alternative outcome variable, the Lyapunov exponent, and provide indications for its possible correlation with the clinical effectiveness of stimulation. In the same framework, we introduce specific modifications with respect to the collective dynamics, parameters and functions of the model, thereby significantly increasing its sensitivity. The validity of our approach is supported through important indirect evidence.

Stimulation patterns are designed to comparatively assess the desynchronizing effect of stimulation with varying temporal characteristics including stimulation frequency and temporal regularity. Accordingly, temporally alternative patterns of stimulation include either high-

frequency (130 Hz) non-regular or low-frequency (80 Hz), regular or non-regular, pulse trains. In the same context, we aim to determine the specific characteristics of non-regular stimulation patterns correlated with a significantly stronger desynchronizing effect: irregularity per se, long pauses or bursts. Respectively, non-regular patterns are either generated by a gamma process with increasing degrees of temporal variability (Dorval et al. 2010) or composed of constant-rate pulses interrupted by long pauses (Kuncel et al. 2012) or bursts of pulses (Birdno et al. 2012, Brocker et al. 2013) (figure 5.2). The desynchronizing effect of the examined patterns of stimulation is further assessed at locations of oscillatory activity within the dorsolateral sensorimotor region versus locations of non-oscillatory activity within the ventromedial limbic region of the STN of patients with PD. The results provide important information relevant to the development of therapeutically- and energy-efficient closed-loop DBS systems.

5.2. Patients and Methods

5.2.1. Data Description

During an one-year period, 8 patients with idiopathic PD underwent bilateral STN-DBS at the Department of Neurosurgery, Evangelismos General Hospital of Athens. Informed consent was provided by each patient. Stereotactic surgery and patients' clinical characteristics have been described in chapter 4 (see also Table 4.1, cases 1-7). A commercially available MER system (Leadpoint TM Neural Activity Monitoring System, Medtronic Inc., Minneapolis, MN) was used intra-operatively for dadta acquisition. Five tungsten microelectrodes (2mm apart, tip diameter < 25 μm, Medtronic Inc., Minneapolis, MN) were used for recording. The recorded signals were pre-amplified, band-pass filtered between 0.1 Hz and 10 kHz, and sampled at 24 kHz. A total of 96 randomly selected, stable MERs corresponding to sites lying within the intraoperatively defined borders of the STN, and acquired at rest, were initially digitally bandpass filtered off-line at 1-300 Hz and 300 Hz - 6 kHz, applying four-pole Butterworth filters (Matlab, Mathworks, Natick, MA).

Secondly, during an one-year period 8 patients with treatment-refractory OCD underwent bilateral STN-DBS at the Grenoble University Hospital. Informed consent was provided by each patient, while strict ethical guidelines and established inclusion criteria were considered (National Consultative Ethics Committee). Patients' clinical characteristics are provided in table 5.1 (including cases O1-O6 and O9 (Piallat et al. 2011) and case P5 (Bastin et al. 2014 (b))). Stereotactic surgery has been described in detail elsewhere (Piallat et al. 2011). The anatomical target was placed in the anteromedial (associative-limbic) part of the STN, 2mm anterior and 1 mm medial to the target used during STN-DBS for PD (Mallet et al. 2008). Five tungsten

Table 5.1. Clinical details of patients with treatment-refractory OCD.

Case	Age (years) and sex	Disease duration (years)	Hemisphere(s) tested	OCD Type	YBOCS pre-op	GAF pre-op	CGI pre-op	Medication (Total Daily Dose-mg) pre-op		
								SNRI and SRI	FGA and SGA	Other Medications
P5	34,m	13	Right STN/Left STN	Doubt/Checking compulsions	16+16	35	6	Clomipramine 225	Cyamemazine 150	Oxazepam 150, Buspirone 30
O3	42,f	25	Right STN/Left STN		15+15	36	5	Fluoxetine 60 Venlafaxine 50	Levomepromazine 25	Bromazepam 6
O6	37,f	5	Right STN		14+18	33	6	Venlafaxine 150		Bromazepam 9 Hydroxizine 25
O1	39,m	18	Right STN	Aggressive obsessions	18+19	26	6	Fluvoxamine 200	Pimozide 1	Clonidine 0.3
O2	43,f	32	Right STN/Left STN	Ordering obsessions/ Checking compulsions	14+18	32	6	Sertraline 100	Risperidone 4	Alprazolam 0.75
O4	34,f	24	Right STN/Left STN		17+17	42	5	Escitalopram 30		Clobazam 5 Lamotrigine 75 Mianserine 20
O5	35,f	15	Right STN/Left STN	Contamination obsessions/ Washing compulsions	14+15	36	6	Paroxetine 60		
O9	36,m	17	Right STN/Left STN	Contamination obsessions/ Washing compulsions	17+15	45	5	Paroxetine 40		

m, male; f, female
YBOCS (Yale-Brown Obsessive Compulsive Scale) scores range from 0 to 40, with higher scores indicating worse function. The 2 YBOCS subscores (evaluating obsessions or compulsions, respectively) range from 0 to 20.
GAF (Global Assessment of Functioning) scores range from 1 to 90, with higher scores indicating the normal global functional status.
CGI (Clinical Global Impression) scores range from 1 to 7, with higher scores indicating the severity of the disease.
SNRI: serotonin and norepinephrine reuptake inhibitors; SRI: serotonin reuptake inhibitors; FGA: first-generation antipsychotics; SGA: second-generation antipsychotics.

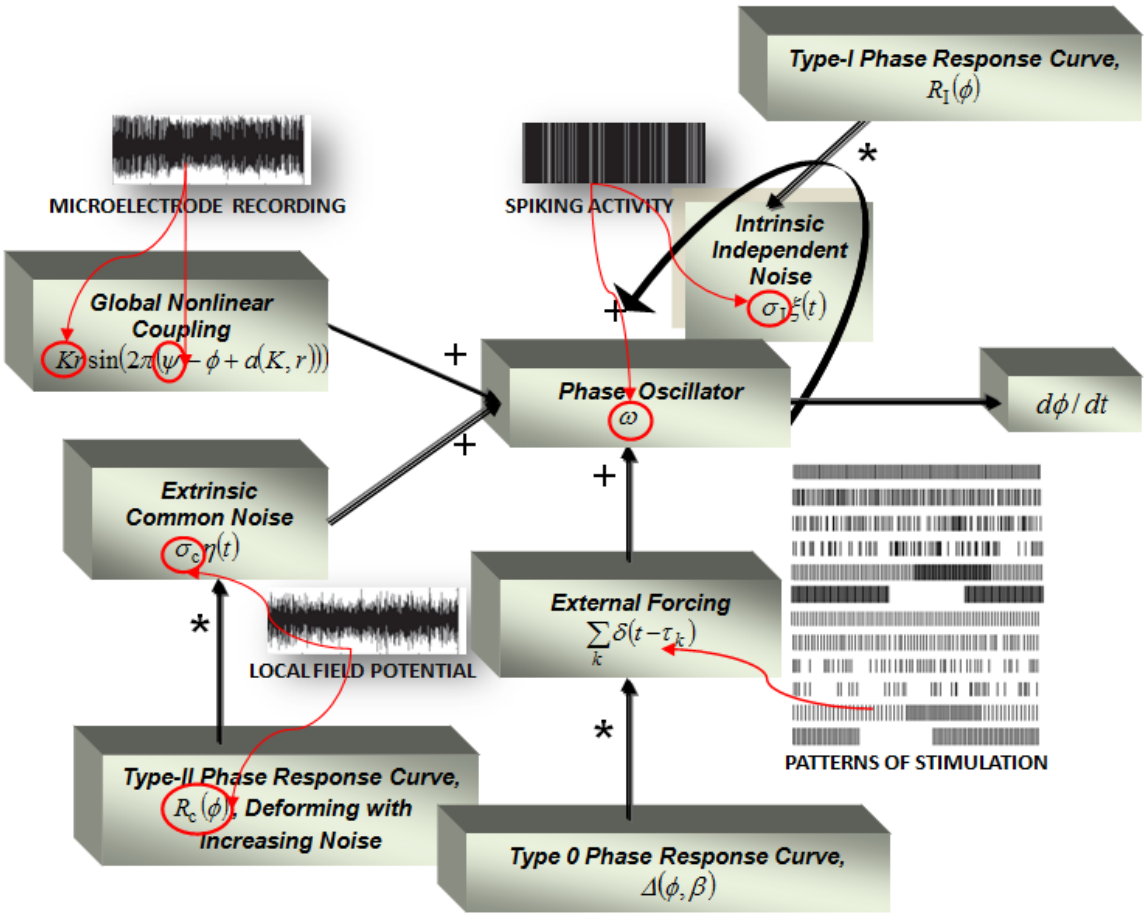


Figure 5.1. The proposed stochastic dynamical model. Determination of the collective dynamics, parameters and functions of the model, based on each MER, was improved in order to more realistically capture the underlying neuronal dynamics. Patterns of stimulation are detailed in figure 5.2.

microelectrodes (2mm apart, tip diameter < 25 μm, FHC Inc., Bowdoinham, ME, USA) were used for recording. Intraoperatively, signals were amplified, band-pass filtered at two frequency bands (1- 300 Hz and 300 Hz - 6 kHz) and sampled at 3 kHz and 48 kHz, respectively, using the Neurotrek System (Alpha-Omega Engineering, Nazareth, Israel). A total of 96 stable MERscorresponding to sites lying within the intraoperatively defined borders of the STN, and acquired at rest, were randomly selected for off-line analysis (Matlab, Mathworks, Natick, MA).

For both data sets we proceeded to the assessment of three-scale neuronal activity as described in chapter 4: (a) spiking activity of one or just a few large isolated cells quantified through the spike detection process, (b) sub-noise level spiking activity of the surrounding neural population extracted based on the background unit activity extraction process, and (c) activity of large neural populations quantified through the LFPs. All signals were further down-sampled to 1 kHz.

5.2.2. The Phase Model

We consider the following Langevin equation (by virtue of the Stratonovich interpretation (Gardiner 1985)) describing an ensemble of N identical phase oscillators with global nonlinear coupling, driven by intrinsic independent and extrinsic common noises, but also subject to external forcing (figure 5.1):

$$\frac{\mathrm{d}\phi_i}{\mathrm{d}t} = \omega + \frac{K}{N}\sum_{j=1}^{N}\sin\left(2\pi\left(\phi_j - \phi_i + a\right)\right) + \sigma_{\mathrm{I}} R_{\mathrm{I}}\left(\phi_i\right)\xi_i(t) + \sigma_{\mathrm{C}} R_{\mathrm{C}}\left(\phi_i\right)\eta(t) + \Delta\left(\phi_i,\beta\right)\sum_k \delta\left(t-\tau_k\right) \tag{5.1}$$

where $\phi_i \in [0,1)$ is the phase variable of the *ith* oscillator, ω is its natural frequency, $K>0$ is the coupling strength and a is the phase shift, inherent to nonlinear coupling (Rosenblum et al. 2007, Temirbayev et al. 2012, Baibolatov et al. 2009). We consider that $\xi_i(t)$ is zero mean Gaussian white noise, added independently to each oscillator, with correlation specified by $\left\langle \xi_i(t)\xi_j(t')\right\rangle = \delta_{ij}\delta(t-t')$, where $\delta_{ij}=1$ if $i=j$ and 0 if $i\neq j$ .We regard $\eta(t)$ as colored noise with zero mean, unitary variance and autocorrelation function $C(t)$. Parameters σ_{I} and σ_{C} are representing the intensity of independent and common noise, respectively. Phase sensitivity functions $R_{\mathrm{C}}(\phi_i)$ and $R_{\mathrm{I}}(\phi_i)$ represent the linear response of the phase variable ϕ_i to the respective infinitesimal noise perturbations, while $\Delta(\phi_i,\beta)$ is the phase response curve (PRC) to a single (DBS) impulse (Kuramoto 1984, Winfree 2001) (figure 5.3B). Parameter β represents the stimulus amplitude and τ_k are the input times. Introducing the Kuramoto order parameter defined by $re^{2\pi\mathrm{i}\psi} = \frac{1}{N}\sum_{j=1}^{N}\mathrm{e}^{2\pi\mathrm{i}\phi_j}$ (Kuramoto 1984, Strogatz 2000) where r characterizes the degree of synchrony and ψ is the mean phase of the oscillators, and defining the effective drift and diffusion coefficients, v and D, respectively (Nakao et al. 2010), the Stratonovich Eq. (5.1) is converted to an equivalent Ito stochastic differential equation (Gardiner 1985):

$$\begin{aligned}\frac{\mathrm{d}\phi}{\mathrm{d}t} = {} & \omega + Kr\sin\left(2\pi\left(\psi-\phi+a\left(K,r\right)\right)\right) + v + \left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)+\sqrt{D}\right)\xi(t) + \frac{\sigma_{\mathrm{I}}}{2}R_{\mathrm{I}}'(\phi)\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)+\sqrt{D}\right) \\ & + \Delta(\phi,\beta)\sum_k \delta\left(t-\tau_k\right)\end{aligned} \tag{5.2}$$

where $v \approx {\sigma_{\mathrm{C}}}^2 \int_0^\infty ds\, C(s)\int_0^1 d\phi\, R_{\mathrm{C}}'(\phi)R_{\mathrm{C}}(\phi-\omega s)$ and $D \approx {\sigma_{\mathrm{C}}}^2 \int_{-\infty}^\infty ds\, C(s)\int_0^1 d\phi\, R_{\mathrm{C}}(\phi)R_{\mathrm{C}}(\phi-\omega s)$. (5.3)

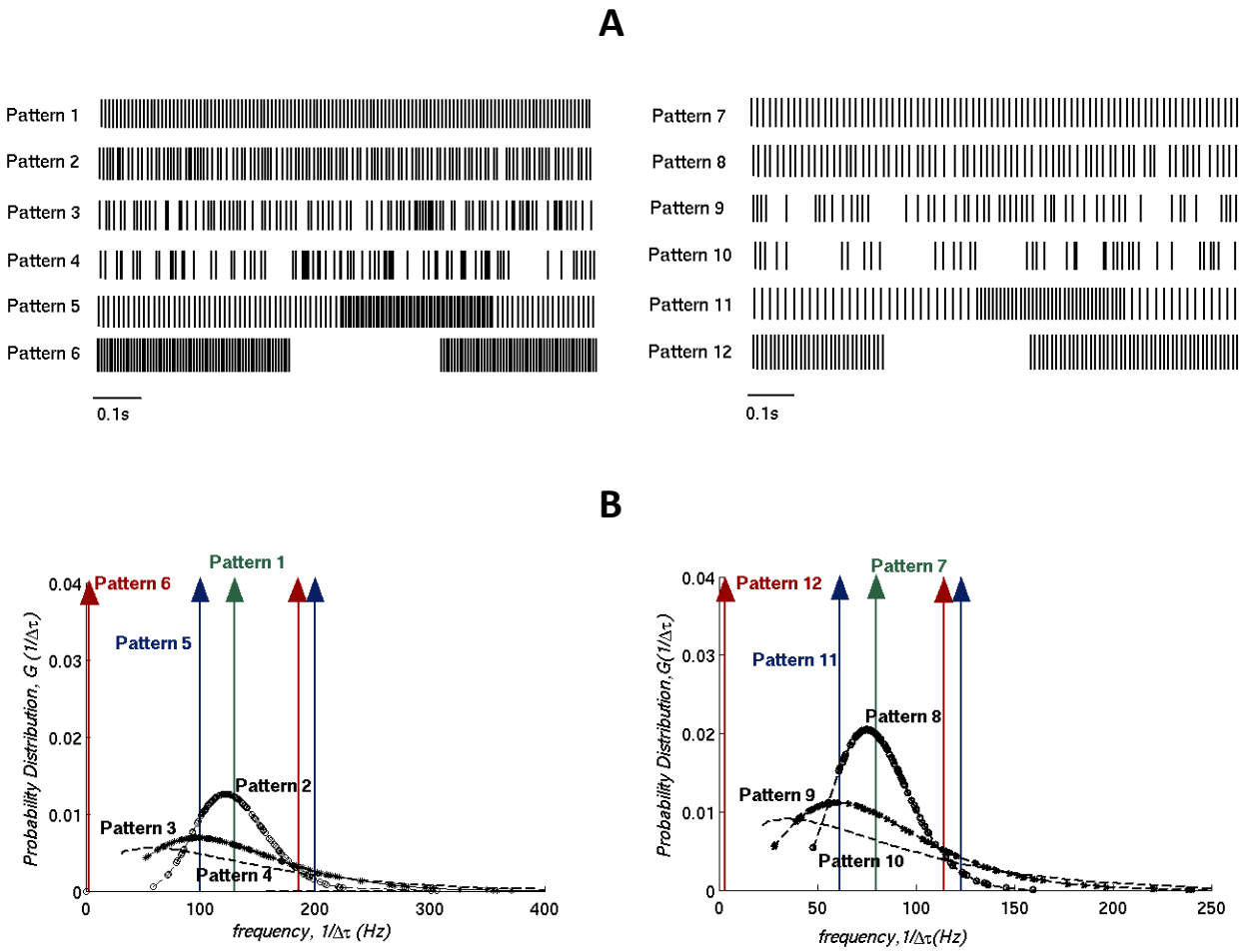


Figure 5.2. Exemplary temporal patterns of stimulation designed to determine the specific characteristics correlated with a strong desynchronizing effect of STN-DBS for PD and OCD. (A) Patterns 1 and 7: regular stimulation at 130 Hz and 80 Hz, respectively; Patterns 2 and 8 : irregular stimulation with a mean frequency of 130 Hz and 80 Hz, respectively, and 25% temporal variability; Patterns 3 and 9: irregular stimulation with a mean frequency of 130 Hz and 80Hz, respectively, and 50% temporal variability; Patterns 4 and 10: irregular stimulation with a mean frequency of 130 Hz and 80 Hz, respectively and 75% temporal variability; Patterns 5 and 11: periodic stimulation with a mean frequency of 130 Hz and 80Hz, respectively, interrupted by bursts of pulses; Patterns 6 and 12: periodic stimulation with a mean frequency of 130 Hz and 80Hz, respectively, interrupted by pauses (B) Respective probability density functions.

5.2.3. Application of Stimulation Patterns

Phase eq. (5.2) is solved through the stochastic map from one stimulus cycle to the next (Nesse and Clark 2010) (figure 5.3A). We consider that the inter-impulse interval (IPI) $\Delta\tau_n = \tau_{n+1} - \tau_n$ either obeys the gamma distribution and increasing degrees of temporal variability (Dorval et al. 2010), or forms a periodic stimulus train. Periodic stimulus trains are either uninterrupted (regular stimulation) or interrupted by either periods of long pauses or periods of bursts of pulses for 30% of the total delivery time (Kuncel et al. 2012, Birdno et al. 2012, Brocker et al. 2013) (figure 5.2). All stimulus trains have either a mean frequency of 130 Hz or a mean frequency of 80 Hz. The phase dynamics during the IPI $\Delta\tau_n$ is described by

$$\phi_{n+1} = \phi_n + \left(\omega + Kr\sin\left(2\pi\left(\psi - \phi_n + a\left(K,r\right)\right)\right)\right) + v + \frac{\sigma_{\mathrm{I}}}{2} R_{\mathrm{I}}'\left(\phi_n\right) \times \left(\sigma_{\mathrm{I}} R_{\mathrm{I}}\left(\phi_n\right) + \sqrt{D}\right)\Delta\tau_n$$
$$+ \left(\sigma_{\mathrm{I}} R_{\mathrm{I}}\left(\phi_n\right) + \sqrt{D}\right) W\left(\Delta\tau_n\right) + \Delta\left(\phi_n, \beta\right) \tag{5.4}$$

where $W(t)$ is a Wiener process with probability density function (PDF) f_{W_t}, which is a Gaussian with zero mean and variance $\Delta\tau$. The stochastic map is defined by the Perron-Frobenius operator, that maps the density of phases at the time of the $(n+1)th$ impulse, $p_{n+1}(\phi)$, onto the density of phases at the time of the nth impulse, $p_n(\phi)$ (Ermentrout and Saunders 2006, Nesse et al. 2007, Yamanobe and Pakdaman 2002, Hata et al. 2010):

$$p_{n+1}\left(\phi\right) = \int_0^1 \int_0^\infty \mathrm{d}\left(\Delta\tau\right) \sum_{j\in Z} f_{W_t} \left(\frac{\phi - \phi' + j - \left(\omega + Kr\sin\left(2\pi\left(\psi - \phi' + a\left(K,r\right)\right)\right) + v + \frac{\sigma_{\mathrm{I}}}{2} R_{\mathrm{I}}'\left(\phi'\right)\left(\sigma_{\mathrm{I}} R_{\mathrm{I}}\left(\phi'\right) + \sqrt{D}\right)\right) \times \Delta\tau - \Delta\left(\phi', \beta\right)}{\left(\sigma_{\mathrm{I}} R_{\mathrm{I}}\left(\phi'\right) + \sqrt{D}\right)} \right)$$
$$\times G\left(\Delta\tau\right) \times \frac{1}{\left(\sigma_{\mathrm{I}} R_{\mathrm{I}}\left(\phi'\right) + \sqrt{D}\right)} p_n\left(\phi'\right) \mathrm{d}\phi' \tag{5.5}$$

where $G(\Delta\tau)$ is the PDF of the IPIs (figure 5.2B). Dicretizing the density into $M = 500$ bins of size $1/M$, the stochastic map for each IPI is approximated using a 500×500 transition matrix (stochastic kernel) $A(\phi', \phi)$ having all positive entries, a spectral radius of 1 and possessing the strong Perron-Frobenius property (Ermentrout and Saunders 2006, Yamanobe and Pakdaman 2002, Noutsos and Tsatsomeros 2008) (figures 5.4, 5.6). The iterated mapping (5.4) converges to the steady-state phase distribution, i.e. the invariant density, $p_{\mathrm{st}}(\phi)$, represented by the eigenvector corresponding to the dominant (unit) eigenvalue of the transition matrix (figures 5.5, 5.7). This distribution is normalized as $\int_0^1 d\phi\, p_{st}\left(\phi\right) = 1$. The variance of the invariant density, $\mathrm{Var}\left(p_{st}\left(\phi\right)\right)$, across phase, ϕ, is a measure inversely related to the desynchronizing effect of the applied pattern of stimulation. The Lyapunov exponent is an alternative measure reflecting the neuronal (de)synchronization dynamics and can be calculated as

$$\lambda = \left\langle \ln\left|\mathrm{d}\phi_{n+1} / \mathrm{d}\phi_n\right| \right\rangle = \int_0^1 \mathrm{d}\phi \int_0^\infty \mathrm{d}\left(\Delta\tau\right) \times \ln\left|1 + \left(-2\pi Kr\cos\left(2\pi\left(\psi - \phi + a\left(K,r\right)\right)\right)\right.\right.$$
$$\left.\left. + \frac{\sigma_{\mathrm{I}}}{2} R_{\mathrm{I}}''\left(\phi\right)\left(\sigma_I R_{\mathrm{I}}\left(\phi\right) + \sqrt{D}\right)\right)\Delta\tau + \Delta'\left(\phi, \beta\right)\right| \times G\left(\Delta\tau\right) \times p_{\mathrm{st}}\left(\phi\right) \tag{5.6}$$

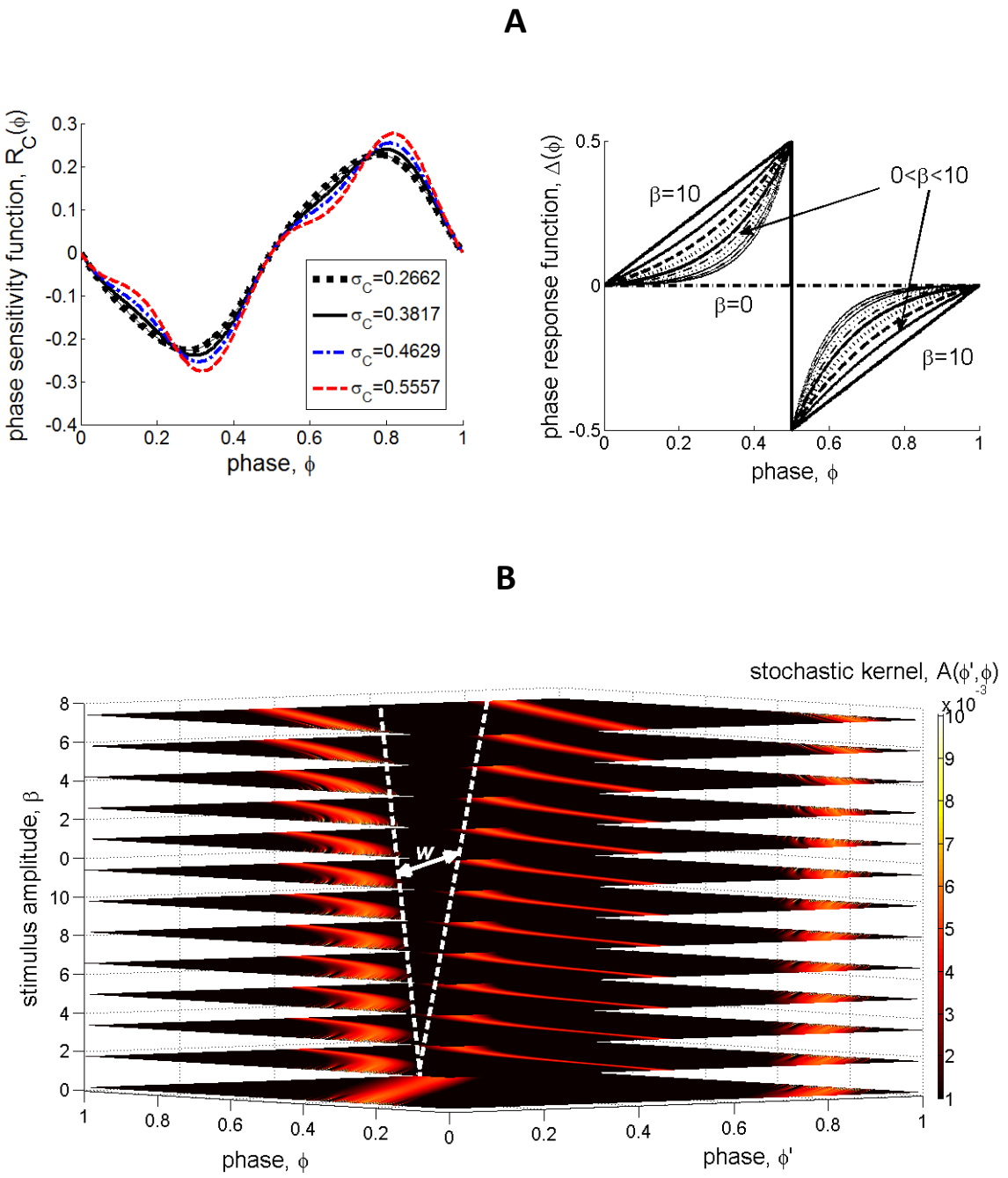


Figure 5.3. (A) The phase sensitivity function, $R_C(\phi)$ (type-II PRC), deforming with increasing common noise intensity, σ_C (left) and the phase response curve, $\Delta(\phi,\beta)$ (type 0 PRC), used to simulate the desynchronizing effect of DBS (right). (B) Stochastic kernel function, $A(\phi',\phi)$, for increasing stimulus amplitude, *β,* of irregular stimulation with a mean frequency of 130Hz and 25% temporal variability, based on the analysis of the recording 'Medial -3.653mm, left STN, case O1' acquired during DBS for OCD. The desynchronizing effect of stimulation is reflected in the increasing split width, *w,* with increasing stimulus amplitude, *β.*

A positive sign of the Lyapunov exponent indicates neuronal desynchronization, while a negative sign indicates neuronal synchronization. Remarkably, Hata et al. (2010) suggested that subtle differences between the desynchronizing effect of heterogeneous patterns of stimulation cannot be optimally captured through the Lyapunov exponent. Instead, they demonstrated that the variance of the Lyapunov exponent

$$\mathrm{Var}(\lambda)=\left\langle\left\{\ln\left|\mathrm{d}\phi_{n+1}/\mathrm{d}\phi_{\mathrm{n}}\right|\right\}^2\right\rangle-\left\{\left\langle\ln\left|\mathrm{d}\phi_{\mathrm{n+1}}\right|/\mathrm{d}\phi_{\mathrm{n}}\right\rangle\right\}^2$$
$$=\int_0^1\mathrm{d}\phi\int_0^\infty\mathrm{d}(\Delta\tau)\times\left\{\begin{array}{l}\ln\left|1+\left(-2\pi Kr\cos\left(2\pi\left(\psi-\phi+a\left(K,r\right)\right)\right)+\frac{\sigma_{\mathrm{I}}}{2}R_{\mathrm{I}}''(\phi)\left(\sigma_I R_{\mathrm{I}}(\phi)+\sqrt{D}\right)\right)\Delta\tau\right.\\\left.+\Delta'(\phi,\beta)\right|\end{array}\right\}^2$$
$$\times G(\Delta\tau)\times p_{\mathrm{st}}(\phi)$$
$$-\left\{\begin{array}{l}\int_0^1\mathrm{d}\phi\int_0^\infty\mathrm{d}(\Delta\tau)\times\ln\left|1+\left(-2\pi Kr\cos\left(2\pi\left(\psi\text{-}\phi+\alpha(K,r)\right)\right)+\frac{\sigma_{\mathrm{I}}}{2}R_{\mathrm{I}}''(\phi)\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}(\phi)+\sqrt{D}\right)\right)\Delta\tau+\Delta'(\phi,\beta)\right|\\\times G(\Delta\tau)\times p_{\mathrm{st}}(\phi)\end{array}\right\}^2 \tag{5.7}$$

may potentially be a more appropriate outcome measure. In this study, we opt for the variance of the invariant density, $\mathrm{Var}(p_{st}(\phi))$, across phase, ϕ, rather than the Lyapunov exponent, λ, or the variance of the Lyapunov exponent, for the final comparative assessment. The rationale behind this selection lies in the fact that the invariant density is a property inherent to the stochastic phase transition operator employed in Eq. (5.5) (Yamanobe et al. 2011) and may therefore reliably characterize the asymptotic dynamics of neuronal responses to distinct stimulation paradigms. Results are compared with those obtained through the employment of the Lyapunov exponent and the variance of the Lyapunov exponent for the PD dataset.

Furthermore, in view of evidence correlating locations of oscillatory activity in the dorsolateral sensorimotor STN with the optimal site of DBS for PD (Guo et al. 2013, Herzog et al. 2004), we assess the dependence of the desynchronizing effect of the examined patterns of stimulation on the location of the recording site within the STN of patients with PD (i.e. dorsolaterally or ventromedially) and on the presence or absence of oscillatory activity. We also consider the sites having been verified intra-operatively to yield the optimal therapeutic window (Table 4.1). Oscillatory regions are discriminated from non-oscillatory regions by means of the chaotic attractor (Babloyantz and Destexhe 1986, Ott 2002) reconstructed from the optimally filtered (Rossberg et al. 2004) spiking activity, using time delay, $\tau=1$ and embedding dimension, $d=3$ (see section 4.6.4.6).

Repeated measures analysis of variance (ANOVA) (Trujillo-Ortiz et al. 2004) with Tukey honestly significant difference (HSD) post-hoc comparisons, and the two-sample t-test are used to determine the statistical significance of the differential effect of stimulation.

5.2.4. Determination of Model Parameters and Functions

Common noise has been proven to reinforce synchronization in populations of globally coupled phase oscillators (Nagai and Kori 2010, Lai and Porter 2013). In line with these indications and in order to simulate the presence of neuronal synchronization within the STN as a characteristic of the pathological unstimulated state, we incorporate the effect of common noise in Eq. (5.1), in addition to global coupling. Furthermore, adapting the stochastic dynamical model developed in chapter 4, in this chapter, we improve the determination of the collective oscillatory dynamics, as well as of specific parameters and functions so as to more realistically capture the underlying neuronal activity corresponding to each MER. Accordingly, we allow for nonlinear coupling, i.e. nonlinear dependence of phase shift, a , on the amplitude of the collective oscillation ($a = a(K,r)$), and set a equal to 1/4, so as to captivate the partially synchronous quasiperiodic dynamics ($0 < r < 1$) of the subthalamic neuronal activity in the pathological unstimulated state (Rosenblum et al. 2007, Temirbayev et al. 2012, Baibolatov et al. 2009). Mean phase, ψ , is set equal to the mean phase of the MER signal components, while natural frequency, ω , is estimated using the mean firing rate of the recorded unit under examination. Extrinsic noise intensity, σ_{C} , and autocorrelation function, $C(t)$, are evaluated on the basis of the respective LFP signal (Moran and Bar-Gad 2010, Wang et al. 2004). Moreover, we consider $R_{\mathrm{C}}(\phi)$ as a type-II PRC, the shape of which is modified according to the extrinsic noise intensity, σ_{C} , (Abouzeid and Ermentrout 2010) in order to increase the phase sensitivity to common noise and to incorporate heterogeneity as a physiological attribute of the PRC (Ly 2014) (figure **3**B). After determining the above parameters, the effective drift and diffusion coefficients, v and D , may be approximately evaluated by applying Eq. (5.3). The remaining parameters, i.e. the degree of synchrony, r , the coupling strength, K , and the intrinsic noise intensity, σ_{I} , as well as the functions $\Delta(\phi,\beta)$ (type 0 PRC) (figure **3**A) and $R_{\mathrm{I}}(\phi)$ (type-I PRC) are determined according to the analysis in chapter 4.

In order to provide evidence for the realistic substructure of the proposed model, we consider null stimulus amplitude (β=0) in Eq. (5.1) and assess the Lyapunov exponent along each MER trajectory, as a quantity reflecting the neuronal synchronization dynamics in the pathological unstimulated state. The Wilcoxon rank sum test is used to determine the statistical significance of the differences within vs. outside the STN borders.

5.3. Results

5.3.1. Evidence for the Realistic Substructure of the Stochastic Phase Model

Figure 5.4A displays an example of neuronal activity recorded during a case of STN-DBS for PD. Evaluation of the synchronization index, Q, indicated the presence of increased neuronal synchronization within the STN. Similarly, on the basis of the stochastic phase model, higher

negative values of the Lyapunov exponent, λ, i.e. increased neuronal synchronization, were obtained within the STN. This result was generalized for a total of 16 acceptable MER trajectories acquired during eight STN-DBS interventions for PD (figure 5.4B). In particular, statistical analysis corroborated the ability of the model to simulate the presence of significant differences in the mean neuronal synchronization dynamics within vs. outside the STN borders (p<.05, Wilcoxon rank sum test), in accordance with strong indications that neuronal synchronization in the pathological unstimulated state is dramatically increased within the STN compared with the dynamics outside the STN borders (Weinberger et al. 2006, Kuhn et al. 2005). Notably, almost equivalent negative values of the Lyapunov exponent (i.e. equivalent neuronal synchronization dynamics) were obtained for either oscillatory or non-oscillatory regions of the STN (p=0.42, Wilcoxon rank sum test). This outcome is in line with evidence that non-oscillatory synchronization may coexist with oscillatory synchronization within the dopamine-depleted basal ganglia, pointing to the fact that synchronization and oscillatory activity might not share common pathophysiological mechanisms in PD (Hammond et al. 2007, Heimer et al. 2002). Further important evidence for the validity of the stochastic phase model is provided through the results presented in section 5.3.4.

5.3.2. Neural Activity-Specific Degree of the Desynchronizing Effect of the Applied Patterns of Stimulation

Figure 5.3B depicts an example of stochastic kernels, $A(\phi', \phi)$, derived based on the analysis of subthalamic neuronal activity recorded at a specific site depth during a case of DBS for OCD and simulating the application of increasing amplitude values, β, of irregular stimulation with a mean frequency of 130 Hz and 25% temporal variability. Remarkably, the desynchronizing effect of stimulation is reflected in the increasing split width, w, with increasing stimulus amplitude. Results illustrated in figure 5.5 were obtained by application of the stochastic model to two pairs of MERs corresponding to sites lying within the intraoperatively confirmed borders of the STN and acquired during DBS for PD (figures 5.5A-B) and DBS for OCD (figures 5.5C-D), respectively. Lower values of the variance of the invariant density, $\mathrm{Var}(p_{st}(\phi))$, indicate a stronger desynchronizing effect of the applied pattern of stimulation. Principally, the desynchronizing effect of the applied patterns of stimulation proved to be dependent on the recording site, i.e. neural activity-specific.

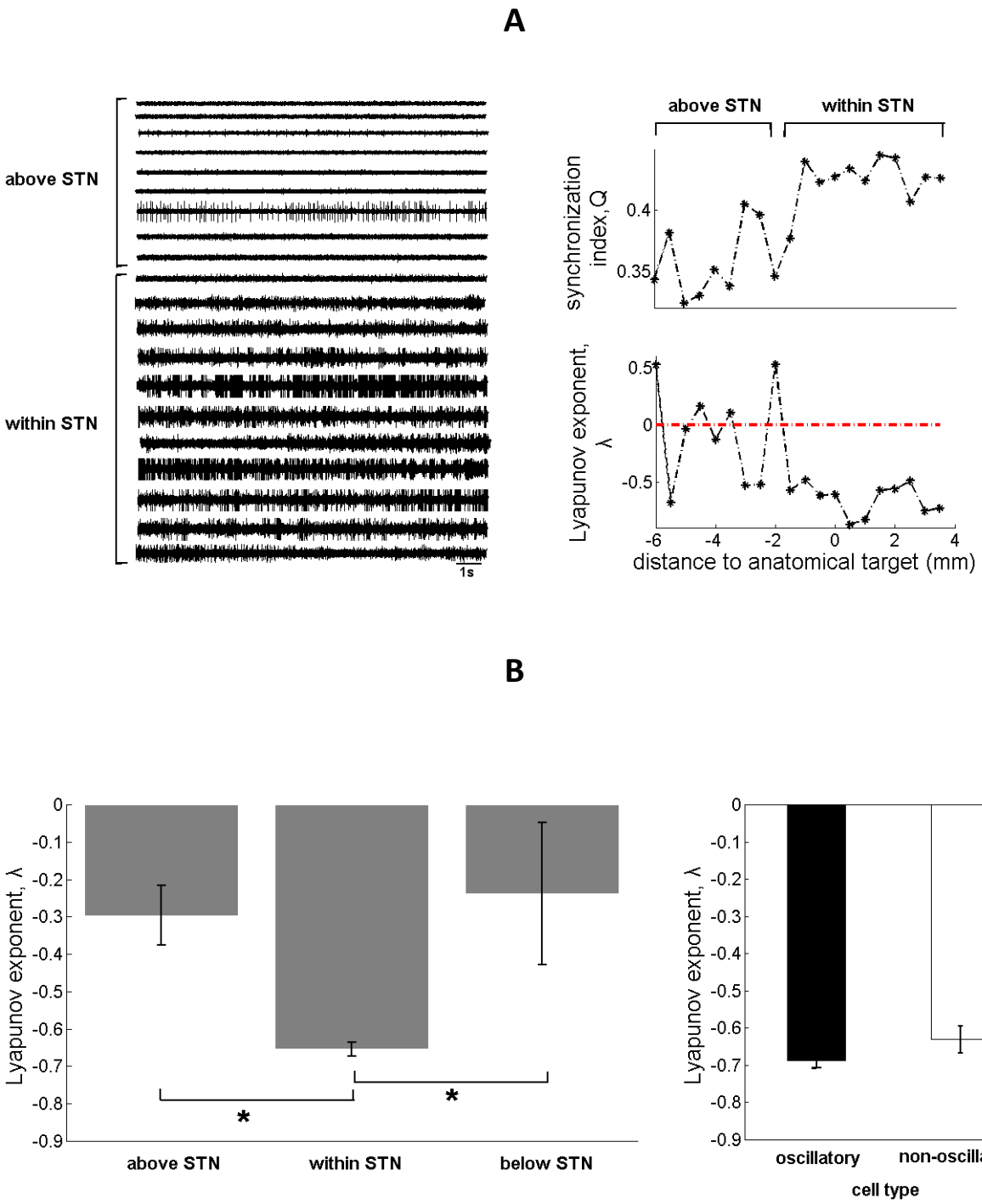


Figure 5.4. Example (A) and cumulative results (B) providing a first piece of evidence for the realistic substructure of the stochastic phase model based on differences in neuronal synchronization dynamics within vs. outside the STN, in the pathological unstimulated state. (A) Neuronal activity (left) recorded along the posterior trajectory of the right hemisphere during STN-DBS for PD - case 8. Evaluation of the synchronization index, *Q*, (upper right panel) indicated the presence of increased neuronal synchronization within the STN borders (depth value 0 corresponds to the anatomical target point determined preoperatively). This dynamics was corroborated by the use of the Lyapunov exponent, λ, calculated on the basis of the stochastic phase model (lower right panel). (B) Assessment of the mean ± standard error mean Lyapunov exponent, λ, based on the stochastic phase model and a total of 16 acceptable MER trajectories acquired during eight STN-DBS interventions for PD (left) (in 8 out of 16 MER trajectories neuronal activity was in addition recorded below the STN). Statistical analysis corroborated the propensity of the model to simulate significant differences in the mean neuronal synchronization dynamics within vs. outside the STN borders (* $p<.05$, Wilcoxon rank sum test). Notably, there was no significant difference of the Lyapunov exponent at oscillatory compared with non-oscillatory regions of the STN ($p=0.42$, Wilcoxon rank sum test) (right).

5.3.3. Stronger Desynchronizing Effect of High- and Low-Frequency Irregular Patterns of Stimulation compared with Standard Stimulation

Figure 5.6 displays, for each pattern of stimulation, the variance of the invariant density as a function of stimulus amplitude and averaged across the datasets acquired during DBS for PD (figure 6A) and DBS for OCD (figure 5.6B). Repeated measures ANOVA corroborated the presence of statistically significant differences in the mean desynchronizing effect of the examined patterns of stimulation (F_{PD}=4133.569, p<.0001 and F_{OCD}=2577.668, p<.0001). In case of PD, Tukey-HSD post-hoc comparisons indicated statistically significant differences between the desynchronizing effect of all patterns of stimulation (p<.0001), except within non-regular patterns of stimulation generated by a gamma process (p>.05). In case of OCD, post-hoc comparisons revealed statistically significant differences between the desynchronizing effect of all patterns of stimulation (p<.01), except between low-frequency periodic stimulation and high-frequency periodic stimulation interrupted by bursts of pulses (p>.05) and within non-regular patterns of stimulation generated by a gamma process (p>.05). Most importantly, in either PD or OCD, irregular patterns of stimulation and low-frequency periodic stimulation interrupted by bursts of pulses yielded a significantly stronger desynchronizing effect compared with standard stimulation (p<.0001) and distinct alternative patterns of stimulation (p<.0001). Furthermore, the stronger desynchronizing effect of irregular patterns compared with standard stimulation was verified to be consistent across MERs, i.e. not neural activity-specific.

5.3.4. Possible Correlation between the Invariant Density Measure and Clinical Effectiveness of Stimulation in PD

Figure 5.7A displays an example of the attractor reconstructed in a three-dimensional phase space from the spiking activity recorded at an oscillatory and a non-oscillatory region of the STN, during a case of DBS for PD. In general, these regions could be differentiated by means of the distinct spatial pattern of the reconstructed attractor. We subsequently assessed the variance of the invariant density based on a total of 30 recordings of oscillatory activity at the dorsolateral STN, including the sites having been verified intra-operatively to yield the optimal therapeutic window, and a total of 30 recordings of non-oscillatory activity at the ventromedial STN, acquired during eight DBS interventions for PD. Simulations revealed a significantly stronger desynchronizing effect of each examined pattern of stimulation at oscillatory regions of the dorsolateral sensorimotor STN, including the sites with the optimal therapeutic window, compared with non-oscillatory regions of the ventromedial limbic STN (p<.0001, two-sample t-test) (figure 5.7B). The significance of these results is multifold: first they provide a further important piece of evidence in support of the validity of the stochastic phase model, since they are in line with strong indications that locations of oscillatory activity at the dorsolateral STN are correlated with the

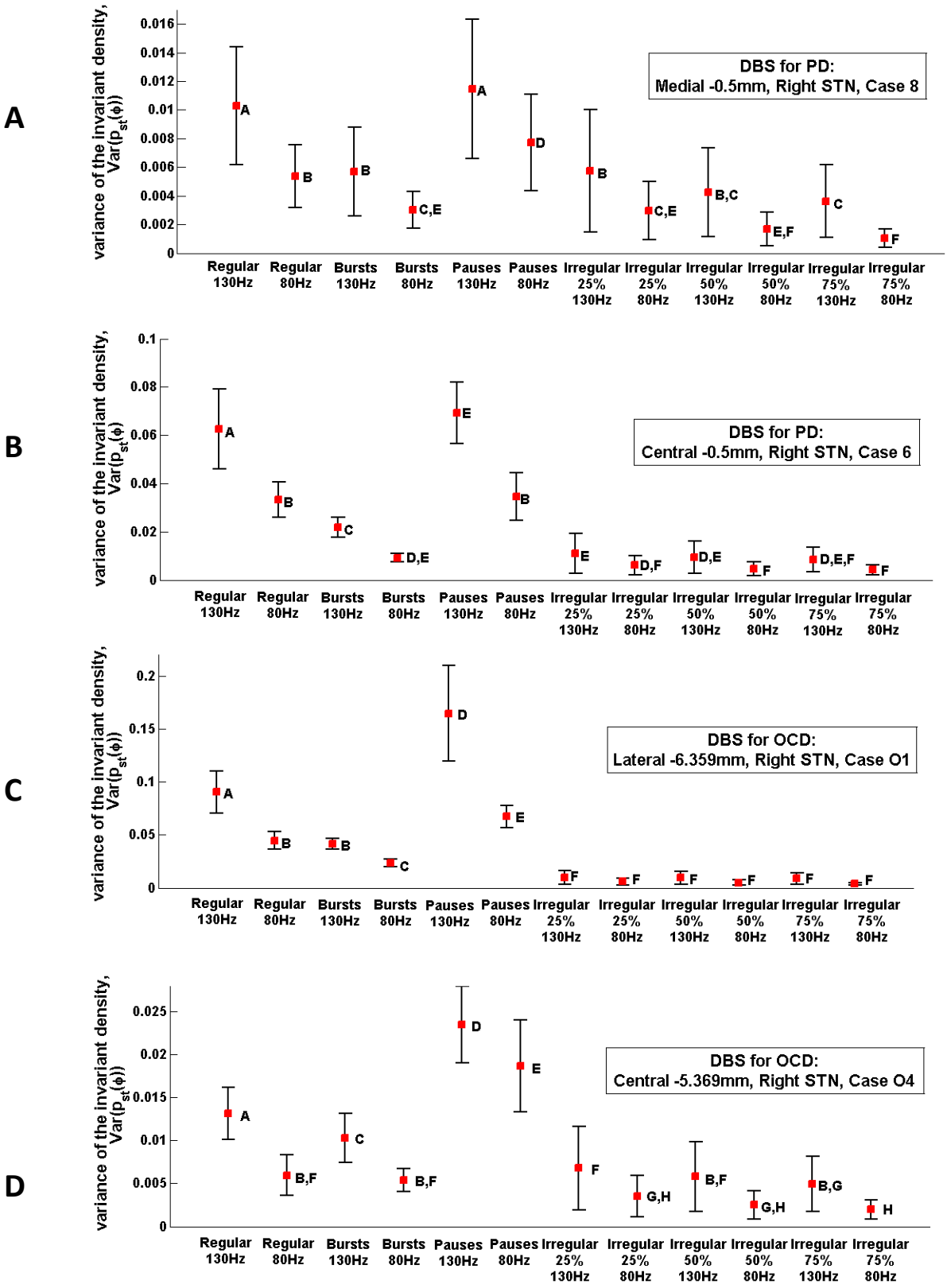
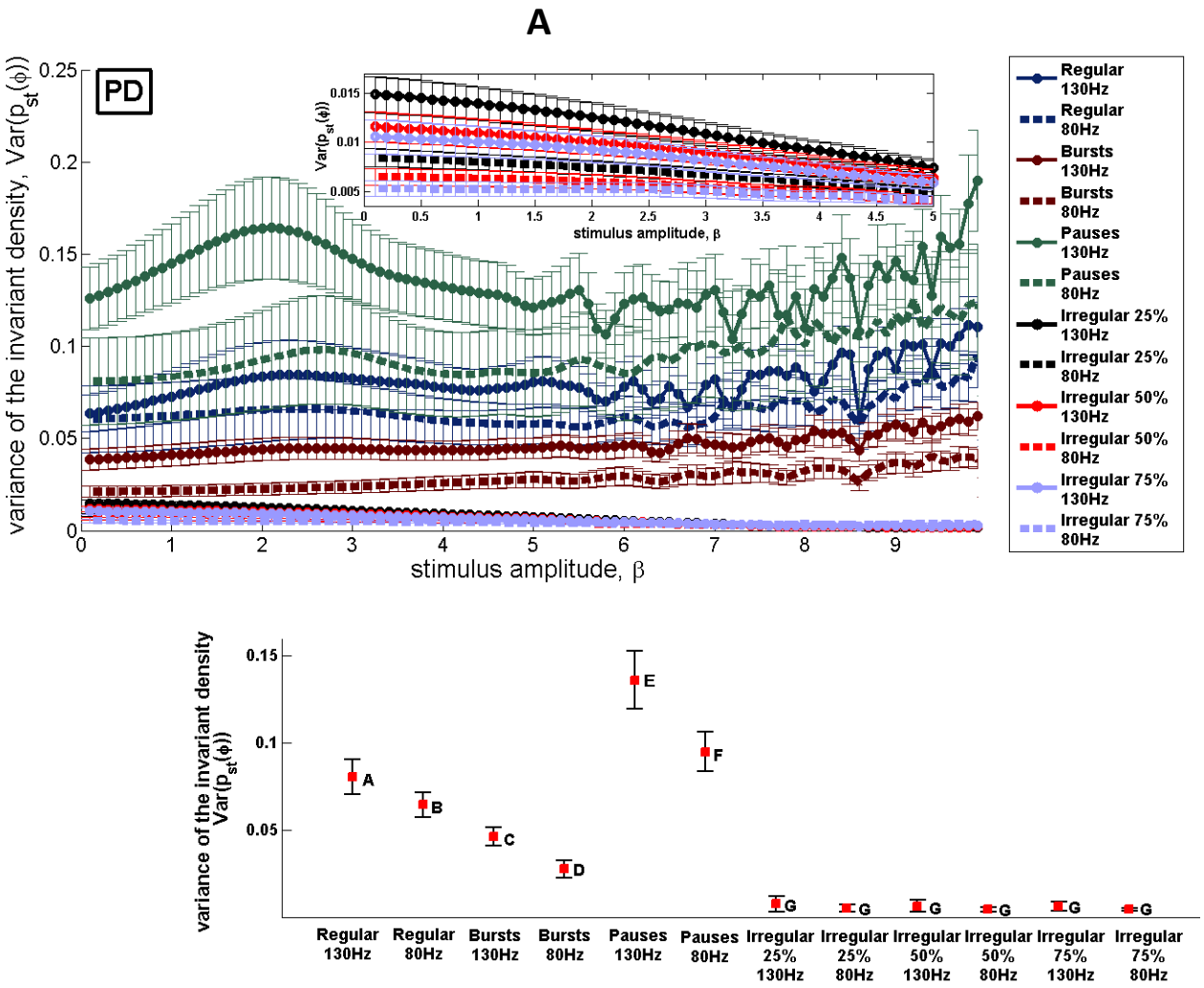


Figure 5.5. Mean ± standard deviation variance of the invariant density, $\mathrm{Var}(p_{st}(\phi))$, for the examined patterns of stimulation, derived by fitting the phase model to MERs acquired at (A) Medial -0.5 mm, right STN - case 8 and (B) Central -0.5 mm, right STN - case 6 during STN-DBS for PD, and at (C) Lateral -6.359 mm, right STN - case O1 and (D) Central -5.369 mm, right STN - case O4 during STN-DBS for OCD. Lower values of the invariant density, $\mathrm{Var}(p_{st}(\phi))$, indicate a stronger desynchronizing effect of stimulation. Stimulation conditions that do not share the same letter are significantly different (p<.01). Principally, the desynchronizing effect of the examined patterns of stimulation proved to be neural-activity specific.


A
PD
variance of the invariant density, Var(p_st(ϕ))
stimulus amplitude, β
Regular 130Hz
Regular 80Hz
Bursts 130Hz
Bursts 80Hz
Pauses 130Hz
Pauses 80Hz
Irregular 25% 130Hz
Irregular 25% 80Hz
Irregular 50% 130Hz
Irregular 50% 80Hz
Irregular 75% 130Hz
Irregular 75% 80Hz
variance of the invariant density Var(p_st(ϕ))
A
B
C
D
E
F
G
Regular 130Hz
Regular 80Hz
Bursts 130Hz
Bursts 80Hz
Pauses 130Hz
Pauses 80Hz
Irregular 25% 130Hz
Irregular 25% 80Hz
Irregular 50% 130Hz
Irregular 50% 80Hz
Irregular 75% 130Hz
Irregular 75% 80Hz

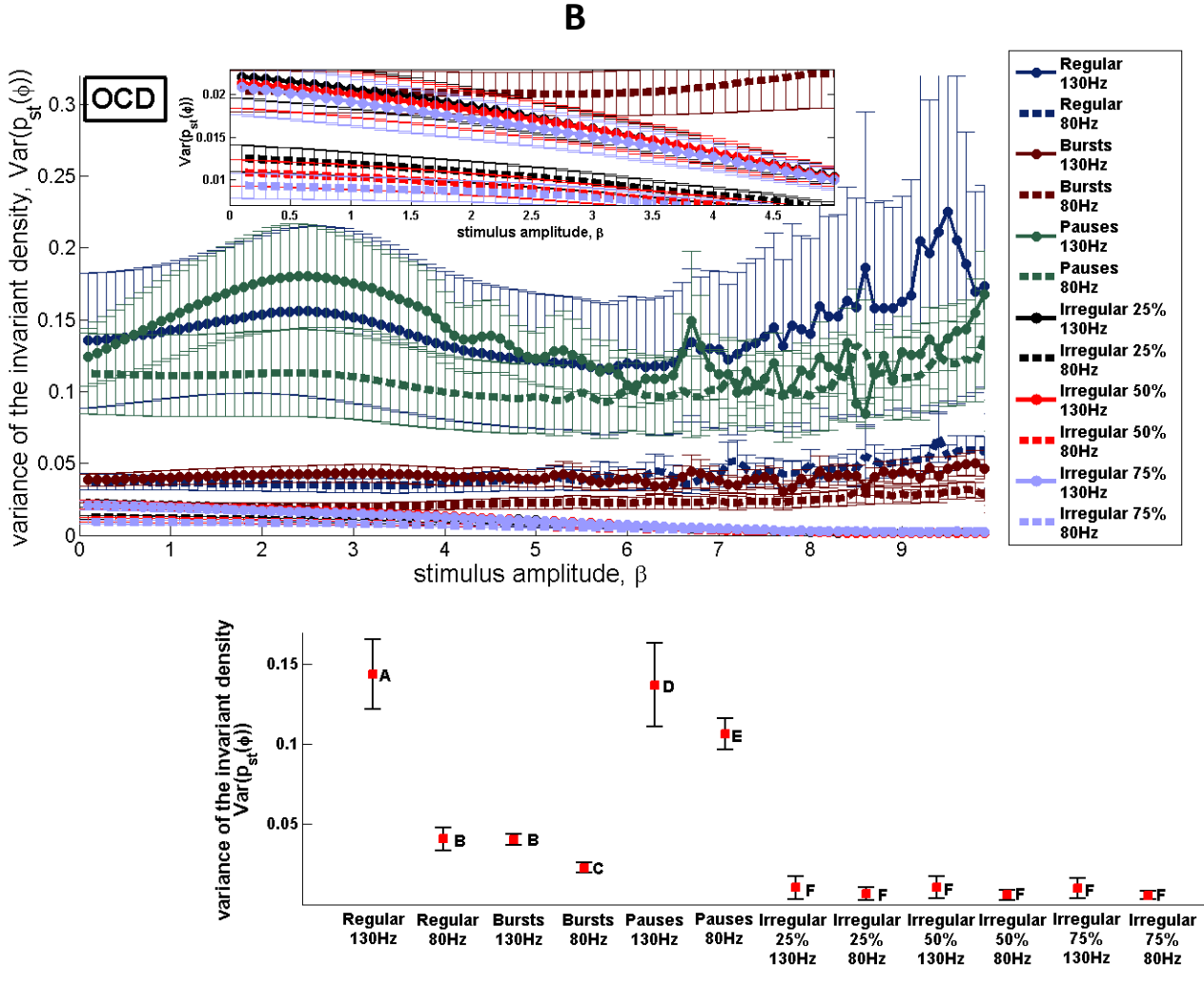

B
OCD
variance of the invariant density, Var(p_st(ϕ))
stimulus amplitude, β
Regular 130Hz
Regular 80Hz
Bursts 130Hz
Bursts 80Hz
Pauses 130Hz
Pauses 80Hz
Irregular 25% 130Hz
Irregular 25% 80Hz
Irregular 50% 130Hz
Irregular 50% 80Hz
Irregular 75% 130Hz
Irregular 75% 80Hz
variance of the invariant density Var(p_st(ϕ))
A
B
C
D
E
F
Regular 130Hz
Regular 80Hz
Bursts 130Hz
Bursts 80Hz
Pauses 130Hz
Pauses 80Hz
Irregular 25% 130Hz
Irregular 25% 80Hz
Irregular 50% 130Hz
Irregular 50% 80Hz
Irregular 75% 130Hz
Irregular 75% 80Hz

Figure 5.6. Variance of the invariant density, $\mathrm{Var}(p_{st}(\phi))$, for the examined patterns of stimulation in PD (A) and OCD (B). The upper panels in (A) and (B) display values of $\mathrm{Var}(p_{st}(\phi))$(mean ± standard error mean) as a function of stimulus amplitude, β, and averaged across the datasets acquired during STN-DBS for PD and STN-DBS for OCD, respectively. The lower panels in (A) and (B) depict the respective mean ± standard deviation $\mathrm{Var}(p_{st}(\phi))$. Lower values of the invariant density, $\mathrm{Var}(p_{st}(\phi))$, indicate a stronger desynchronizing effect of stimulation. Repeated measures ANOVA indicated the presence of statistically significant differences in the mean desynchronizing effect of the examined patterns of stimulation (F_{PD}=4133.569, p<.0001 and F_{OCD}=2577.668, p<.0001). Stimulation conditions that do not share the same letter are significantly different (p<.01, *post-hoc* analysis).

optimal site of 130Hz regular stimulation in PD (Guo et al. 2013, Herzog et al. 2004); second, they highlight a further correlation of locations of oscillatory activity at the dorsolateral STN with the optimal desynchronizing effect of alternative patterns of DBS for PD, including low-frequency irregular stimulation; and, third, they point to a possible correlation of the principal model outcome measure, the variance of the invariant density, with clinical effectiveness of stimulation, since values of this measure are proven to be lower at the dorsolateral oscillatory region of the STN that has been consistently correlated with the best clinical outcome of STN-DBS for PD (Guo et al. 2013, Herzog et al. 2004), as well as at sites having been verified intra-operatively to yield the optimal therapeutic window.

Remarkably, clinical effectiveness of low-frequency STN-DBS on axial parkinsonian symptoms might not be sustained over time (Sidiropoulos and Moro 2014), while the therapeutic effect of DBS for neuropsychiatric disorders manifests to the full extent only over a period of weeks to months (Bourne et al. 2012, Kuhn et al. 2010, Lujan and McIntyre 2012). Lourens et al. (2015) have recently proved, by means of a model describing the STN - GPe network dynamics, that spike-timingdependent plasticity (STDP) stabilizes the desynchronized neural activity in the healthy state and that this stabilizing effect of STDP may favor the use of alternative stimulation protocols designed to induce neuronal desynchronization, in terms of both short- and long-term clinical effectiveness. In view of this evidence, and given the fact that the model-based outcome measure proposed in our study is a quantity directly related to the desynchronizing effect of temporally alternative patterns of stimulation, the same measure may also reliably reflect short- and long-term clinical effectiveness. Thus, high and lowfrequency irregular patterns of STN-DBS for advanced PD and treatment-refractory OCD, that, according to the results of our study, have been associated with a significantly stronger desynchronizing effect compared with standard STN-DBS, may also be associated with sustained clinical effectiveness over both short and long time scales, due to the existence of STDP.

5.3.5 Disorder-Specific Desynchronizing Effect of Stimulation

Comparing the optimal alternative patterns, irregular patterns significantly outperformed low-frequency periodic stimulation interrupted by bursts of pulses (p<.0001, two-sample t-test) in about 69% of the total simulations in case of PD and 46% of the total simulations in case of OCD

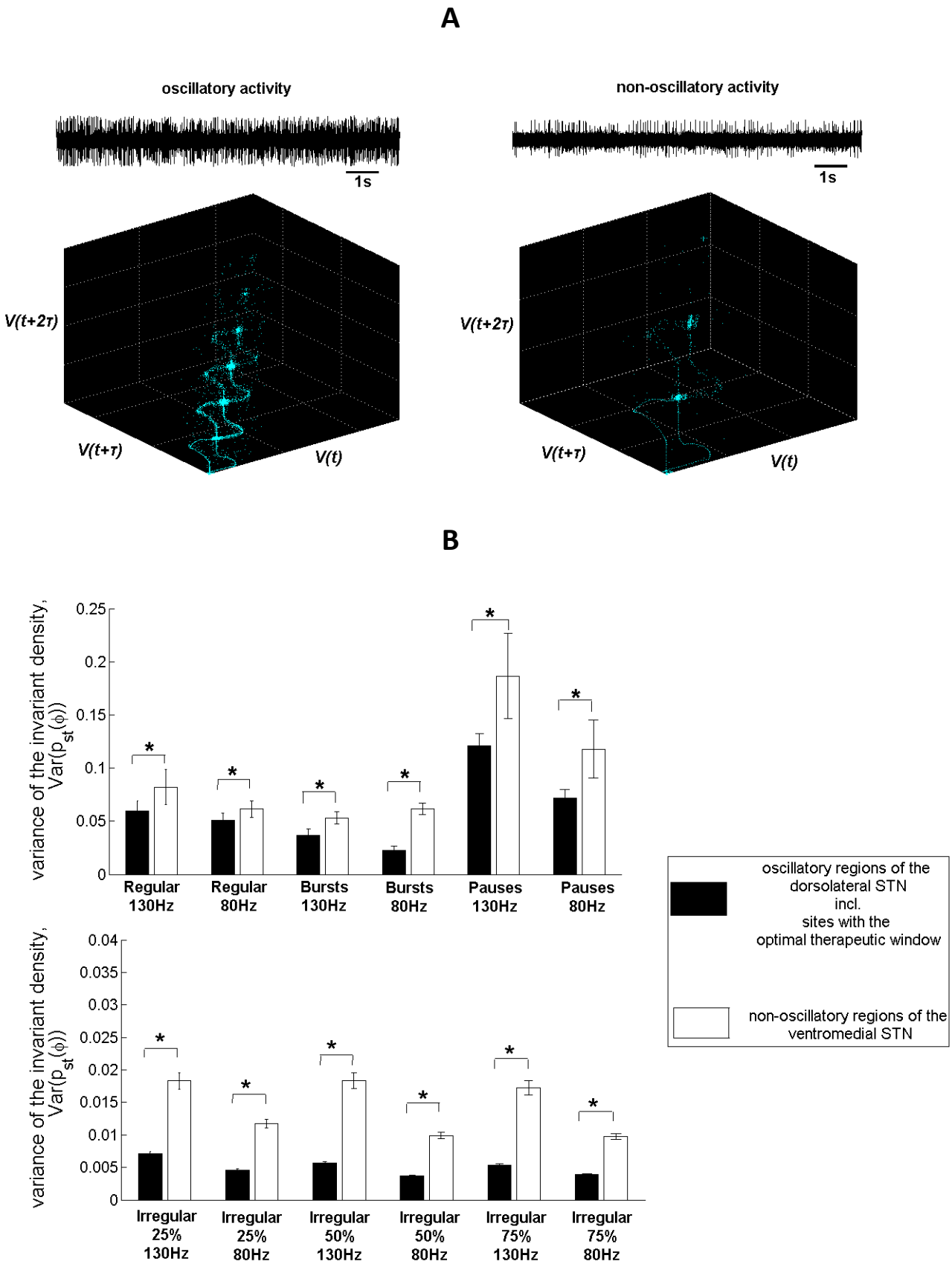


Figure 5.7. Dependence of the desynchronizing effect of the examined patterns of stimulation on locations of oscillatory activity in the STN of patients with PD. (A) Oscillatory regions were discriminated from non-oscillatory regions by means of the pattern of the attractor reconstructed in a three-dimensional phase space from the filtered spiking activity, using time delay, $\tau = 1$ and embedding dimension, $d = 3$. In this particular example, neuronal activity was recorded at 'Posterior, left STN - case 8'. (B) Assessment of the mean ± standard error mean variance of the invariant density, $\mathrm{Var}(p_{st}(\phi))$, based on a total of 30 recordings of oscillatory activity at the dorsolateral STN, incl. sites with the optimal therapeutic window, and a total of 30 recordings of non-oscillatory activity at the ventromedial STN, acquired during eight DBS interventions for PD, revealed a significantly stronger desynchronizing effect of each examined pattern of stimulation at oscillatory regions of the dorsolateral sensorimotor STN, incl. sites with the optimal therapeutic window, compared with non-oscillatory regions of the ventromedial limbic STN (* p<.0001, two-sample t-test).

(example illustrated in figure 5.5C). In the remaining 31% of the total simulations in PD and 54% of the total simulations in OCD low-frequency periodic stimulation interrupted by bursts of pulses was significantly more efficient than at least one of the irregular patterns of stimulation for $\beta \leq 5$ (p<.001, two-sample t-test) (example illustrated in figure 5.5A). Interestingly, standard DBS was associated with a significantly stronger desynchronizing effect in PD compared with OCD (p<.0001, two-sample t-test). Results also underscored a more favorable response profile of low-frequency periodic stimulation compared with standard stimulation (p<.0001, *post-hoc* analysis) (figure 5.6), that was, however, more pronounced in case of OCD (p<.0001, two-sample t-test). High-frequency periodic stimulation interrupted by bursts of pulses outperformed low-frequency periodic stimulation in PD (p<.0001, *post-hoc* analysis), but both patterns yielded an equivalent desynchronizing effect in case of OCD (p>.05, *post-hoc* analysis). Notably, high- and low-frequency stimulation interrupted by long pauses were the alternative patterns associated with the weakest desynchronizing effect in both pathologic conditions (figure 5.6). Nonetheless, while in case of PD these patterns were significantly less efficient than standard stimulation (p<.0001, *post-hoc* analysis) (figure 5.6A), the reverse held true in case of OCD (p<.01, *post-hoc* analysis) (figure 5.6B). Thus, in OCD, all alternative patterns of stimulation proved to exert a stronger desynchronizing effect on neuronal activity compared with standard DBS. Noteworthily, however, the relative desynchronizing effect of the aforementioned patterns proved primarily to be neural activity-specific, in both PD and OCD, as previously stated (figure 5.5).

5.3.6 Limited Suitability of the Lyapunov Exponent for the Discrimination of Desynchronization Scenarios

Figure 5.8A illustrates the desynchronizing effect of the examined patterns of stimulation in PD based on the use of the Lyapunov exponent, λ. Repeated measures ANOVA corroborated the presence of statistically significant differences in the mean desynchronizing effect of the examined patterns of stimulation (F=1564.173, p<.0001). In particular, similar to the results obtained through the employment of the invariant density measure (figure 5.6), high- and low-frequency stimulation interrupted by long pauses proved to exert a significantly weaker desynchronizing effect on neuronal activity (indicated by lower positive values of the Lyapunov exponent) compared with standard stimulation (p<.0001, *post-hoc* analysis). Most importantly, however, discrimination between the desynchronizing effect of patterns derived based on other probability distributions (including irregular stimulation with 25% and 50% temporal variability or stimulation characterized by bursts) and the desynchronizing effect of high-frequency periodic stimulation was not possible through the employment of the Lyapunov exponent (p>.05, *post-hoc* analysis). This equivalent desynchronizing effect on neuronal activity may be considered as a rather implausible scenario, since in no way does it reflect the observed qualitative change of the stochastic kernel function upon application of alternative patterns of stimulation (figures 5.9,

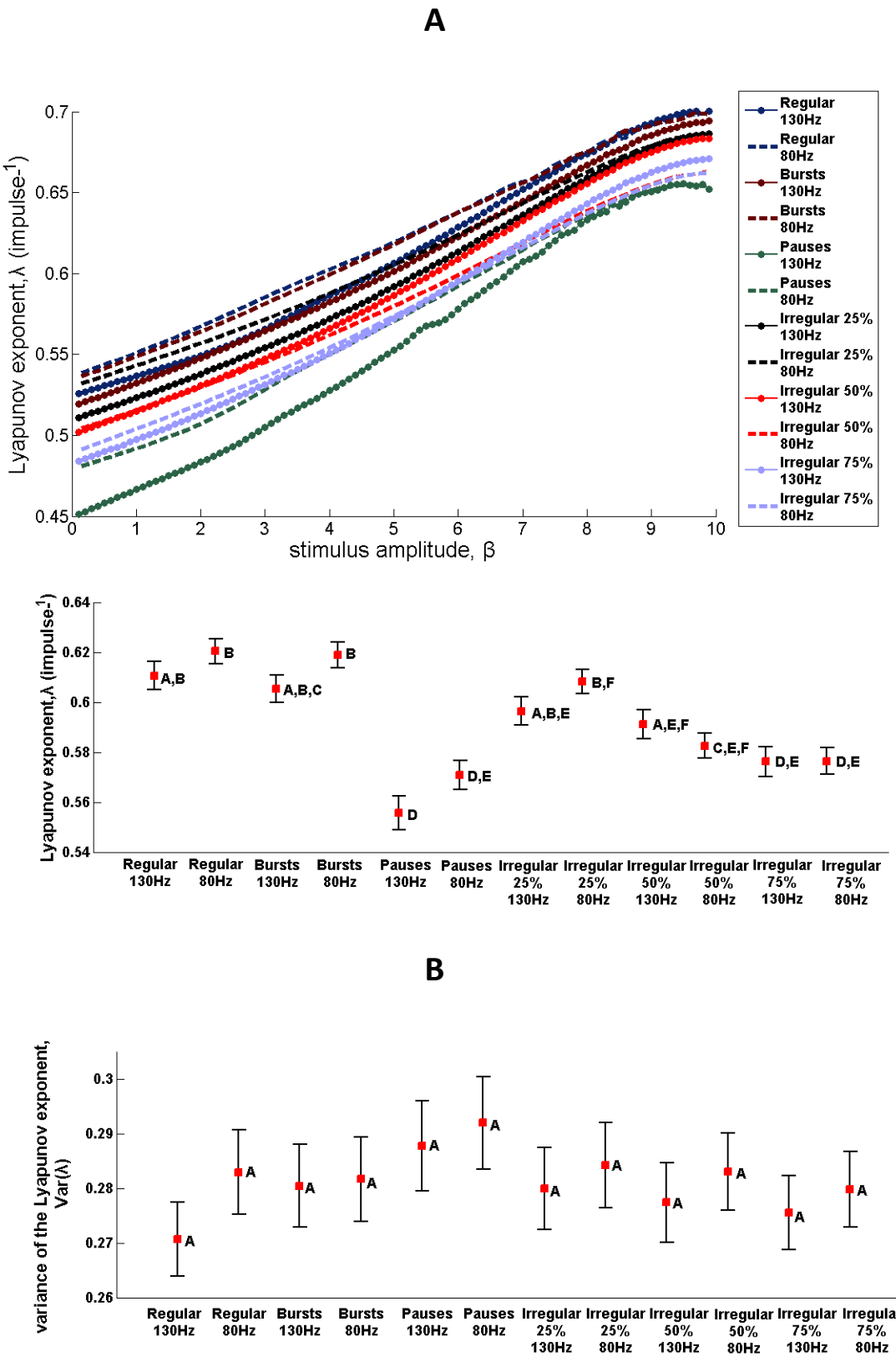


Figure 5.8. Evaluation of the Lyapunov exponent, λ , as an outcome measure for the assessment of the desynchronizing effect of the examined patterns of stimulation in PD. (A) The upper panel displays the value of the Lyapunov exponent, λ , for each pattern of stimulation, as a function of stimulus amplitude, β, and averaged across the dataset acquired during STN-DBS for PD. The lower panel depicts the respective mean ± standard error mean Lyapunov exponent, λ . Higher positive values of the Lyapunov exponent, λ , indicate a stronger desynchronizing effect of stimulation. *Post-hoc* analysis revealed no significant differences between the effect of low-frequency periodic stimulation and high-frequency periodic stimulation (p>.05), irregular stimulation with 25% and 50% temporal variability and high-frequency periodic stimulation (p>.05) or stimulation characterized by bursts and high-frequency periodic stimulation (p>.05). Stimulation conditions that do not share the same letter are significantly different (ANOVA: F=1564.173, p<.05). (B) No significant differences between the effect of the examined patterns of stimulation were identified by means of the variance of the Lyapunov exponent, *Var(λ)* (ANOVA: F=80.157, p>.05).

5.10). Similar conclusions with respect to the limited suitability of the Lyapunov exponent for characterizing differences between distinct synchronization scenarios corresponding to the application of distinct patterns of stimulation have been derived in Hata et al. (2010). In the current analysis, however, contrary to the conclusions in Hata et al. (2010), neither the variance of the Lyapunov exponent proved to be an appropriate outcome measure for discriminating between the desynchronizing effect of the examined patterns of stimulation (F=80.157, p>.05) (figure 5.8B).

5.4. Discussion

5.4.1 Significance and Clinical Implications

Closed-loop neuromodulation is emerging as one of the most revolutionary scenarios in the continuously evolving field of DBS (Gross and McDougal 2013, Herron et al. 2015, Widge and Moritz 2014). In this framework, model-based control systems are a powerful means for determination of optimal feedback parameters (Schiff 2010; 2012, Little and Brown 2012, Tass et al. 2003) and identification of novel stimulation protocols (Feng et al. 2007(a); b), Wilson and Moehlis 2014, Nabi et al. 2013, Danzl et al. 2009, Gorzelic et al. 2013, Iolov et al. 2013, Lourens et al. 2015). In the majority of the respective published approaches, minimum energy desynchronizing control of neuronal activity has been the common touchstone. In line with these indications, in this work, we employed methods from stochastic nonlinear dynamics in order to provide deeper insights into the most effective patterns of subthalamic DBS for advanced PD and treatment-refractory OCD, subsequently having the potential to be incorporated in an energy- and therapeutically-efficient closed-loop neuromodulation system. To this end, the fact that the STN is currently used as an anatomical target during DBS for both pathologic conditions (Williams et al. 2010, Hamani et al. 2014) merged with one of the hypotheses on the mechanisms of action of standard and alternative patterns of STN-DBS at a local level (Carlson et al. 2010, Hauptmann and Tass 2006, Rubin et al. 2012, Feng et al. 2007(a);(b), Adamchic et al. 2014) allowed for the development of a common modeling approach. Respectively, we elaborated a stochastic dynamical model having been previously designed to support clinical decision making during STN-DBS surgery. Throughout this chapter, we provided evidence that the fundamental strength of the proposed stochastic model lies in its realistic substructure: not only did we allow for global nonlinear coupling, but we also incorporated the effect of common and independent noise sources and considered the phase dependence of common noise with respect to each particular MER. Likewise, parameters of the model were estimated on the basis of the recorded neural activity. Upon constructing the stochastic model, the variance of the invariant density was employed as a measure inversely related to the desynchronizing effect of each examined pattern of stimulation. A quantitative comparison of the differential effect of stimulation patterns was thereby

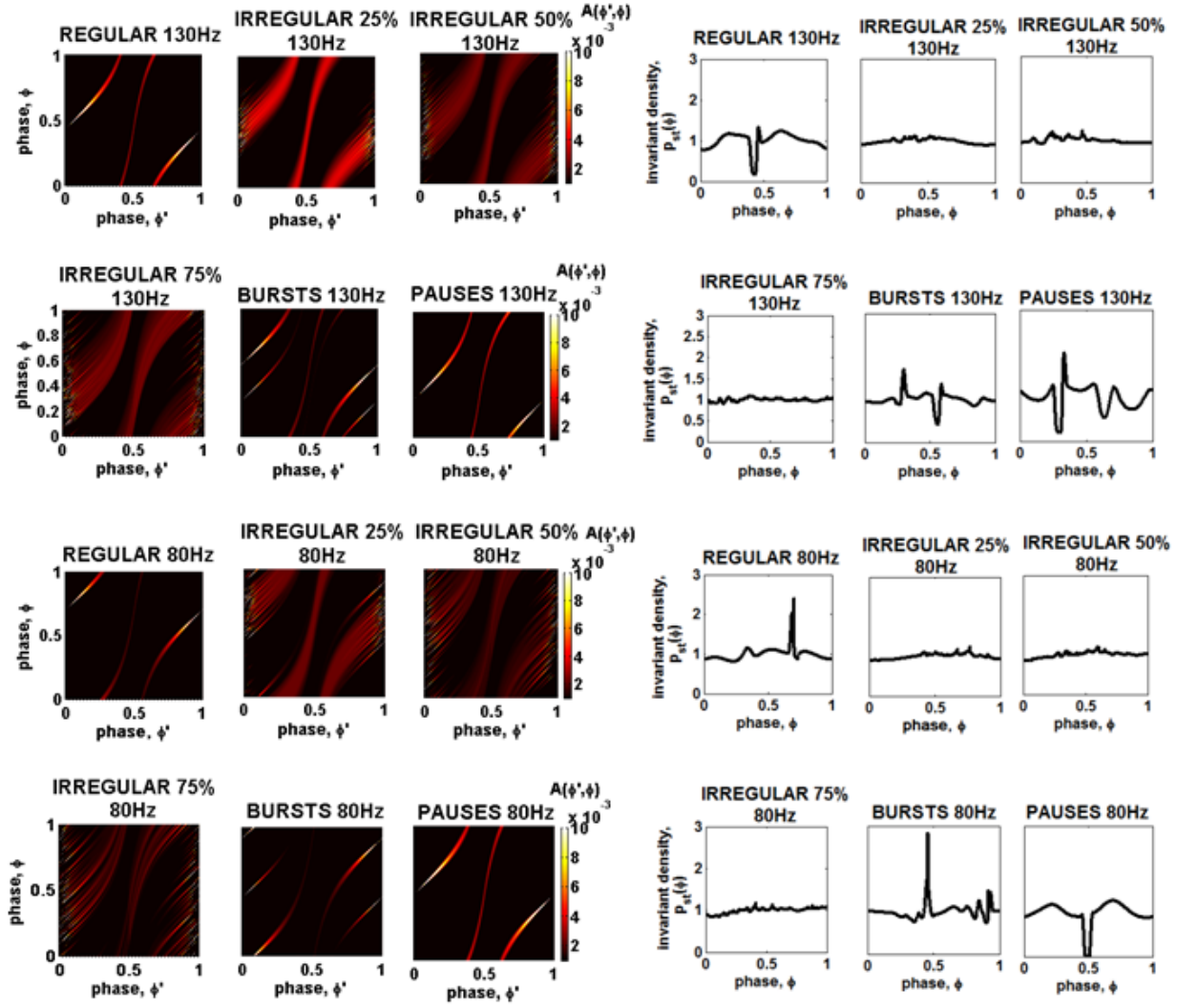


Figure 5.9. Stochastic kernels (left) and respective invariant densities (right) derived by fitting the phase model to a MER acquired at 'Lateral -2.852 mm, right STN - case O5', during STN-DBS for OCD, and simulating application of the 12 patterns of stimulation with stimulus amplitude β=0.5. According to the simulations, high- and low-frequency irregular patterns of stimulation exerted the strongest desynchronizing effect on neuronal activity, as reflected in the intense form of the respective stochastic kernels, as well as the low variance of the respective invariant densities.

straightforward and reliable. On the contrary, application of the Lyapunov exponent as an alternative variable reflecting neuronal desynchronization dynamics failed to be adequately informative. Most importantly, the results highlighted a possible correlation between the invariant density measure and clinical effectiveness of stimulation.

Our results emphasized the superior efficiency of high (130Hz) - and low (80Hz) - frequency irregular patterns of stimulation, and low-frequency periodic stimulation interrupted by bursts of pulses, compared with standard stimulation (regular, 130Hz) and distinct alternative patterns, including high- and low-frequency stimulation interrupted by long pauses, low-frequency periodic stimulation and high-frequency stimulation interrupted by bursts of pulses. Importantly, this particular outcome was not disorder-specific, while the superior efficiency of irregular patterns of stimulation was, moreover, not neural activity-specific. Consistently with these results,

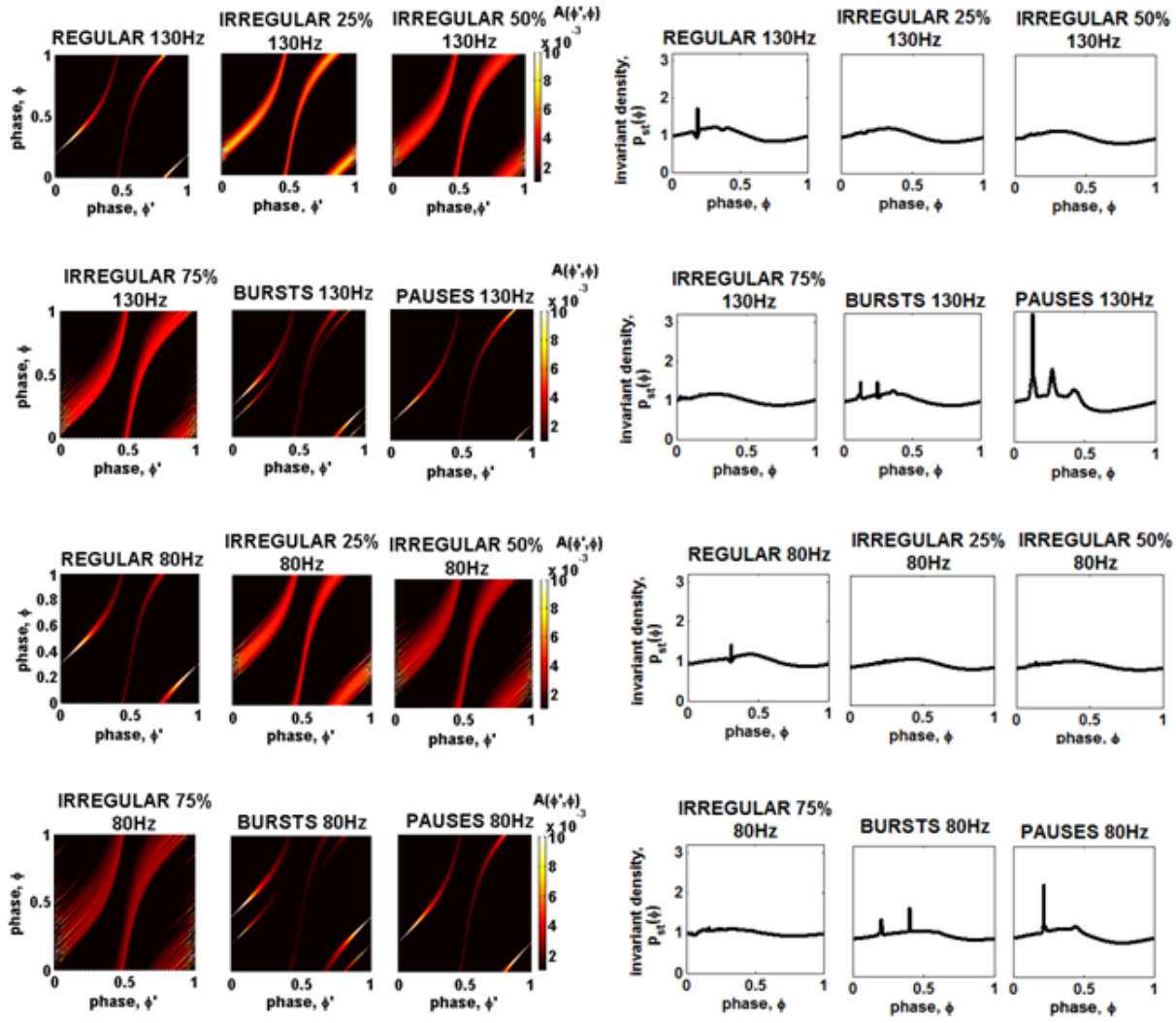


Figure 5.10. Stochastic kernels (left) and respective invariant densities (right) derived by fitting the phase model to a MER acquired at 'Anterior -3mm, right STN - case 2', during STN-DBS for PD, and simulating application of the 12 patterns of stimulation with stimulus amplitude β=0.5. According to the simulations, low-frequency irregular patterns of stimulation and low-frequency periodic stimulation interrupted by bursts of pulses exerted the strongest desynchronizing effect on neuronal activity, as reflected in the intense form of the respective stochastic kernels, as well as the low variance of the respective invariant densities.

Birdno *et al.* (2012) and Brocker *et al.* (2013) suggested that neither bursts nor irregularity *per se* are correlated with decreased clinical effectiveness of high-frequency thalamic and subthalamic DBS for essential tremor and advanced PD, respectively. Additionally, in a short communication, Baker *et al.* (2011) underlined the effectiveness of low (80Hz) - frequency pallidal stimulation delivered in a regular bursting pattern in ameliorating bradykinesia in the non-human primate model of PD. Our work adds to the aforementioned studies by extending their validity to low-frequency subthalamic DBS for advanced PD and by offering insights into the efficiency of alternative patterns of STN-DBS for treatment-refractory OCD. Very interestingly, the desynchronizing effect of the examined patterns of stimulation in PD proved to be optimal at the dorsolateral oscillatory region of the STN. Overall, these results may be of particular importance for the development of energy- and therapeutically-efficient closed-loop DBS systems.

5.4.2 Disorder- and Neural Activity-Specific Effect of Stimulation

Contrary to Brocker *et al.* (2013) and Kuncel *et al.* (2012), Birdno *et al.* (2012) reported that high-frequency stimulation characterized by pauses is significantly less effective than regular stimulation for tremor suppression. This suggestion is corroborated and extended by our study, wherein both high- and low-frequency stimulation interrupted by long pauses were associated with a weaker desynchronizing effect compared with standard stimulation in PD. Nevertheless, in case of OCD we could not reach a similar conclusion. Accordingly, stimulation characterized by pauses proved to exert a significantly stronger desynchronizing effect on neuronal activity compared with standard DBS in OCD, particularly if being delivered in a low-frequency mode. Interestingly, Gazit *et al.* (2015) have recently suggested that low-frequency stimulation characterized by pauses may alleviate symptoms more effectively than regular stimulation in an animal model of a neuropsychiatric disorder. Perhaps more importantly, all alternative patterns of stimulation considered in our approach proved to be associated with a stronger desynchronizing effect compared with standard DBS in OCD. In addition, standard DBS was associated with a significantly stronger desynchronizing effect in PD compared with OCD. Conversely, low-frequency periodic stimulation proved to be more efficient in OCD compared with PD. This disorder-specific effect of certain stimulation pattern characteristics, revealed by the computational model, may be rooted in a dissimilar profile of neuronal activity in the two pathologic conditions, i.e. significantly lower discharge rates and 'lower'- frequency oscillations in treatment-refractory OCD compared with advanced PD (Piallat et al. 2011, Welter et al. 2011).

Apart from the aforementioned general conclusions, we ought to highlight the fact that, with the exception of irregular patterns, the relative desynchronizing effect of the examined alternative patterns of stimulation with respect to standard DBS was substantially dependent on the recorded neural activity. Thereupon, we implicitly suggest that in any closed-loop DBS system configuration, maximal information about the underlying neuronal dynamics captured by real-time recordings should be carefully considered, before proceeding to define optimal stimulation pattern characteristics.

5.4.4. Insights into the Efficiency of Low-Frequency Periodic Stimulation

Evidently, our approach underscores the superior efficiency of low-frequency periodic stimulation to the efficiency of standard stimulation in both PD and OCD, albeit - as already mentioned - more prominently in the latter disorder. Clinical application of low-frequency periodic stimulation instead of its high-frequency counterpart has been a topic of controversy in the field of STN-DBS for PD over the last years (Sidiropoulos and Moro 2014). Though some clinical data seem to incline towards a similar effect of the two modes of stimulation on axial

(Sidiropoulos et al. 2013, Vallabhajosula et al. 2015) or distal symptoms (Tsang et al. 2012), some other studies suggest that a greater improvement of axial symptoms or involuntary movements, after the switch of stimulation frequency from 130 Hz to 80 Hz, may be possible, but also to a great extent patient-specific (Ricchi et al. 2012, Merola et al. 2013). Our modeling approach is rather reinforcing the latter suggestion, since it is, on the one hand, giving prominence to the efficiency of low-frequency periodic stimulation, and on the other hand pointing to a neural activity- and thus potentially patient-specific effect of temporally alternative patterns of STN-DBS. Most importantly, it provides novel evidence for an outstanding efficiency of low-frequency DBS for treatment-refractory OCD. Certain limitations, however, should be taken into consideration, as discussed in the next paragraph.

5.4.5 Study Limitations

One of the limitations of this study is rooted in the exclusion of the further hypotheses on the therapeutic mechanisms of action of STN-DBS that go beyond the hypothesis of the local desynchronizing effect (de Hemptinne et al. 2015, Li et al. 2012, Bahramisharif et al. 2015). Accordingly, an intriguing perspective would be related to the consideration of these assumptions that would in turn possibly provide more powerful clues for the degree of the efficiency of alternative patterns of stimulation. A related limitation refers to the fact that the stochastic model was not adapted to capture the neuronal interactions within the motor cortico–basal ganglia–thalamo–cortical circuit (Tsirogiannis et al. 2009) or within key pathways involved in the pathophysiology of OCD (Stathis et al. 2007). In this respect, the employment of a biophysically plausible, conductance-based model would probably be a more appropriate alternative approach for describing neuronal network dynamics and simulating neuronal responses to stimulation protocols (Feng et al. 2007(b), Rubin and Terman 2004). Importantly, however, the latter approach in the study of Feng *et al.* (2007(a); (b)) has led to similar conclusions regarding the higher efficiency of non-regular patterns of stimulation. In general, despite the aforementioned limitation, phase reduction remains a powerful method for describing the response dynamics of local neuronal populations, while its validity is being extended beyond the supra-threshold regime to account for the dynamics of neuronal bursting activity that constitutes a hallmark of PD and OCD pathophysiology (Piallat et al. 2011, Sherwood and Guckenheimer 2010, Mauroy et al. 2014). Another challenge for the presented modeling approach would be to assess the desynchronizing effect of individualized gamma frequencies (Tsang et al. 2012) and to allow for the clinically used values of stimulus amplitude and stimulus pulse width, as well as the role of electrode polarity, in view of the fact that these parameters are especially critical to the clinical effectiveness of DBS (Volkmann et al. 2006). Last, on account of the heterogeneous nature of PD and OCD symptoms (Summerfeldt et al. 1999, Feng et al. 2015), part of future research work

should be directed towards the determination of optimal pattern characteristics for distinct phenotypes of these disorders.

5.5. Conclusion

Temporally alternative patterns of DBS with the potential to generate maximal clinical benefit at the lowest possible power consumption and reduce stimulation-related complications are being intensively investigated over the last years. In this chapter, we provided model-based indications for the optimal alternative patterns of STN-DBS for treatment-refractory OCD and extended the validity of previous reports on the efficiency of temporally non-regular DBS for advanced PD. Accordingly, on grounds of a data-driven stochastic dynamical model, we highlighted the pivotal role of high-, and, most importantly, low-frequency variability, as well as of low-frequency bursts of pulses in the efficiency of STN-DBS for both pathologic conditions. In PD, optimal results were achieved at the dorsolateral oscillatory region of the STN. Moreover, we provided indications for a possible correlation of the principal model-based outcome measure, the invariant density, with clinical effectiveness of stimulation. Taking the modeling approach one step further, our key priority should be the clinical validation of these predictions, potentially in patient populations undergoing implantable pulse generator (IPG) replacement, since temporary connection to the DBS electrode during this surgical procedure has been proven to provide advantageous conditions for the analysis of novel stimulation protocols (Birdno et al. 2012).

6

Algorithmic Design of a Therapeutically- and Energy-Efficient Closed-Loop Deep Brain Stimulation System for Parkinson's Disease and Obsessive-Compulsive Disorder

Approaches using closed-loop stimulation are inherently state dependent and require computational neurostimulation.

M Bikson et al. (2015)

Abstract

Objective. We elaborate on the algorithmic aspects of a closed-loop subthalamic nucleus (STN) deep brain stimulation (DBS) system for advanced Parkinson's disease (PD) and treatment-refractory obsessive-compulsive disorder (OCD), ensuring optimal performance in terms of both efficiency and selectivity of stimulation, as well as in terms of computational speed. *Approach.* Relying upon a series of methods robust to the presence of measurement noise, we first assess the presence of significant nonlinear coupling between beta and high-frequency subthalamic neuronal activity, as a biomarker for feedback control in the proposed closed-loop neuromodulation scheme, and further present a strategy, incorporating the application of a phase-reduced bursting neuron model and a derivative-free optimization algorithm, through which optimal stochastic patterns and parameters of stimulation for minimum energy desynchronizing control of neuronal activity are being identified. Simulations are being performed utilizing microelectrode recordings (MERs) acquired during 8 and 8 STN-DBS surgical interventions for PD and OCD, respectively. *Main Results.* Cross-frequency

coupling proves to be a consistently appropriate biomarker for feedback control in case of PD, but may display subject-specific applicability in case of OCD. In light of our previous report pointing to a possible correlation of the principal model-based outcome measure with clinical effectiveness of stimulation in PD, we demonstrate the ability of the presented modeling approach to identify, at a relatively low computational cost, stimulation settings associated with a significantly higher efficiency and selectivity compared with stimulation settings determined during post-operative clinical management of patients with PD. The validity of these results is further corroborated in case of treatment-refractory OCD. *Significance.* Together, our data provide strong evidence for the applicability of computational neurostimulation to real-time, closed-loop DBS systems.

6.1. Introduction

As reported in chapter 1, in addition to appropriate patient selection and anatomical target determination (Widge et al. 2015), the outcome of DBS may be strongly influenced by the quality of post-operative clinical management, i.e. the adjustment of stimulation parameters and the selection of the optimal contact, usually over periods of weeks to months (Benabid et al. 2009, Volkmann et al. 2006). Apart from being considerably time consuming, this trial-and-error procedure may not necessarily yield the optimal trade-off between maximal therapeutic benefit and minimal stimulation-induced side-effects (Kuncel and Grill 2004). Moreover, it fails to keep pace with the fact that movement and neuropsychiatric disorder symptoms may fluctuate over significantly shorter time-scales of seconds to days. Chronically, the open-loop nature and monomorph pattern of conventional high-frequency stimulation appears to favor tolerance/habituation phenomena, while being associated with a maximal rate of power consumption (Carron et al. 2013).

Against this background, closed-loop neuromodulation is emerging as a more reliable alternative and one of the most promising breakthroughs in the field of DBS (Metman and Slavin 2015, Hariz et al. 2013, Rosin et al. 2011) (figure 6.1). In an optimal closed-loop-stimulation scenario, delivery of maximally efficient DBS patterns is adjusted to the fast dynamics of movement and neuropsychiatric disorder symptoms through utilization of specific biomarkers that capture the patient's clinical state in real time (Rise and King 1998). This would, in turn, insure minimal energy consumption and reduce the physical size of the battery (Grill 2015), the frequency of generator replacement surgery, the concomitant risk of hardware infection (Boviatsis et al. 2010, Pepper et al. 2013), or the rate of recharging procedures. It would moreover be associated with significant savings in clinical resources (Gross and McDougal 2013, McIntosh et al. 2003). Principally, any algorithm designed for a maximally efficient closed loop DBS system shall conceptually satisfy two core specifications (Afshar et al. 2013): the reliable assessment of optimal biomarkers for feedback control and the

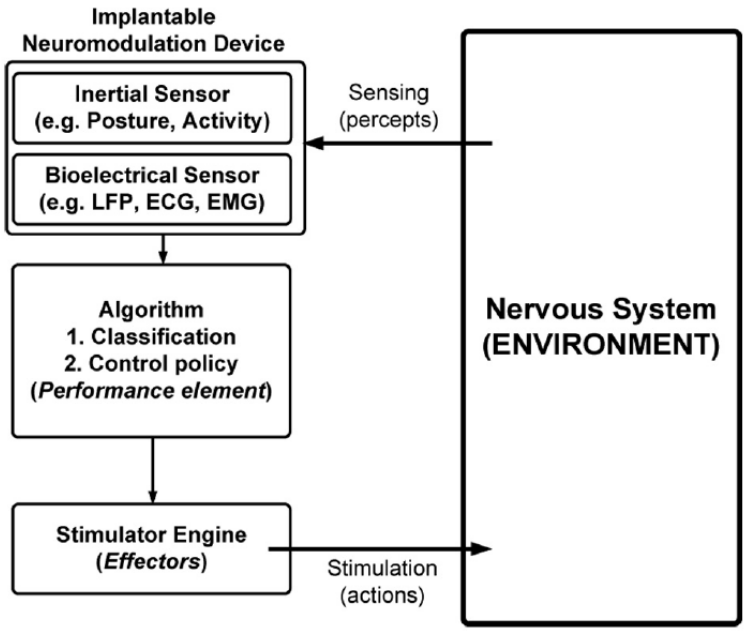


Figure 6.1. Simplified model of a closed-loop neuromodulation system (adapted from Afshar et al. 2013).

identification of alternative stimulation protocols that may be more therapeutically- and energy-efficient compared with the conventional pattern of stimulation (Little and Brown 2012, Feng et al. 2007(a)).

One of the proposed biomarkers for closed-loop DBS for PD, recordable directly from the DBS electrode and used as a surrogate of pathological neuronal synchronization, is the subthalamic LFP beta activity (Brittain et al. 2014), in light of strong evidence that stimulation-induced suppression of pathological beta oscillatory activity correlates with improvement in both bradykinesia and rigidity (Kuhn et al. 2008, Eusebio et al. 2010, Priori et al. 2013). Moreover, analysis of subthalamic LFPs may be extended to the chronic condition (Rosa et al. 2010). Feedback controlled stimulation based on LFP beta power has been proven to be clinically more effective than both standard and random intermittent stimulation, and has been correlated to lower energy requirements in a pilot clinical study (Little et al. 2013). Nevertheless, the presence of large stimulation artifacts in LFP recordings, the relatively low complexity dynamics captured by this signal, the normal phenomenon of suppression of LFP beta-band activity prior to or during movement and the absence of a reported positive correlation between treatment-induced suppression of beta oscillatory activity in the STN and the improvement in tremor or dyskinesias point to the need for exploring more sensitive biomarker approaches (Starr and Ostrem 2013, Little and Brown 2012). One alternative is the long-term recording of cortical local field potentials (Ryapolova-Webb et al. 2014) using the Activa ® PC + S neurostimulator (Medtronic, Inc., Minneapolis, MN) (Afshar et al. 2013, Rouse et al. 2012), a bidirectional investigational device that provides the possibility of both therapeutic stimulation and LFP recording (Sun and Morrell 2014). This approach has been motivated by the fact that cortical LFPs may be recorded with minimal intervention and stimulation artifact, and may effectively

capture the degree of pathological neuronal synchronization in PD, reflected in beta phase - gamma amplitude coupling in the primary motor cortex (M1) (de Hemptinne et al. 2013, Starr and Ostrem 2013). Besides, employment of cortical recordings as a control signal in closed-loop stimulation has been correlated to increased clinical effectiveness compared with standard open loop stimulation in a pre-clinical proof-of-concept study (Rosin et al. 2011). Analysis of electromyography (EMG) signals during periods of movement and rest constitutes a further significant possibility provided by the Activa PC + S neurostimulator (Ryapolova-Webb et al. 2014). A related approach to non-invasive feedback control has been suggested by a pilot clinical study conducted by Basu *et al* (2013), wherein surface EMG in conjunction with an appropriately designed algorithm were used in order to predict the onset of tremor during time intervals of no stimulation. Meanwhile, novel neural probes offering the capability of concomitant DBS and recording are being gradually introduced (Lai et al. 2012, Stypulkowski et al. 2013). In light of evidence that the therapeutic mechanism of stimulation may be partially explained by neurotransmitter release, 'smart' DBS systems with electrochemical feedback may represent a further appealing option for closed-loop neuromodulation (Behrend et al. 2009, Grahn et al. 2014, Farina et al. 2014, Jackowska and Krysinski 2013, Gross and McDougal 2013). Within this framework, application of the Wireless Instantaneous Neurochemical Concentration Sensing System (WINCS) that incorporates both in vivo fast-scan cyclic voltammetry (FSCV) and amperometry for real-time detection of dopamine, adenosine, and serotonin is being investigated (Van Gompel et al. 2010, Parpura et al. 2013). Integration of carbon nanofiber nanoelectrodes in this system may allow for improved selectivity and sensitivity compared with traditional carbon fiber microelectrodes (Zhang et al. 2013, Koehne et al. 2011).

At the same time, even more vigorous predictive biomarkers of PD and OCD pathophysiology are being intensively highlighted, including *nonlinear coupling* across multiple frequency bands in the basal ganglia and in cortical structures (Lopez et al. 2010, Yang et al. 2014, de Hemptinne et al. 2013, Shimamoto et al. 2013, Connolly et al. 2015(a), Bahramisharif et al. 2015). Assessment of the latter biomarker has largely relied on the evaluation of phase-amplitude coupling by means of the Hilbert transform (Tort et al. 2010). Remarkably however, the respective phase reconstruction method may be characterized by a high level of susceptibility to *measurement noise* (Sun et al. 2008). We therefore suggest that by eliminating the sensitivity to measurement noise (Sun et al. 2008, Rossberg et al. 2005) and by employing phase reconstruction-free methods (Gottwald and Melbourne 2009) in an automated closed- loop DBS system, the reliable assessment of cross-frequency interactions may be substantially facilitated.

Meanwhile, model-based control policies for the determination of *temporally alternative stimulation protocols* are being investigated (Wilson and Moehlis 2014, Danzl et al. 2009, Liu et al. 2011, Nabi et al. 2013, Lourens et al. 2015, Gorzelic et al. 2013, Dasanayke and Li 2015, Iolov et al. 2014, Tass and Hauptmann 2007, Tass et al. 2003, Hauptmann and Tass 2010, Tukhlina et al. 2007, Montaseri

et al. 2015, Su et al. 2014), while a positive proof-of-concept has been recently provided for coordinated reset neuromodulation (Adamchic et al. 2014). Very interestingly, a common denominator across the majority of these approaches has been the *minimum energy desynchronizing control* of neuronal activity. The rationale behind this objective lies in indications that temporally alternative DBS waveforms hold the potential to drive the neuronal dynamics within the basal ganglia back to the normal desynchronized state (Feng et al. 2007(a), (b)), thereby outperforming the action of standard DBS waveforms, the mechanism of which has been principally attributed to the reinforcement-driven regularization of neural firing patterns in the vicinity of the stimulated nucleus (McConnell et al. 2012, Grill et al. 2004, Santaniello et al. 2015). Perhaps more importantly, the use of alternative stimulation protocols may be favored, in terms of both short- and long-term clinical effectiveness, by the stabilizing effect of spike-timing dependent plasticity (STDP) on the desynchronized neuronal activity (Lourens et al. 2015). In our previous analysis (chapter 5), we employed a data-driven stochastic dynamical model and provided evidence for a possible correlation of the primary outcome measure, a quantity inversely related to the desynchronizing effect of temporally alternative patterns of stimulation, with *clinical effectiveness* of stimulation in PD.

Relying upon the aforedescribed indications, in this study we elaborate on the algorithmic aspectst of a therapeutically- and energy-efficient closed-loop neuromodulation system for advanced PD and treatment-refractory OCD (figure 6.2). Specifically, we are first stating a series of methods robust to the presence of measurement noise (Rossberg et al. 2005, Gottwald and Melbourne 2009) that are employed in order to assess the presence of significant nonlinear coupling between beta and high-frequency subthalamic activity, as a biomarker for feedback control, and further suggest a model-based strategy through which optimal patterns and parameters of stimulation for minimum energy desynchronizing control of neuronal activity are being identified. We opt for a phase-reduced bursting neuron model (Sherwood and Guckenheimer 2010, Mauroy et al. 2014), given that increased neuronal bursting activity in the basal ganglia has been related to the pathophysiology of both PD and OCD (Piallat et al. 2011, Welter et al. 2011). Temporal patterns of stimulation are generated based upon a random (Poisson) process, since the desynchronizing and probably also the therapeutic effect of stochastic DBS waveforms has been previously proven to be significantly stronger compared with the effect of standard stimulation. Moreover, the efficiency of stochastic waveforms has been demonstrated to be robust against variations in neural activity and, therefore, possibly also against the non-stationary settings expected in clinical conditions. Determination of the precise optimal temporal pattern and parameters of stimulation is accomplished through the application of a derivative-free optimization algorithm (Custódio and Vicente 2007; Custódio et al. 2010), in view of the fact that the neural response to DBS parameters may be a complex, non-differentiable function (Feng et al. 2007(a)). Simulations are performed utilizing microelectrode recordings (MERs) acquired during 8 and 8 STN-DBS surgical interventions for PD and OCD, respectively. Finally, extending the results of our previous work, in this study, we attempt to provide

indications for a possible correlation of the principal model-based outcome measure, i.e. the invariant density of the simulated dynamical system, with clinical effectiveness of stimulation in treatment-refractory OCD. Overall, the results corroborate the ability of the presented modeling approach to identify stimulation settings associated with a significantly higher *efficiency* and *selectivity* compared with stimulation settings determined during post-operative clinical management of patients with PD or treatment-refractory OCD, while guaranteeing a relatively low computational cost.

6.2. Patients and Methods

6.2.1. Data Description

We used MER data acquired during 8 STN-DBS surgical interventions for advanced PD at Evangelismos General Hospital of Athens and 8 STN-DBS surgical interventions for treatment-refractory OCD at Grenoble University Hospital. This dataset was also used in our previous analysis (chapter 5). A total of 31 acceptable MER trajectories acquired during STN-DBS for PD and 12 acceptable MER trajectories acquired during STN-DBS for OCD was selected for off-line analysis. Preprocessing of each MER included its subdivision into three distinct neuronal populations: spiking activity acquired employing a five-point spike template (Wong et al. 2009), background unit activity reconstructed according to Moran *et al.* (2008), and local field potential (LFP) activity (1-300Hz). In order to keep pace with the proposed phase reduced bursting neuron model, following the assessment of the biomarker for feedback control, optimal patterns and parameters of stimulation were assessed only for sites at which bursting activity was recorded. A bursting or burst-like firing pattern of neuronal activity was identified as described in Steigerwald *et al.* (2008).

6.2.2. Assessment of Cross-Frequency Coupling as a Biomarker for Feedback Control

On grounds of an extensive body of evidence pointing to increased nonlinear coupling between beta and high-frequency activity in cortical and subcortical structures as a pathophysiological correlate in PD and OCD (Lopez et al. 2010, Yang et al. 2014, Connolly et al. 2015 (a), Bahramisharif et al. 2015), the beta-band-frequency (13-30Hz) envelope of the high-pass filtered (200-300Hz) LFPs or of the high-frequency signal component (300-500Hz) was first introduced as a biomarker for feedback control in the proposed closed-loop DBS scheme (figure 6.2). Analytically, the high-pass filtered signal was full-wave rectified, mean subtracted and downsampled to 1kHz. Subsequently, the derived signal was band-pass filtered at 13-30Hz by applying a complex-valued filter proposed by Rossberg *et al.* (2004). The robustness of this filter lies at its property to increase the signal to measurement noise ratio with respect to the complete dynamics of its impulse response. Moreover,

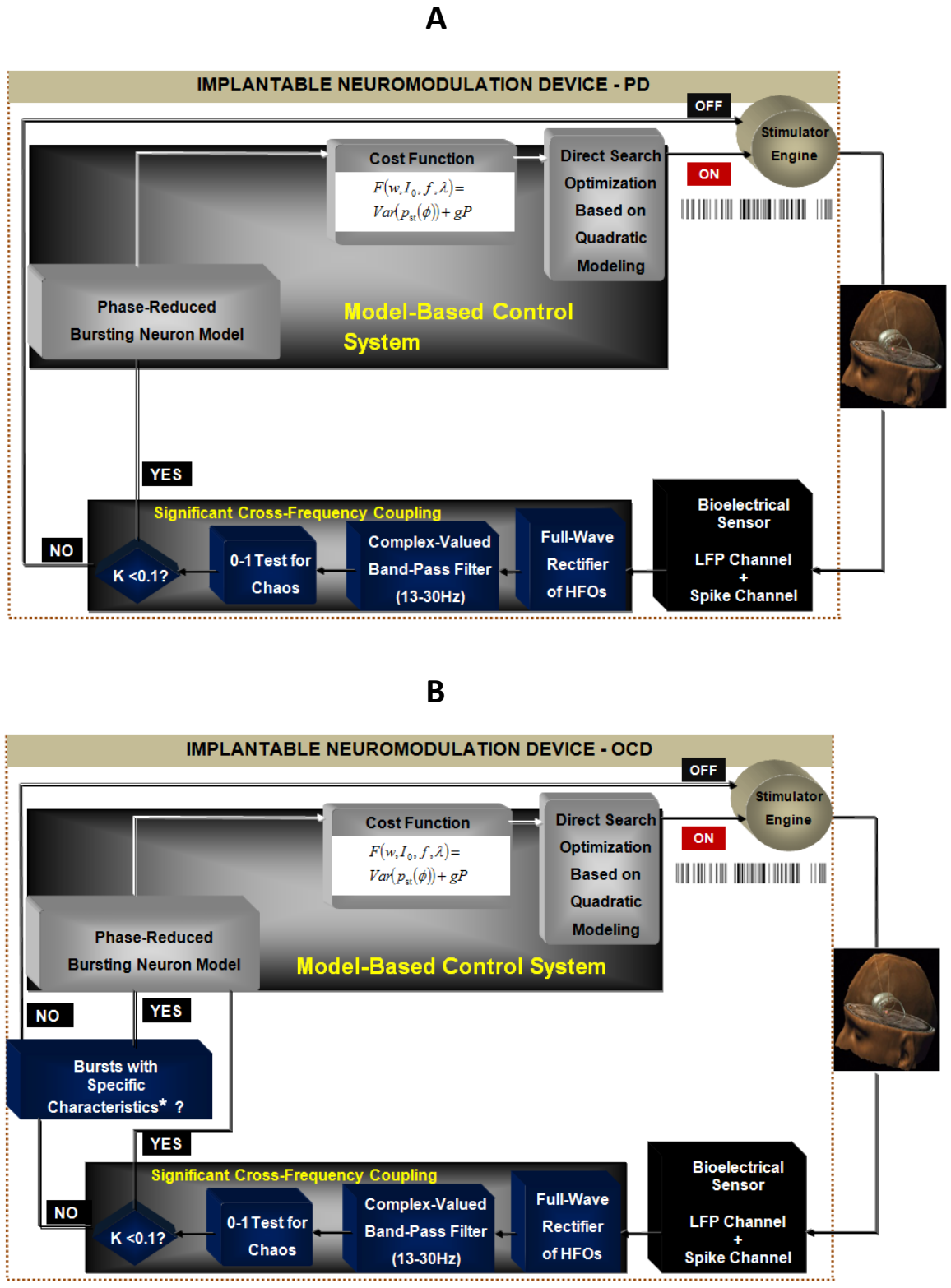


Figure 6.2. Schematic of the proposed closed-loop DBS system for (A) advanced PD and (B) treatment-refractory OCD. Applicability of cross-frequency coupling as a biomarker for feedback control in case of treatment-refractory OCD may be subject-specific. Accordingly, the presence of bursting neuronal activity was included as an alternative biomarker for feedback control in the respective closed-loop neuromodulation scheme. LFP: local field potential, HFOs: high-frequency oscillations; *short interburst interval and high intraburst frequency. Head model reproduced with permission from Inserm /Eric Bardinet, Jerome Yelnik and Luc Mallet.

the filter has been proven to cope with strong internal noise that constitutes a prominent characteristic of the recorded subthalamic neuronal activity.

Following the employment of the complex-valued filter, we applied the 0-1 test for chaos (Gottwald and Melbourne 2009) to a logarithmic transformation of the complex magnitude of the filter output in order to assess the presence of significant nonlinear coupling between beta and high-frequency activity in the STN of patients with PD or OCD (figure 6.3). In addition to being a phase reconstruction-free method for the determination of regular or chaotic dynamics in a deterministic dynamical system, the 0-1 test for chaos retains the advantage, over the traditional methods for detecting chaos (using the maximal Lyapunov exponent), of displaying reduced sensitivity to measurement noise (Gottwald and Melbourne 2005). Briefly, for the first n=1,…, $n_{\max}$=1000 samples of the input signal and N_c =100 values of c chosen randomly in the interval $(0,\pi)$ we evaluated the translation variables

$$p_c(n) = \sum_{j=1}^{n} V(j)\cos(jc) \quad \text{and} \quad q_c(n) = \sum_{j=1}^{n} V(j)\sin(jc) \tag{6.1}$$

where V is the amplitude of the input signal. Secondly, considering the presence of measurement noise, we quantified for $n \le \frac{n_{\max}}{10}$ the damped mean squared displacement of the translation variables, as follows

$$D_c^*(n) = M_c(n) - (EV)^2 \frac{1-\cos nc}{1-\cos c} + h \cdot (EV)^2 \sin\left(\sqrt{2}n\right), \tag{6.2}$$

where $M_c(n)$ is the mean squared displacement of the translation variables, EV is the expectation of V, while parameter h is optimized as described in the next paragraph. After computing the strength of correlation of $D_c^*(n)$ with linear growth, K_c, the outcome of the test, K_{t} , was given by

$$K_{\mathrm{t}} = median(K_c) \tag{6.3}$$

With respect to parameter determination, parameter h in (6.2) was defined based upon optimization of the outcome of the test across a subset of 12 MER trajectories in PD and 12 MER trajectories in OCD (figure 6.4A). We also used 1s (i.e. 1000 samples) of the input signal, since this value yielded the best trade-off between low computational cost and optimal outcome of the test (data not shown). In addition, $N_c = 100$ different values of c have been explicitly suggested to constitute an appropriate variable selection by Gottwald and Melbourne (2009).

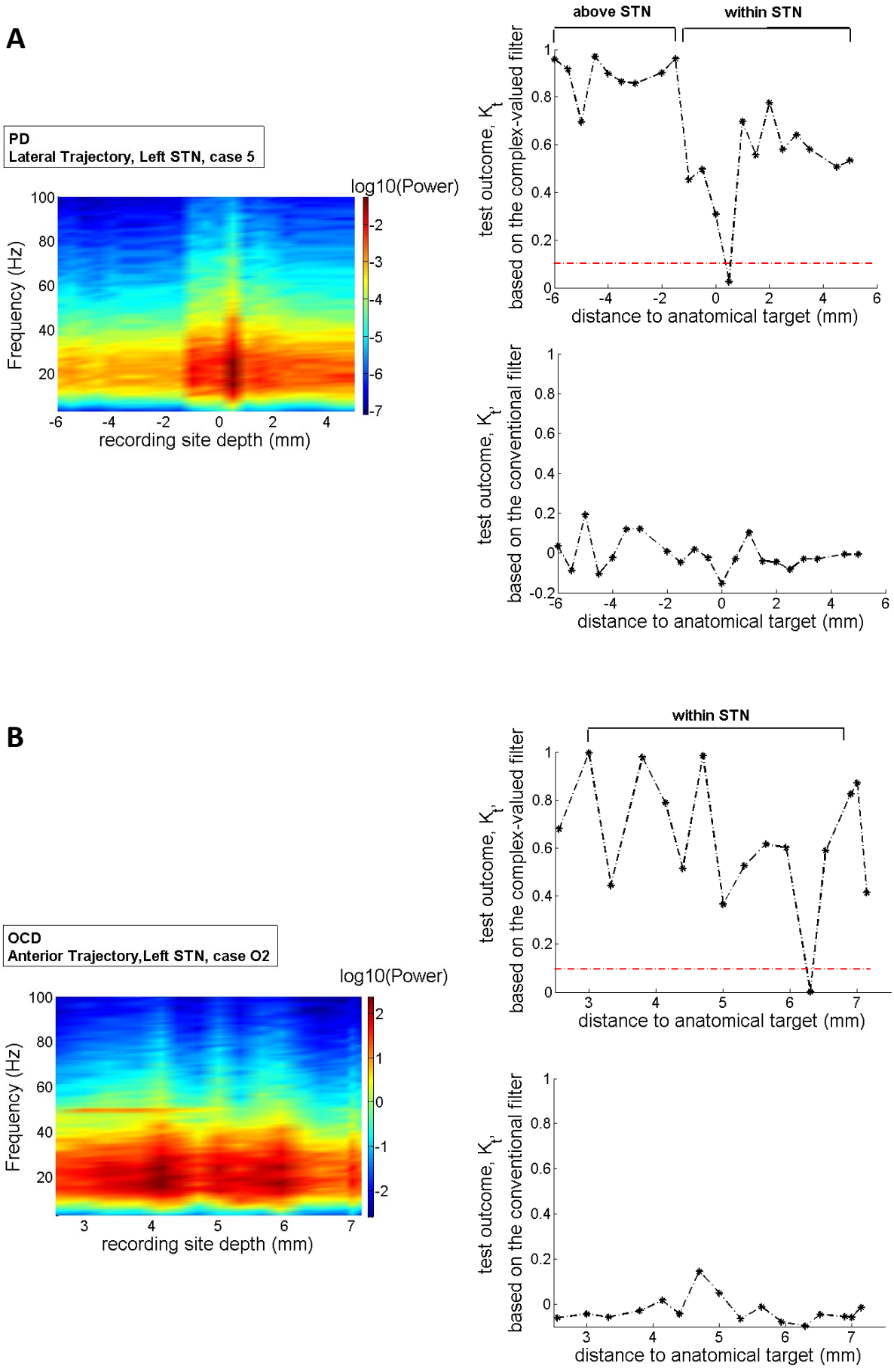


Figure 6.3: Exemplary results of the methodology applied for the assessment of cross-frequency coupling, as a biomarker for feedback control, in the STN of a patient with (A) PD and (B) OCD. Employment of the 0-1 test for chaos, following the application of the complex valued-filter proposed by Rossberg et al. (2004), singled out sites with significant cross-frequency coupling (test outcome < 0.1). On the contrary, following the application of a conventional, Butterworth band-pass filter, the 0-1 test for chaos did not discriminate sites with significant cross-frequency coupling from sites without. Figures on the left display the power spectrum of the filtered signals (13-30Hz) along each exemplary trajectory.

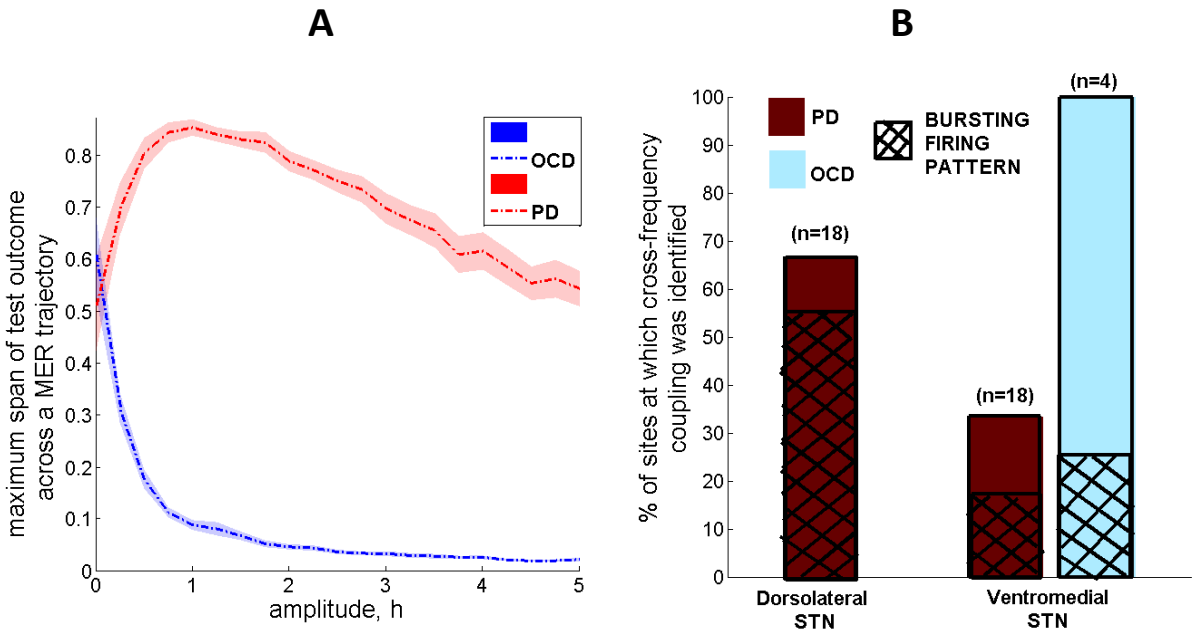


Figure 6.4: (A) Determination of parameter *h* (eq. (6.2)), based upon optimization of the outcome of the 0-1 test for chaos across a subset of 12 MER trajectories in PD and 12 MER trajectories in OCD. According to the results, in case of PD, sensitivity to measurement noise had to be further decreased by assigning a unitary value to parameter *h*. (B) Cross-frequency coupling was identified at at least 1 site within the STN of each patient with PD (total:18 MERs). Approximately 67% of these sites were located at the dorsal border of the STN, while at 72.2% of these sites neuronal activity followed a bursting or burst-like firing pattern and was considered for further processing in the phase-reduced bursting neuron model. Contrary to the case of PD, cross-frequency coupling was identified within the STN of only 2 patients with treatment-refractory OCD (total:4 MERs).

6.2.3. Model-Based Strategy for the Identification of the Optimal Stimulation Protocol

6.2.3.1 The Phase Model

We used the stochastic phase model presented in chapter 5, inclusively allowing for the phase response dynamics of a bursting neuron in both weak and strong perturbation regimes (Sherwood and Guckenheimer 2010, Mauroy et al. 2014). The phase model is described by an Ito stochastic differential equation:

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = \omega + Kr\sin\left(2\pi\left(\psi - \phi + a\left(K,r\right)\right)\right) + v + \left(\sigma_{\mathrm{I}}R_{\mathrm{I}}\left(\phi\right) + \sqrt{D}\right)\xi\left(t\right) + \frac{\sigma_{\mathrm{I}}}{2}R_{\mathrm{I}}'\left(\phi\right)\left(\sigma_{\mathrm{I}}R_{\mathrm{I}}\left(\phi\right) + \sqrt{D}\right)$$

$$+ \Delta\left(\phi,\beta\right)\sum_{k}\delta\left(t - \tau_k\right) \qquad (6.4)$$

where $v \approx {\sigma_{\mathrm{C}}}^2 \int_0^\infty dsC\left(s\right)\int_0^1 d\phi R_{\mathrm{C}}'\left(\phi\right)R_{\mathrm{C}}\left(\phi - \omega s\right)$, $D \approx {\sigma_{\mathrm{C}}}^2 \int_{-\infty}^\infty dsC\left(s\right)\int_0^1 d\phi R_{\mathrm{C}}\left(\phi\right)R_{\mathrm{C}}\left(\phi - \omega s\right)$

and, considering rectangular stimulation waveform, $\beta = wI_0 / C$ (Ermentrout et al. 2011), C=1μF/cm^2.

Variable $\phi \in [0,1)$ denotes the oscillator's phase, ω is its natural frequency (considered equal to the mean firing rate), while K, r and ψ symbolize the coupling strength, the degree of synchrony and the mean phase of the oscillators in the surrounding neural population, respectively. Also, a represents the phase shift (set equal to ¼), inherent to nonlinear coupling (Rosenblum and Pikovsky 2007). $\xi(t)$ is zero mean Gaussian white noise, added independently to each oscillator, and $\eta(t)$ is colored (common) noise with zero mean, unitary variance and autocorrelation function $C(t)$. Parameters σ_{I} and σ_{C} denote the intensity of independent and common noise, and are determined based on the spiking activity signal component and the LFP signal component, respectively. Phase sensitivity functions $R_{\mathrm{I}}(\phi)$ and $R_{\mathrm{C}}(\phi)$ are evaluated according to Sherwood and Guckenheimer (2010) and Abouzeid and Ermentrout (2009), respectively. Function $\Delta(\phi, \beta)$ represents the phase response curve (PRC) to a single (DBS) impulse and is evaluated according to Mauroy et al. (2014) (figure 6.5B). Parameter w represents the stimulus pulse width, I_0 is the stimulus current amplitude and τ_k are the input times ($0 \le k < \infty$). Values of β are appropiately scaled according to the size of perturbations upon which the PRC is constructed. We consider that the inter-impulse interval (IPI) $\Delta\tau_n = \tau_{n+1} - \tau_n$ obeys a Poisson distribution with parameter λ and that stimulus trains have a mean frequency f.

On grounds of the above assumptions, phase Eq. (6.4) was solved according to the analysis described in chapter 5, i.e. by employing the Perron-Frobenius operator in order to extract the stochastic phase map from one stimulus cycle to the next. The iterative process converges to the steady-state phase distribution, i.e. the invariant density, $p_{\mathrm{st}}(\phi)$, normalized as $\int_0^1 d\phi\, p_{st}(\phi) = 1$. Accordingly, we assessed the variance of the invariant density, $Var(p_{st}(\phi))$, as a quantity inversely related to the desynchronizing effect, but potentially also to the clinical effectiveness of stimulation. Ultimately, identification of the optimal stimulation protocol was based on minimization of the cost function

$$F(w, I_0, f, \lambda) = Var(p_{\mathrm{st}}(\phi)) + gP \tag{6.5}$$

where $P = I_0{}^2 wf \cdot R$ is the stimulation power (Koss et al. 2005). Parameter g is a penalizing scalar (we set $g = 0.25$), while R represents the electrode impendance (we consider R=1000Ω).

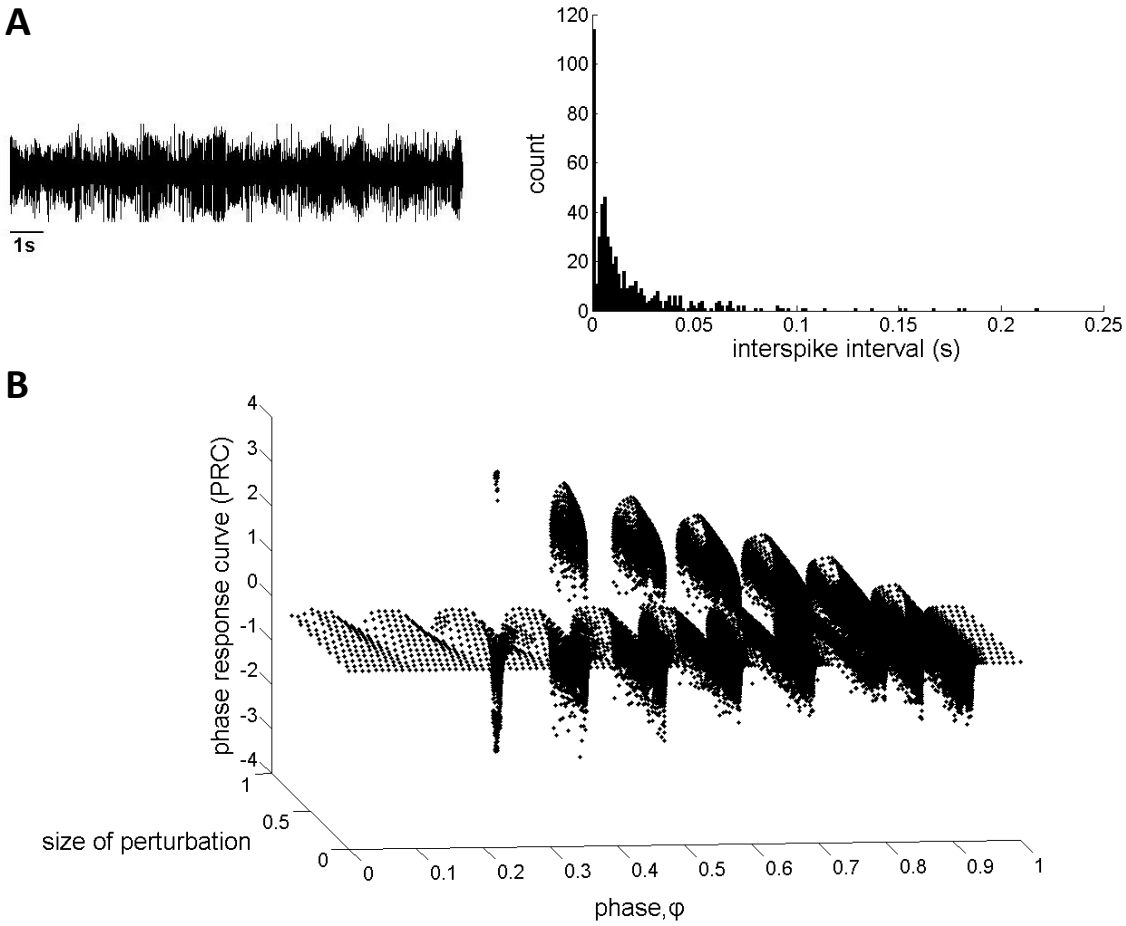


Figure 6.5: (A) Identification of a bursting firing pattern of neuronal activity at Central, -2.56mm, Left STN, case O2 (left) based on the interspike interval (ISI) histogram (right). The histogram is characterized by a positively skewed distribution indicating a large fraction of short ISIs and a high intraburst frequency ($\mu_{ISI} = 0.0179$s; $Var_{ISI} = 0.00069$). (B) The phase response curve (PRC) evaluated according to Mauroy et al. (2014).

6.2.3.2. The Model-Based Direct Search Method

Cost function (6.5) is expected to exhibit a non-smooth behavior. We therefore employed a derivative-free optimization algorithm, in particular, a model-based direct search method (Custodio et al. 2010). This hybrid algorithm relies on the incorporation of minimum Frobenius norm (MFN) quadratic modeling into a direct search method of directional type. Thereby, the performance of the direct search method may be significantly improved. The respective code (SID-PSM) is a MATLAB implementation of a generalized pattern search method wherein the *search* step is enhanced by means of minimization of the MFN model and the *poll* step is evaluated according to a negative simplex gradient. The poll step will be only performed if the search step is not successful in assessing a lower objective function value. A mesh is considered, defined from a set of directions with proper descent properties. In case both search and poll steps are unsuccessful, the mesh is contracted by decreasing the mesh size parameter. In case of success, the mesh size parameter can be maintained or increased. During the course of

Table 6.1. Stimulation settings determined post-operatively during the last follow-up visit for patients with PD

case	Brain Hemi-	pulse width (μs)	voltage (V)	frequency (Hz)
1	Right	60	3.8	140
	Left	60	2.6	140
2	Right	60	1.8	130
	Left	60	1.7	130
3	Right	60	2.2	130
	Left	60	2	130
4	Right	60	1.5	130
	Left	60	1.3	130
5	Right	60	3.4	130
	Left	60	2.2	130
7	Right	90	2.7	150
	Left	90	2.9	150
8	Right	60	3.7	150
	Left	60	2.9	150
9	Right	90	3.2	140
	Left	60	2.7	140

Table 6.2. Stimulation settings determined post-operatively during the last follow-up visit for patients with treatment-refractory OCD

case	Brain Hemi-	pulse width (μs)	voltage (V)	frequency (Hz)
O1	Right	60	2	130
	Left	60	2	130
O2	Right	60	4	130
	Left	60	4	130
O3	Right	60	1.9	130
	Left	60	2	130
O4	Right	60	2.4	130
	Left	60	2.4	130
O5	Right	60	2	130
	Left	60	2	130
O6	Right	60	1.5	130
	Left	60	1.5	130
O9	Right	60	3	130
	Left	60	2.3	130
P5	Right	60	2	130
	Left	60	2	130

iterations, a pattern search method generates a number of function evaluations (figure 6.6). For the application of the algorithm, we consider the following constraints:

$$0.001 < I_0 < 0.004A,\ 30 < w < 210\ \mu s,\ 20 < f < 150Hz \text{ and } 3 < \lambda < 30. \quad (6.6)$$

Determination of pulse-width constraints is based on evidence that pulse durations <60 μs

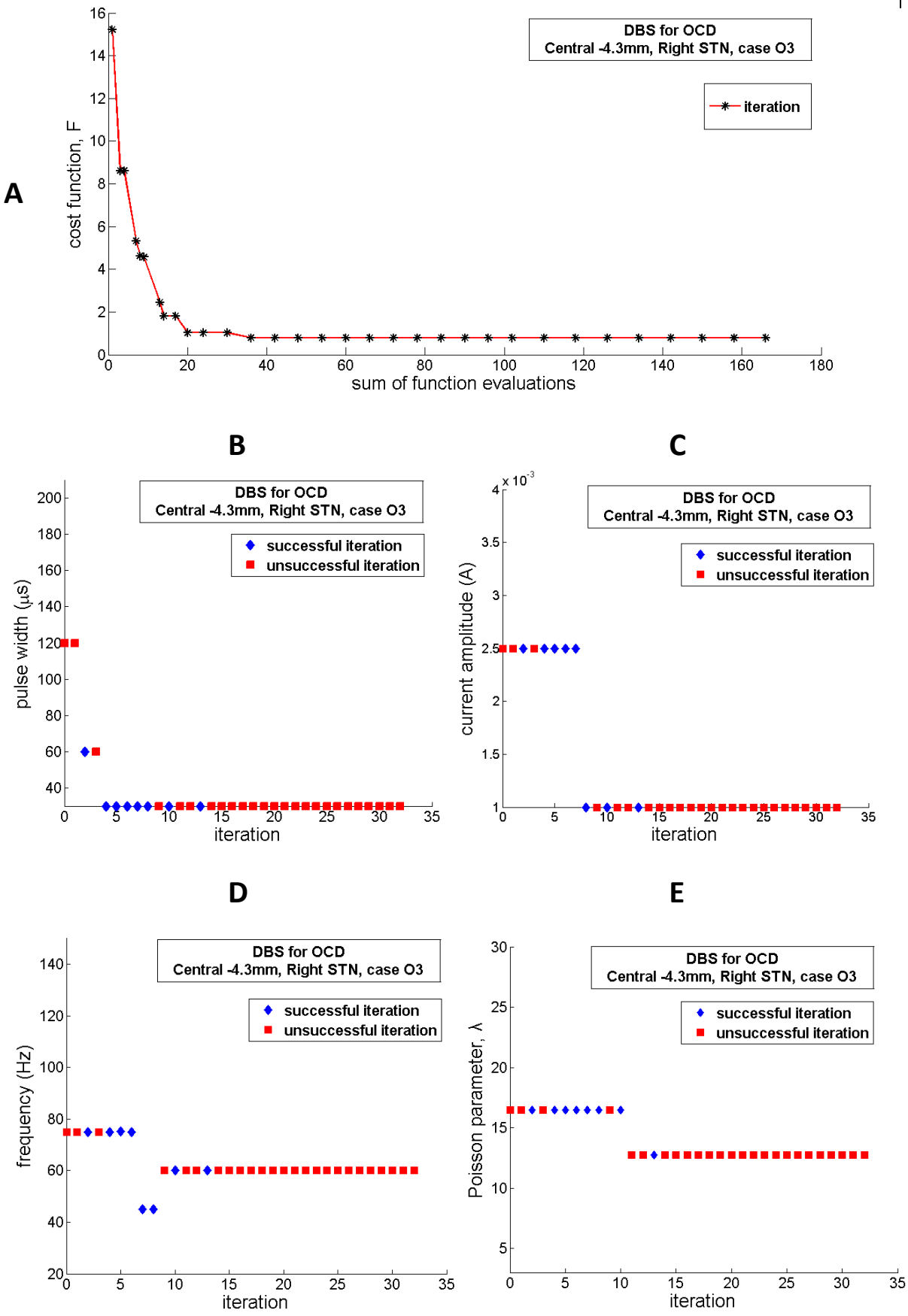


Figure 6.6: Progression of the model-based direct search method for a single trial (Central -4.3mm, Right STN, case O3). (A) Cost function minimization was achieved after a total of 13 iterations and approximately 38 function evaluations. According to the algorithm, optimal stimulation settings for this particular example included a pulse width of 30μs (B), a current amplitude equal to 1mA (C), a stimulation frequency of 60Hz (D) and a Poisson parameter equal to 13 (E) .

may lead to increased selectivity of stimulation, i.e. activation of the targeted neural elements without activation of distant pyramidal tract fibers, and therefore possibly also to an increased therapeutic window of DBS (Reich et al. 2015, Grill 2015).

The performance of the model-based direct search method (SID-PSM) in cases of PD and OCD was compared with the performance of a non-model-based generalized pattern search method (Matlab, Mathworks, Natick, MA), in terms of the resulting values of the invariant density measure, the stimulation power and the total computation time. We also assessed differences in terms of total computation time between the aforementioned methods and the genetic algorithm that has been previously recommended as appropriate for closed-loop optimization of DBS for PD (Feng et al. 2007(a)). Furthermore, stimulation settings determined by means of the presented modeling approach (combined application of the stochastic phase model and the model-based direct search method) were compared with stimulation settings determined post-operatively during the last follow-up for patients having undergone STN-DBS for PD or treatment refractory-OCD (tables 6.1-6.2). The Mann–Whitney *U* test was used to determine the statistical significance of the differential performances.

6.2.4 Assessment of a Possible Correlation of the Model-Based Outcome Measure with Clinical Effectiveness of Stimulation in OCD

In order to assess a possible correlation of the invariant density measure with clinical effectiveness of stimulation in treatment-refractory OCD, we evaluated the variance of the invariant density, $Var(p_{st}(\phi))$, simulating the application of regular, 130 Hz stimulation, based on a total of 39 MERs of subthalamic neuronal activity acquired during DBS for OCD and characterized by a high discharge rate, a high intraburst frequency and a short interburst interval vs. a total of 39 MERs of subthalamic neuronal activity characterized by a low discharge rate, a low intraburst frequency and a long interburst interval. This specific approach was based on indications correlating the efficacy of standard STN-DBS for OCD with locations of neuronal activity characterized by a high discharge rate and intraburst frequency, and a short interburt interval (Welter et al. 2011). Statistical significance was determined by means of the Mann–Whitney *U* test.

6.3. Results

6.3.1 Combined Application of Complex-Valued Filtering and the 0-1 Test for Chaos for the Evaluation of Nonlinear Coupling

Figure 6.3 depicts exemplary results of the methodology applied for the assessment of cross-frequency coupling, in the STN of a patient with PD (figure 6.3A) and a patient with OCD (figure 6.3B), as a biomarker for feedback control in the proposed closed-loop neuromodulation schemes. Employment of the 0-1 test for chaos following the application of the complex valued-filter proposed by Rossberg *et al.* (2004) singled out sites with significant nonlinear coupling between beta and high-frequency activity (test outcome<0.1). Conversely, following the application of a conventional, Butterworth band-pass filter, the 0-1 test for chaos did not discriminate sites with significant non-linear coupling from sites without. This result was corroborated across the total of the MER trajectories examined and underscored the fact that the combined application of the complex-valued filter and the 0-1 test for chaos may successfully lead to the assessment of cross-frequency coupling within the STN of patients with PD or OCD. In case of PD, sensitivity to measurement noise had to be further decreased by assigning a positive value to parameter h in eq. (2) (h=1, figure 6.4A). On the contrary, this improvement did not prove to be a prerequisite in case of OCD (h=0, figure 6.4A).

6.3.2 Nonlinear Coupling may be a Reliable Biomarker for Feedback Control in case of PD

Cross-frequency coupling was identified at a total of 18 MERs - sites within the STN of 8 patients with PD (case1: 2 sites; case 2: 1 site; case 3: 3 sites; case 4: 2 sites; case 5: 3 sites; case 7: 2 sites; case 8: 1 site; case 9: 4 sites). Approximately 67% of these sites (n=12) were located at the dorsal border of the STN (figure 6.4B). These results are in line with evidence that beta-HFO coupling is closely correlated with the pathophysiology of PD and strongest at the dorsal border of the STN (Yang et al. 2014, Connolly et al. 2015 (a), Lopez et al. 2010), and further highlight the appropriateness of nonlinear coupling between beta and high-frequency neuronal activity as a biomarker for feedback control in PD. Neuronal activity at 13 out of the 18 sites with cross-frequency coupling followed a bursting or burst-like firing pattern (figure 6.5A) (case1: 1 site; case 2: 1 site; case 3: 3 sites; case 4: 1 site; case 5: 3 sites; case 7: 2 sites; case 8: 1 site; case 9: 1 site) and was considered for further processing in the bursting neuron model. At the remaining 5 sites a rather irregular firing pattern was observed, and therefore these sites were excluded from subsequent analysis.

6.3.3 Nonlinear Coupling may display Subject-Specific Applicability as a Biomarker for Feedback Control in case of OCD

Contrary to the case of PD, cross-frequency coupling was identified at only 4 MERs - sites within the STN of 2 patients with OCD (case O2: 2 sites; case O3: 2 sites) (figure 6.5B). The latter fact

may be attributable to the low number of acceptable MER trajectories in case of STN – DBS for OCD. Otherwise, it may imply that nonlinear coupling between beta and high-frequency activity is not consistently an appropriate biomarker for feedback control in closed-loop DBS for OCD (Bahramisharif et al. 2015) and that an alternative biomarker should be additionally considered (figure 6.2B). For this reason, on the basis of evidence pointing to a correlation of subthalamic bursting neuronal activity, characterized by certain features, with symptom severity and stimulation efficacy in OCD (Welter et al. 2011), we assessed, for the remaining of the cases wherein no cross-frequency coupling could be identified (or, despite the presence of cross-frequency coupling, no bursting activity was observed at the respective site), the presence of bursting neuronal activity with specific characteristics, i.e. a short interburst interval and a high intraburst frequency (μ_{ISI}=0.0242 ± 0.0113s, Var_{ISI}=0.0059 ± 0.0083). Specifically, we considered for further processing a total of 12 MERs (case O1: 1 site; case O2: 2 sites; case O3: 2 sites; case O4: 1 site; case O5: 1 site; case O6: 1 site; case O9: 2 sites; case P5: 2 sites).

6.3.4 Performance of the Presented Modeling Approach in terms of Efficiency, Selectivity of Stimulation and Computational Cost

Implementation of the model-based direct search method (SID-PSM) and the non-model-based generalized pattern search method (Matlab, Mathworks, Natick, MA) for the determination of the optimal temporal pattern and parameters of stimulation indicated that, except for the current amplitude that was consistently maintained at its minimal value ($I_0 = 0.001A$), both optimization procedures may discover multiple parameter values for a specific site that are considerably different. This result is in line with the conclusions reported in Feng *et al.* (2007(a)). Accordingly, for each site, we acquired 5 sets of parameter values, by means of each distinct solver, and assessed the respective mean values illustrated in figures 6.7 and 6.8.

Statistical analysis in cases of PD and OCD corroborated a significantly higher performance of the model-based direct search method, in terms of both stimulation power and computation time corresponding to the optimal stimulation settings, compared with the generalized pattern search method (p< 0.0001, Mann–Whitney U test), while an almost equivalent effect was observed on the invariant density measure (p_{PD}=0.3299, p_{OCD}=0.4705, Mann–Whitney U test) (figures 6.9, 6.10). Remarkably, and contrary to the suggestion in Feng *et al.* (2007(a)), implementation of the genetic algorithm was associated with prohibitively long execution times (> 1 hour). Optimal stimulation settings determined by means of the model-based direct search method in case of PD included a pulse width equal to 33.36 ± 1.06 μs, a frequency equal to 39 ± 3.43 Hz and a Poisson parameter equal to 19.8 ± 0.92 (mean ± standard error mean), and in case of OCD, a pulse width equal to 33.75 ± 1.29 μs, a frequency equal to 53.24 ± 5.2 Hz and a Poisson parameter

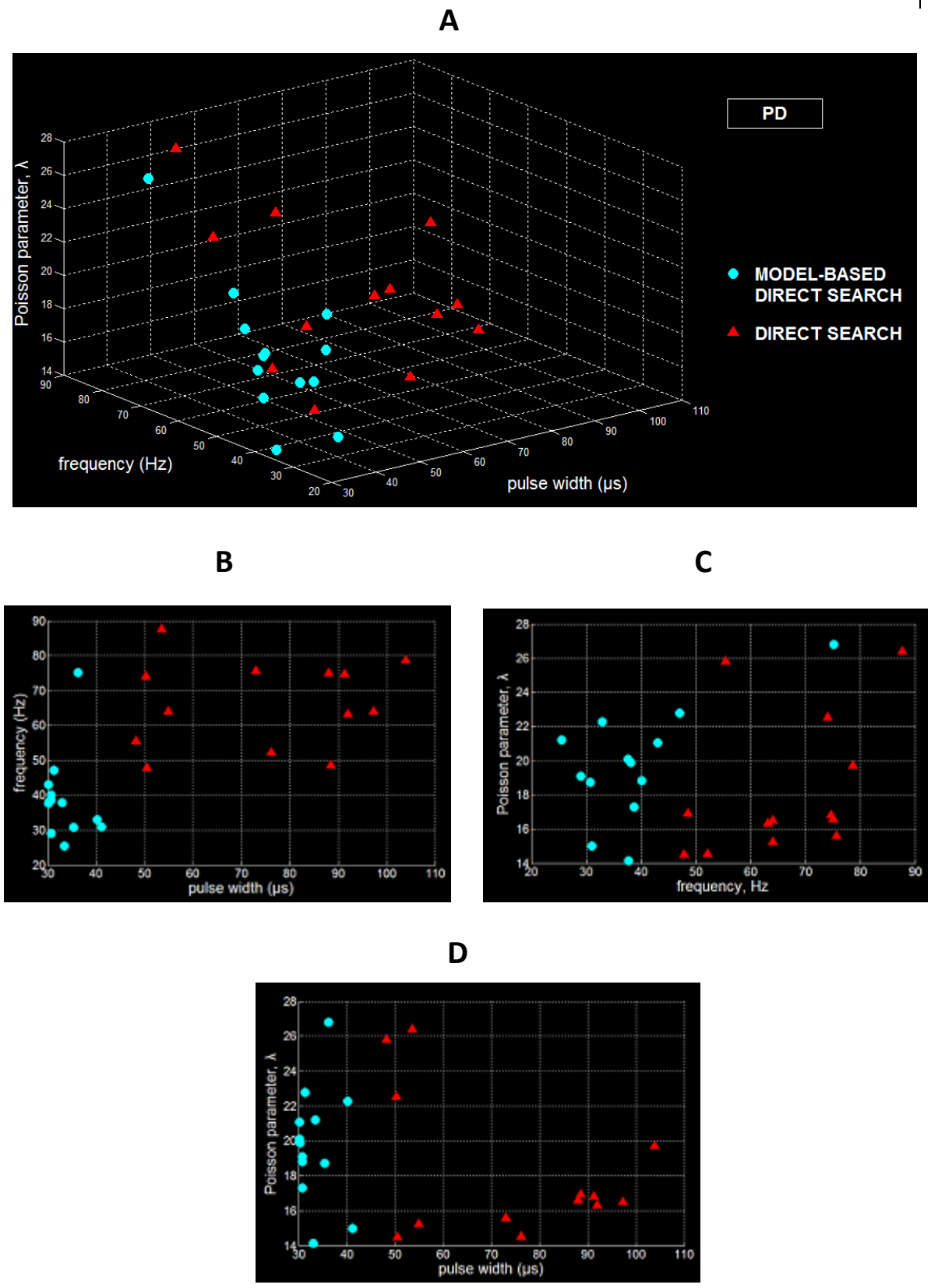


Figure 6.7: Implementation results of the model-based direct search method (SID-PSM) vs. a non-model-based direct search method (Matlab, Mathworks, Natick, MA) for the determination of the optimal temporal pattern and parameters of stimulation based on 13 MERs acquired during STN-DBS surgery for advanced PD. For each site, we acquired 5 sets of parameter values, by means of each distinct solver, and assessed the respective mean values displayed in (A)-(D). The current amplitude, after application of both optimization procedures, was consistently maintained at its minimal value ($I_0 = 0.001A$).

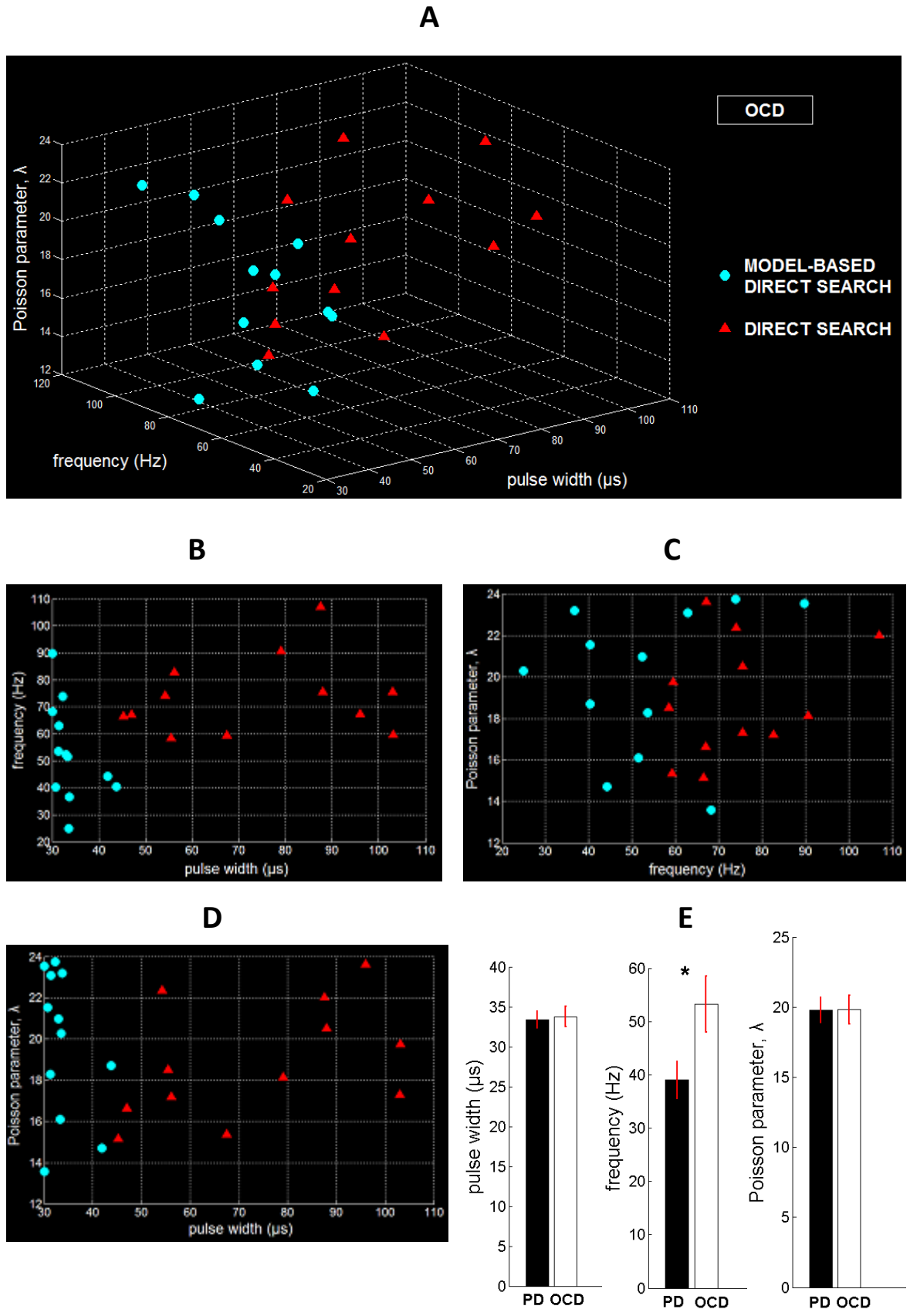


Figure 6.8: Implementation results of the model-based direct search method (SID-PSM) vs. a non-model-based direct search method (Matlab, Mathworks, Natick, MA) for the determination of the optimal temporal pattern and parameters of stimulation based on 12 MERs acquired during STN-DBS surgery for treatment-refractory OCD. For each site, we acquired 5 sets of parameter values, by means of each distinct solver, and assessed the respective mean values depicted in (A)-(D). The current amplitude, after application of both optimization procedures, was consistently maintained at its minimal value ($I_0 = 0.001A$). (E) Taking into consideration the results presented in figure 6.6, following the application of the model-based direct search method, the mean optimal stimulation frequency proved to be significantly higher in case of OCD compared with PD (*p=0.02, Mann–Whitney U test).

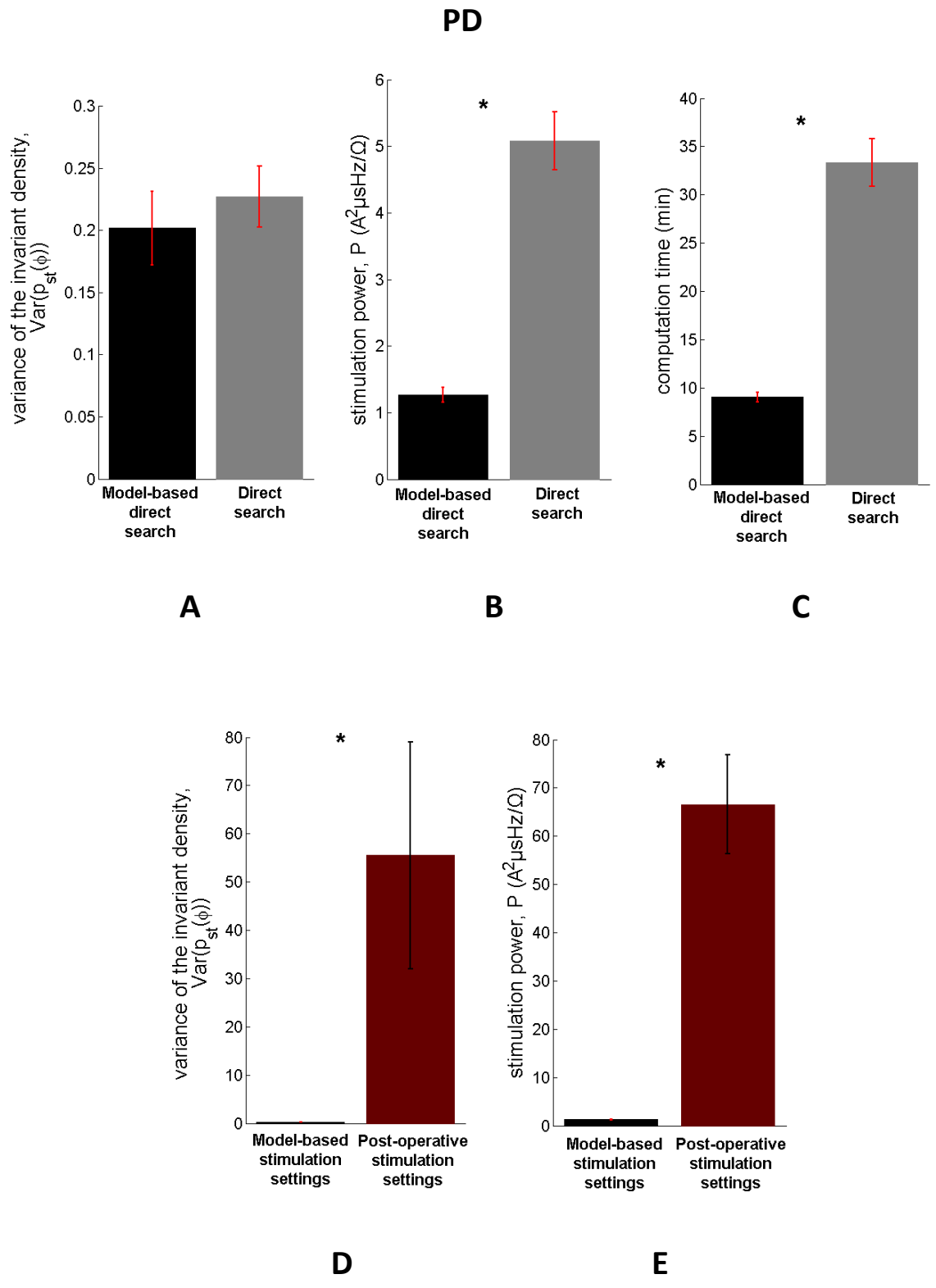


Figure 6.9: Performance of the proposed modeling approach in terms of efficiency of stimulation and computational speed in case of advanced PD. (A)-(C) Comparison of the model-based direct search method (SID-PSM) with a non-model-based direct search method (Matlab, Mathworks, Natick, MA) corroborated a significantly higher performance of the former method, in terms of both (B) stimulation power and (C) computation time (*p<0.0001, Mann–Whitney U test) corresponding to the optimal stimulation settings, while an almost equivalent effect was observed on the invariant density measure (p_{PD}=0.3299, Mann–Whitney U test). (D)-(E) Statistical analysis corroborated the ability of the proposed model-based strategy (combined application of the stochastic phase model and the model-based direct search method) to identify stimulation settings that yield significantly lower values of the invariant density measure and stimulation power compared with the stimulation settings determined post-operatively during the last follow-up (*p<0.0001, Mann–Whitney U test). Errorbars indicate standard error mean.

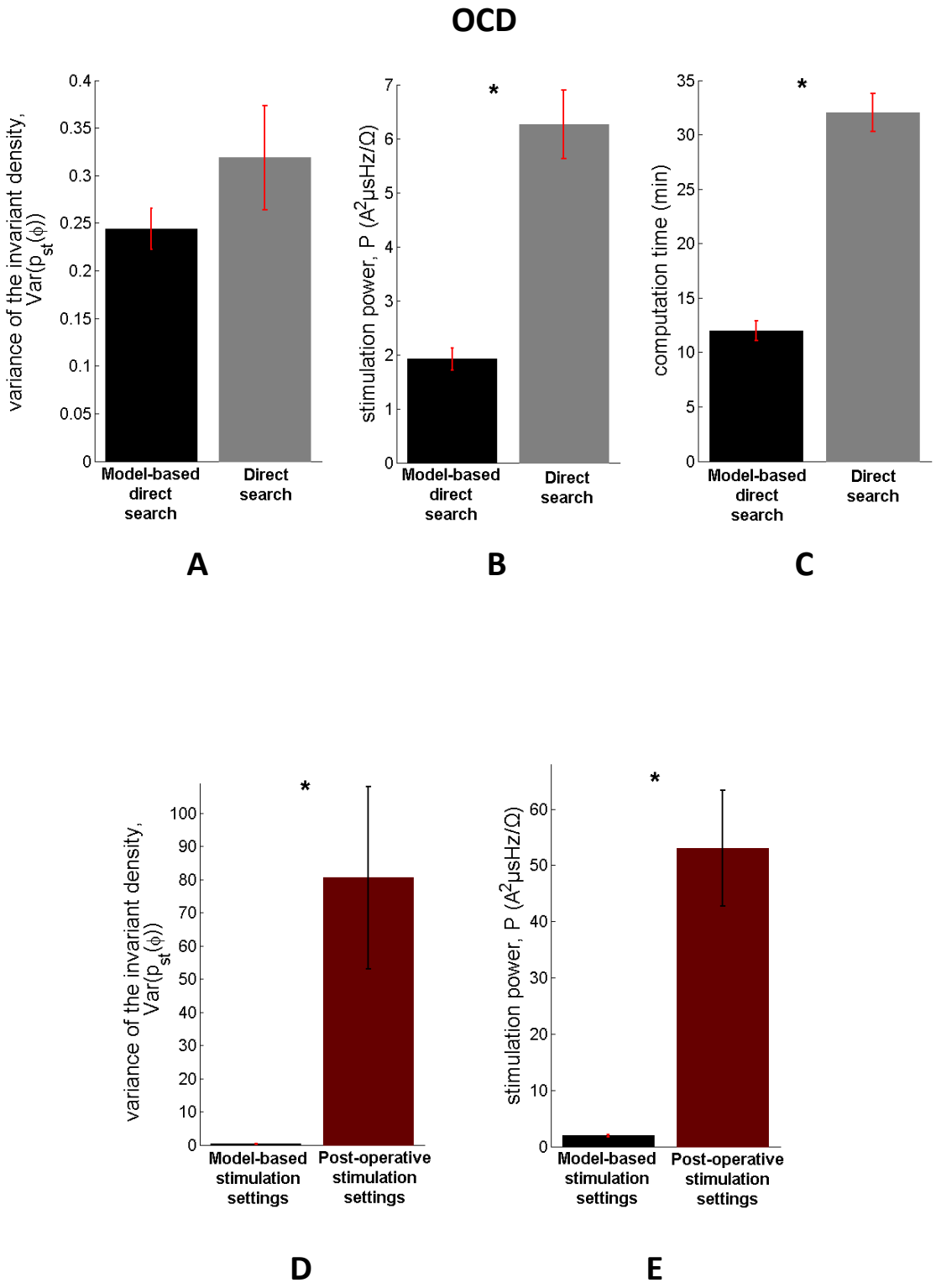


Figure 6.10: Performance of the proposed modeling approach in terms of efficiency of stimulation and computational speed in case of treatment-refractory OCD. (A)-(C) Comparison of the model-based direct search method (SID-PSM) with a non model-based direct search method (Matlab, Mathworks, Natick, MA) corroborated a significantly higher performance of the former method, in terms of both (B) stimulation power and (C) computation time (*p<0.0001, Mann–Whitney U test) corresponding to the optimal stimulation settings, while an almost equivalent effect was observed on the invariant density measure (p_{OCD}=0.4705, Mann–Whitney U test). (D)-(E) Statistical analysis corroborated the ability of the proposed model-based strategy (combined application of the stochastic phase model and the model-based direct search method) to identify stimulation settings that yield significantly lower values of the invariant density measure and stimulation power compared with the stimulation settings determined post-operatively during the last follow-up (*p<0.0001, Mann–Whitney U test). Errorbars indicate standard error mean.

equal to 19.81 ± 1.02 (mean ± standard error mean) (figure 6.8E). In addition, statistical analysis corroborated the ability of the proposed model-based strategy (combined application of the stochastic phase model and the model-based direct search method) to identify stimulation settings that yield significantly lower values of the invariant density measure and stimulation power compared with the stimulation settings determined post-operatively (p<0.0001, Mann–Whitney U test) (figures 6.9D-E, 6.10D-E). Notably, the differential desynchronizing effect on neuronal activity exerted by the model-based stimulation settings vs. the stimulation settings determined post-operatively may be qualitatively reflected in the distinct form of the respective stochastic kernels (figure 6.12). Overall, the above results combined with the reported possible correlation of the invariant density measure with clinical effectiveness of stimulation in PD, but probably also in OCD (see next paragraph), highlight an outstanding performance of the proposed modeling approach not only in terms of efficiency and selectivity of stimulation (Grill 2015), but also in terms of computational speed.

6.3.5 Possible Correlation between the Invariant Density Measure and Clinical Effectiveness of Stimulation in OCD

Figure 6.11 displays the results obtained by assessing the variance of the invariant density based on a total of 39 MERs of subthalamic neuronal activity acquired during DBS for OCD and characterized by a high discharge rate, a high intraburst frequency and a short interburst interval vs. a total of 39 MERs of subthalamic neuronal activity characterized by a low discharge rate, a low intraburst frequency and a long interburst interval. Essentially, the desynchronizing effect of standard 130Hz stimulation proved to be significantly stronger in the former case compared with the latter (p< 0.01, Mann–Whitney U test). This result points to a possible correlation of the principal model outcome measure, the variance of the invariant density, with clinical effectiveness of stimulation in OCD, since values of this measure are proven to be lower at locations of neuronal activity that have been correlated with the best clinical outcome of STN-DBS for OCD (Welter et al. 2011).

Last, we should comment on the fact that, following the application of the model-based direct search method, the mean optimal stimulation frequency proved to be significantly higher in case of OCD compared with PD (p<0.05, Mann–Whitney U test), while a similar outcome was obtained with respect to the mean optimal pulse width and the mean optimal Poisson parameter (figure 6.8E). We suggest that differences in the underlying pathophysiology (Piallat et al. 2011, Welter et al. 2011) may have led to the observed differences in optimal stimulation frequency in case of PD vs. treatment-refractory OCD.

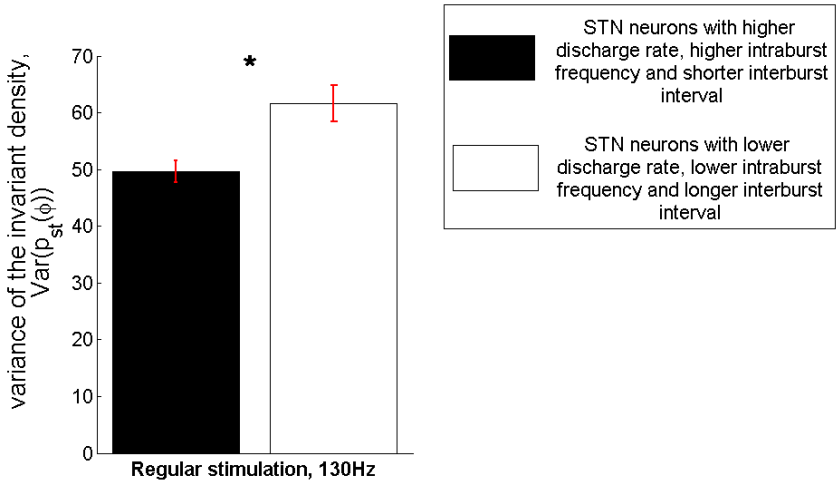


Figure 6.11: Assessment of the mean ± standard error mean variance of the invariant density based on a total of 39 MERs of subthalamic neuronal activity acquired during DBS surgery for treatment-refractory OCD and characterized by a high mean discharge rate (39.7 ± 14.71 Hz), a high intraburst frequency and a short interburst interval (μ_{ISI} = 0.0289 ± 0.0114 s, Var_{ISI} = 0.0038 ± 0.0056) vs. a total of 39 MERs of subthalamic neuronal activity characterized by a low mean discharge rate (13.53 ± 7.13 Hz), a low intraburst frequency and a long interburst interval (μ_{ISI} = 0.1072 ± 0.093 s, Var_{ISI} = 0.0265 ± 0.0542). The mean desynchronizing effect of standard, 130Hz stimulation proved to be significanlty stronger in the former case compared with the latter (*p< 0.01, Mann–Whitney U test).

6.4. Discussion

Bikson et al. (2015) remark: "Approaches using closed-loop stimulation are inherently *state* dependent and require *computational neurostimulation*." Elaborating on this concept and considering the implications of the current approach, we make the following two key observations: first, though evidence about the pathophysiology of medically refractory neurological and neuropsychiatric disorders remains to date to a large extent inconclusive, a growing body of basic and clinical work supports the important role of nonlinear coupling between beta and high-frequency activity in the pathophysiology of PD (Voytek and Knight 2015), thereby pointing to a possible utility of this measure as a *state* biomarker in closed-loop neuromodulation approaches for PD. The results of this study incline towards this hypothesis by corroborating the presence of cross-frequency coupling for each case with advanced PD. On the contrary, the appropriatness of this feature as a *state* biomarker proved rather subject-specific in case of treatment-refractory OCD. An alternative biomarker of OCD severity, intense subthalamic bursting activity (Welter et al. 2011), had, therefore, to be applied. Second, throughout this analysis, we attempted to provide compelling evidence for the applicability of *computational neurostimulation* to real-time, closed-loop DBS systems (Little and Bestmann 2015). The computational model used operates on the principles of phase reduction and phase- resetting (Canavier 2015) that are inherently characterized by simplicity and analytical tractability (Kiss et

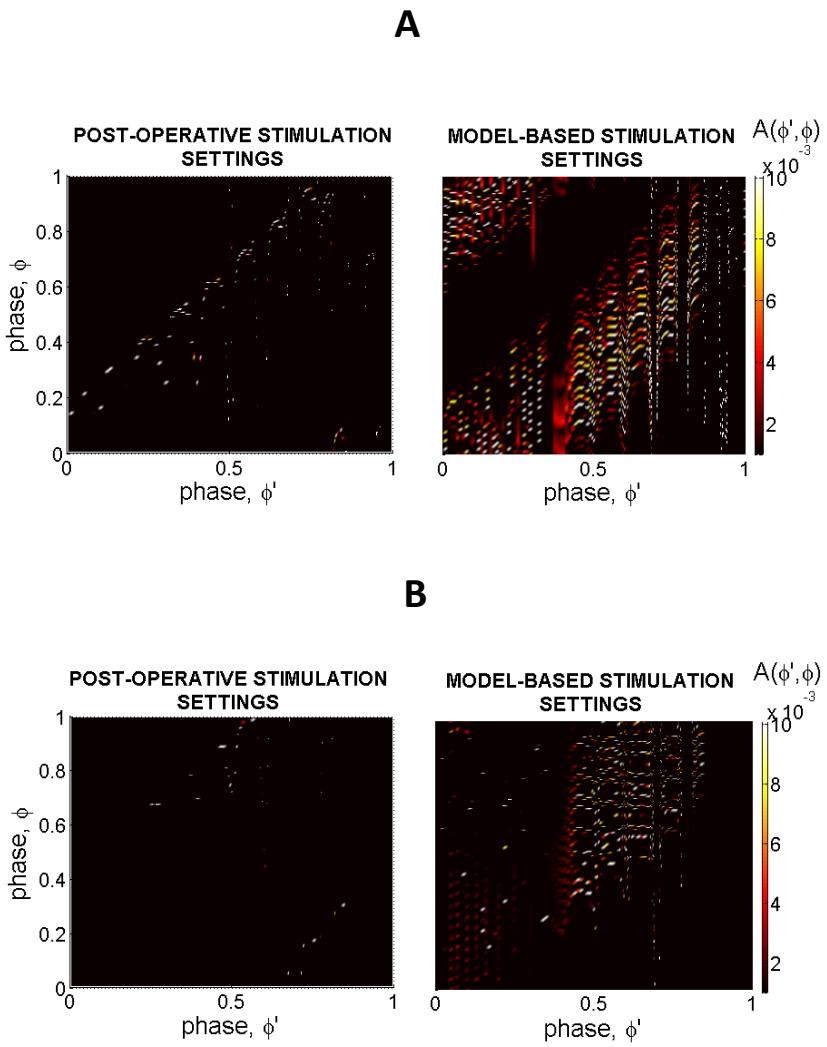


Figure 6.12: Stochastic kernels derived by fitting the phase-reduced bursting neuron model to a MER acquired during STN-DBS surgery for (A) PD and (B) OCD, and simulating application of post-operative (left panels) vs. model-based stimulation settings (right panels). The stronger desynchronizing effect on neuronal activity exerted by the model-based stimulation settings is qualitatively reflected in the intense form of the respective stochastic kernels.

al. 2007), and further incorporates the dynamics of neuronal bursting activity that comprises a hallmark of PD and OCD pathophysiology.

In the previous chapter, we provided important indications for the realistic substructure of the stochastic phase model and further highlighted a possible correlation of the primary outcome measure with clinical effectiveness of stimulation in PD. By extending the latter result to the case of treatment-refractory OCD, we here prove that the proposed model-based strategy may outperform post-operative clinical management in terms of therapeutic efficiency of stimulation for both pathologic conditions. By yielding a mean optimal pulse width equal to ~33μs, values of stimulation frequency significantly lower as compared to standard stimulation and by maintaining the optimal current amplitude at its minimal value, the model-based strategy proves to further achieve a significanlty higher performance in terms of both selectivity and energy efficiency of stimulation compared with post-operative clinical management. In addition to the employment of the phase-reduced bursting neuron model, the application of direct search optimization based on

quadratic modeling has significantly contributed to the performance of the presented approach. In particular, beyond the aforementioned outcome, application of the model-based direct search method has been associated with a significantly higher computational speed compared with alternative derivative-free optimization algorithms (generalized pattern search method, genetic algorithm).

Modeling approaches similar to those proposed in this work may display greater fidelity in the framework of constant current stimulation. The evolution from the use of constant-voltage to constant-current DBS devices appears to have been motivated by the rationale that constant-current stimulation would accommodate for inter-patient and temporal fluctuations in the impedance of the tissue and electrode-tissue interface (Lempka et al. 2009;2010, Bronstein et al. 2014, Hartmann et al. 2015). Though no randomized trials comparing the effects of constant-voltage vs current-controlled pulse generators have to date been conducted, it has been suggested that a constant current device may be correlated with improved clinical effectiveness (Gross and McDougal 2013, Okun et al. 2012, Timmermann et al. 2015).

7

Contribution of the Dissertation and Research Perspectives

Whereas DBS merits further study as a treatment for carefully selected patients with severe, chronic, and treatment-resistant psychiatric illness, the long-term value of DBS might be to help elucidate the underlying neurocircuitry of psychiatric syndromes so that new, less invasive but anatomically targeted treatments can be developed.

W K Goodman and T R Insel (2009)

7.1. Contribution of the Dissertation

Optimization of stimulation parameters and patterns, as well as adaptive stimulation paradigms lie within the core future developments in the field of DBS for neurological and psychiatric disorders (Metman and Slavin 2015, Wojtecki et al. 2012). Moving into the mainstream, the principal contribution of this dissertation has been the algorithmic design of a therapeutically- and energy-efficient closed-loop deep brain stimulation (DBS) system for Parkinson's disease (PD) and treatment-refractory obsessive-compulsive disorder (OCD), by means of stochastic dynamical modeling. In that respect, we provided strong indications for the applicability of computational neurostimulation to the optimization of the clinical outcome of electrical DBS in movement and neuropsychiatric disorders.

In particular, throughout this work we provided evidence

- for the realistic substructure of the developed stochastic dynamical models simulating the collective dynamical and response properties of subthalamic oscillatory activity in the pathological state.

- for a possible correlation between the principal model-based outcome measure, a quantity inversely related to the speculative desynchronizing effect of stimulation, and clinical effectiveness of stimulation in advanced PD and treatment-refractory OCD.

- that the desynchronizing and probably also the therapeutic effect of low-frequency stochastic DBS waveforms may be significantly stronger compared with the effect of standard stimulation (periodic at 130Hz) in advanced PD and treatment-refractory OCD.

- for the ability of the presented model-based, closed-loop neuromodulation scheme to identify, at a relatively low computational cost, stimulation settings associated with a significantly higher efficiency and selectivity compared with stimulation settings determined during post-operative clinical management of patients with advanced PD and treatment-refractory OCD.

- that cross-frequency coupling may be an appropriate biomarker for feedback control in closed-loop DBS for advanced PD, but may display subject-specific applicability in closed-loop DBS for treatment-refractory OCD.

7.2. Research Perspectives

Advances in neuroengineering, neurosurgery and robotics coupled with a deeper understanding of neuronal circuits underlying the pathophysiology of brain disorders have paved the way for groundbreaking applications in a broad field of research termed *neuroprosthetics* (Borton et al. 2013, Patil and Turner 2008, Schwartz et al. 2006). One of the major approaches in this field exploits electrical and/or chemical neuromodulation paradigms, aiming at the improvement of the lives of people not only with movement and neuropsychiatric disorders, but also with spinal cord injury (van den Brand et al. 2015), chronic pain (Al-Kaisy et al. 2014) and blindness (Lovell et al. 2007, Hadjinicolaou et al. 2015). If appropiately adapted, some of the methods elaborated in this thesis may be applied to the optimization of stimulation in the aforementioned latter cases as well.

Further important considerations for efficient closed-loop neuromodulation include the optimization of the stimulation waveform (Wongsarnpigoon and Grill 2010, Foutz and McIntyre 2010, Hofmann et al. 2011), of the circuit topology (Stanslaski et al. 2012, Rouse et al. 2011, Lee et al. 2015) and of contact selection (Connolly et al. 2015(b)), as well as the incorporation of

neurochemical control (Grahn et al. 2014, Ward and Irazoqui 2010) and the adjustment of closed-loop neuromodulation systems to the phenotypical heterogeneity of neurological and neuropsychiatric disorders (Connolly et al. 2015(c), Widge and Moritz 2014). Cumulative research towards these directions may ultimately favor the optimization of less invasive, groundbreaking treatment options including closed-loop optogenetic control (Nguyen et al. 2014, Grosenick et al. 2015).

Finally, along other avenues of research, there exist especially optimistic perspectives for the applicability of model-based feedback control principles to the control of epidemic infections including neonatal sepsis, one of the leading killers of children worldwide (Schiff 2015[1]).

[1]https://projectreporter.nih.gov/project_info_description.cfm?icde=0&aid=8754244

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Publications

Journal Papers

[1] S.D. Karamintziou, G.L. Tsirogiannis, P.G. Stathis, G.A. Tagaris, E.J. Boviatsis, D.E. Sakas, and K.S. Nikita 2014 Supporting clinical decision making during deep brain stimulation surgery by means of a stochastic dynamical model *J Neural Eng* **11** 056019.

[2] S.D. Karamintziou, N.G. Deligiannis, B. Piallat, M. Polosan, S. Chabardès, O. David, P.G. Stathis, G.A. Tagaris, E.J. Boviatsis, D.E. Sakas, G.E. Polychronaki, G.L. Tsirogiannis and K.S. Nikita 2016 Dominant efficiency of non-regular patterns of subthalamic nucleus deep brain stimulation for Parkinson's disease and obsessive-compulsive disorder in a data-driven computational model *J Neural Eng* **13**.

[3] S.D. Karamintziou, A. L. Custódio, B. Piallat, M. Polosan, S. Chabardès, O. David, P.G. Stathis, G.A. Tagaris, D.E. Sakas, G.E. Polychronaki, G.L. Tsirogiannis and K.S. Nikita Algorithmic design of a therapeutically- and energy-efficient closed-loop deep brain stimulation system for Parkinson's disease and obsessive-compulsive disorder (under review).

[4] Affective-motivational dimensions underlying obsessive-compulsive symptom manifestation: possible implications for improved efficacy of deep brain stimulation (in preparation).

Conference Papers

[1] S.D. Karamintziou, N.G. Deligiannis, B. Piallat, M. Polosan, S. Chabardès, O. David, P.G. Stathis, G.A. Tagaris, E.J. Boviatsis, D.E. Sakas, G.E. Polychronaki, G.L. Tsirogiannis and K.S. Nikita Dominant efficiency of non-regular patterns of subthalamic nucleus deep brain stimulation for Parkinson's disease and obsessive-compulsive disorder In Proceedings of the *Interim Meeting of the World Society for Stereotactic and Functional Neurosurgery (WSSFN)*, September 3-6, 2015, Mumbai, India.

[2] S.D. Karamintziou, B. Piallat, S. Chabardès, M. Polosan, O. David, G.L. Tsirogiannis, N.G. Deligiannis, P.G. Stathis, G.A. Tagaris, E.J. Boviatsis, D.E. Sakas, G.E. Polychronaki and K.S. Nikita Design of a Novel Closed-Loop Deep Brain Stimulation System for Parkinson's Disease and Obsessive-Compulsive Disorder In Proceedings of the *7th International IEEE/EMBS Conference on Neural Engineering (NER2015),* April 22-24, 2015, Montpellier, France.

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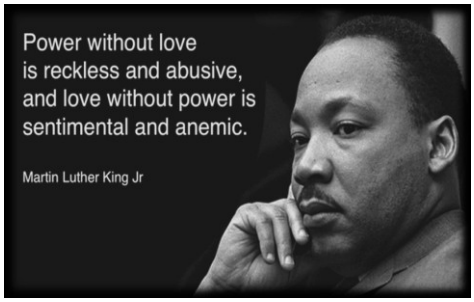
Power without love
is reckless and abusive,
and love without power is
sentimental and anemic.
Martin Luther King Jr