Rôle des boucles cortico-ganglions de la base sur l'attention visuelle : effets de la stimulation dopaminergique et du noyau subthalamique dans la maladie de Parkinson

Giorgio Tommasi

UNIVERSITÉ DE GRENOBLE

THÈSE

pour obtenir le grade de

DOCTEUR DE L'UNIVERSITÉ DE GRENOBLE

Spécialité : **Neurosciences - Neurobiologie**

Arrêté ministériel : 7 août 2006 et Arrêté ministériel : 6 janvier 2005

Préparée dans le cadre d'une cotutelle entre
L'UNIVERSITÉ DE GRENOBLE ET L'UNIVERSITÉ DE VÉRONE, ITALIE

Présentée par

GIORGIO TOMMASI

Thèse dirigée par Prof. **Pierre Pollak** et Prof. **Leonardo Chelazzi**
codirigée par Prof. **Antonio Fiaschi**

préparée au sein du **Laboratoire « Grenoble Institut des Neurosciences »** dans **l'École Doctorale « Chimie et Sciences du Vivant » de l'Université de Grenoble** et au sein du « **Dipartimento di Scienze Neurologiche, Neuropsicologiche, Morfologiche e Motorie** » (précédemment nommé Dipartimento di Scienze Neurologiche e della Visione) et de **l'Ecole Doctorale «Scienze, Ingegneria, Medicina » de l'Université de Vérone**, **Italie.**

Rôle des boucles cortico-ganglions de la base sur l'attention visuelle: effets de la stimulation dopaminergique et du noyau subthalamique dans la maladie de Parkinson

Thèse soutenue publiquement le **« 16.05.2011 »**,
devant le jury composé de :

Mr EMMANUEL BROUSSOLLE
Professor, Hospital Neurologique Pierre Wertheimer, Lyon (FR) Rapporteur
Mr LEONARDO CHELAZZI
Professor,Università degli Studi di Verona (IT), Membre
Mme ROSHAN COOLS
Principal Investigator, Radboud University Nijmegen, (NL), Membre
Mme MARJAN JAHANSHAHI
Professor, UCL Institute of Neurology, London (GB), Président
Mr PIERRE POLLAK
Professor, Centre Hospitalier Universitaire de Grenoble (FR), Membre
Mr JAN THEEUWES
Professor, Vrije Universiteit, Amsterdam (NL), Rapporteur

UNIVERSITÀ DEGLI STUDI DI VERONA

DIPARTIMENTO DI SCIENZE NEUROLOGICHE,
NEUROPSICOLOGICHE, MORFOLOGICHE E MOTORIE

DOTTORATO DI RICERCA IN NEUROSCIENZE
SCUOLA DI DOTTORATO "SCIENZE INGEGNERIA MEDICINA"

CICLO XXIII

TITOLO DELLA TESI DI DOTTORATO

ROLE OF THE CORTICO-BASAL GANGLIA LOOPS IN VISUAL ATTENTION: EFFECTS OF DOPAMINERGIC AND SUBTHALAMIC NUCLEUS STIMULATION IN PARKINSON'S DISEASE

RUOLO DEI CIRCUITI CORTICO-SOTTOCORTICALI NELL'ATTENZIONE VISIVA: EFFETTI DELLA STIMOLAZIONE DOPAMINERGICA E DEL NUCLEO SUBTALAMICO NELLA MALATTIA DI PARKINSON

RÔLE DES BOUCLES CORTICO-GANGLIONS DE LA BASE SUR L'ATTENTION VISUELLE: EFFETS DE LA STIMULATION DOPAMINERGIQUE ET DU NOYAU SUBTHALAMIQUE DANS LA MALADIE DE PARKINSON

REALIZZATA IN COTUTELA CON L'UNIVERSITÀ DI GRENOBLE

S.S.D.: MED/26-Neurologia e BIO/09-Fisiologia

Coordinatori:	Per l'Università di Verona	Prof. LEONARDO CHELAZZI
	Per l'Università di Grenoble	Prof. MARC SAVASTA
Tutori:	Per l'Università di Verona	Prof. LEONARDO CHELAZZI
	Per l'Università di Grenoble	Prof. PIERRE POLLAK
Co-tutor:	Per l'Università di Verona	Prof. ANTONIO FIASCHI

Dottorando: Dott. GIORGIO TOMMASI

Table of contents

Brief summary

We aimed to investigate the possible role of cortico-basal ganglia loops and dopaminergic pathways in the mechanisms of top-down and bottom-up control of visual attention (VA).

We compared the performances on 3 computerized tasks, respectively suitable to study attentional capture (AC), motor response selection and movement initiation, of two groups of patients with Parkinson's disease (PD), one evaluated in different sets of electrical stimulation (without stimulation, or selective stimulation of the sensorimotor, SM, or associative, AS, parts of the subthalamic nucleus, STN), the other in different conditions of medication (with or without levodopa), with those of a group of controls.

Our results showed that in PD there is a weakening of the mechanisms underlying the top-down control of VA, which also would account indirectly account for the enhancement of AC. Dopaminergic treatment proved to be effective in restoring the top-down mechanisms of VA, suggesting an involvement of dopaminergic pathways in this cognitive domain. These pathways seem to play a role also in the bottom-up mechanisms of attention, as suggested by the enhancement of AC under dopaminergic treatment.

The STN-stimulation showed a similar effect to that obtained by dopaminergic treatment, establishing a direct involvement of the basal ganglia loops in VA control. Our results highlighted a functional specialization of different sub-territories of the STN in relation to the top-down mechanisms. SM stimulation produced marked effects on the movement initiation processes and appreciable positive effects on endogenous VA mechanisms, while AS stimulation seems to be especially effective in improving the mechanisms of target selection.

Keywords: visual selective attention, attentional capture, deep brain stimulation, subthalamic nucleus, Parkinson's disease.

Bref résumé

Le but de cette étude était d'évaluer le rôle des boucles des ganglions de la base et des voies dopaminergiques sur les mécanismes « bottom-up » et « « top-down » du contrôle de l'attention visuelle (AV).

Nous avons comparé les performances sur 3 tâches informatisés, appropriées à l'étude de la capture attentionnelle (CA), des mécanismes de sélection de la réponse motrice et d'initiation du mouvement, de deux groupes de patients avec maladie de Parkinson (MP) - un groupe étant évalué dans trois différentes conditions de stimulation électrique (sans stimulation, ou stimulation sélective de la partie sensorimotrice, SM, ou de la partie associative, AS, du noyau subthalamique, NST), l'autre groupe étant évalué dans deux différentes conditions de traitement médical (avec ou sans levodopa) - avec celles d'un groupe des sujets contrôles.

Nos résultats suggèrent dans la MP un affaiblissement des mécanismes « top-down » de contrôle de l'AV, ce qui pourrait aussi expliquer indirectement l'augmentation de la CA. Le traitement dopaminergique est efficace dans le rétablissement des mécanismes « top-down » de l'AV, suggérant une implication des voies dopaminergiques dans ce domaine cognitif. Ces voies semblent aussi jouer un rôle dans les mécanismes « bottom-up » de l'attention, comme l'a suggéré le renforcement de la CA sous traitement dopaminergique.

La stimulation du NST a montré un effet similaire à celui obtenu par un traitement dopaminergique, en favour d'une implication directe des boucles des ganglions de la base dans le contrôle de l'AV. Nos résultats ont mis en évidence une spécialisation fonctionnelle de différents sous-territoires du NST en ce qui concerne les mécanismes de « top-down ». La stimulation SM produit des effets marqués sur les processus d'initiation de mouvement et des effets positifs sur les mécanismes endogènes de l'AV, alors que la stimulation de la partie AS semble être plus particulièrement efficace dans l'amélioration des mécanismes de sélection de cible.

Mots clés: attention visuelle sélective, capture attentionelle, stimulation cérébrale profonde, nayaux subthalmique, maladie de Parkinson.

Riassunto sintetico

Lo scopo di questo studio è stato quello di valutare il possibile ruolo dei diversi circuiti cortico-sottocorticali passanti per i gangli della base e della via dopaminergica sui meccanismi di top-down e bottom-up dell'attenzione visiva (AV).

A tal fine, abbiamo confrontato le prestazioni in 3 paradigmi computerizzati, adatti a studiare la cattura attenzionale (AC), la selezione della risposta motoria, e l'avvio del movimento, di due gruppi di pazienti affetti da malattia di parkinson (MP) - uno valutato in differenti condizioni di stimolazione elettrica (senza stimolazione, con stimolazione selettiva dell'area sensorimotoria, SM, o di quella associativa, AS, del nucleo subtalamico, NST), l'altro in differenti condizioni terapeutiche (con o senza trattamento dopaminergico) - con quelle di un gruppo di soggetti di controllo.

I nostri risultati hanno evidenziato che nella MP vi è un indebolimento dei meccanismi top-down di controllo dell'AV, che può spiegare, indirettamente, il parallelo incremento dell'AC osservato nelle medesime condizioni. Il trattamento dopaminergico si è dimostrato efficace nel ricondurre alla normalità i meccanismi top-down dell'AV, suggerendo un coinvolgimento della via dopaminergica in questa funzione della sfera cognitiva. Questa via sembra giocare un ruolo anche nei meccaniesmi di bottom-up dell'attenzione, come suggerito dall'aumento della CA osservato per effetto del trattamento dopaminergico.

La stimolazione del NST ha evidenziato un quadro simile a quello ottenuto con il trattamento dopaminergico, indicando un coinvolgimento diretto dei gangli della base nel controllo dell'AV. In particolare, i nostri risultati evidenziano una specializzazione funzionale dei differenti sub-territori del NST, nei meccanismi top-down. La stimolazione dell'area SM ha degli effetti pronunciati sui meccanismi d'avvio del movimento e un effetto positivo sui meccanismi dell'AVE, mentre la stimolazione AS sembra essere efficace soprattutto sui meccanismi di selezione del target.

Parole chiave: attenzione visiva selettiva, cattura attenzionale, stimolazione cerebrale profonda, nucleo subtalamico, malattia di Parkinson.

Abstract

Introduction. Some findings suggest that non-demented Parkinson's disease (PD) patients may be impaired in visual selective attention tasks, which involve the ability to focus on relevant information in a goal-direct manner (endogenous visual attention, EVA), while ignoring other interfering irrelevant stimuli. Indeed, patients may present enhanced distractibility in the presence of salient objects/events, which are able to capture their attention, determining a cost in terms of reaction time and accuracy during a goal-directed behaviour (attentional capture, AC), sufficiently to interfere with their daily activity. These observations suggest a possible involvement of the basal ganglia in visual attention (VA), since PD symptoms are mainly related to a striatal (dopaminergic) defect. Up to now, evidence for a role of the cortico-basal-ganglia loops in modulating VA mechanisms is poor and indirect.

Objective. To assess the role of different cortico-basal ganglia loops and dopaminergic pathways on the mechanisms underlying EVA and AC, by using two effective treatments in PD, that is dopaminergic and subthalamic nucleus (STN) stimulation.

Methods. The main instrument for our study was an AC task, which was appropriately integrated with a choice reaction time task and a simple motor reaction time task, to assess the effectiveness of the mechanisms underlying AC and visual selection of the target (EVA), as well as the mechanisms of motor response selection and movement initiation. We compared the performance on these tasks of two groups of PD patients, one evaluated in different sets of electrical (without stimulation, or selective stimulation of the sensorimotor, SM, or associative, AS, parts of the STN) stimulation, the other in different conditions of medication (with or without dopaminergic treatment), with those of a group of healthy subjects.

Results. PD patients assessed after withdrawal of dopaminergic treatment and after turning-off stimulation (stim-off) showed increased AC compared to healthy subjects. Also, target selection (EVA) and movement initiation times were prolonged in both groups of patients, while motor response selection time was significantly increased only in the otherwise stimulated group. It is noteworthy that the usual dopaminergic treatment of otherwise electrically stimulated patients was at significantly lower dosage than that of the otherwise pharmacologically treated group.

Under usual dopaminergic treatment and stimulation of the SM as well as AS part of the STN, patients showed similarly increased AC in terms of ΔRT (difference in reaction times between trials with and without singleton distractor of the AC task). Dopaminergic treatment and AS stimulation improved EVA, restoring it to the level of control subjects. Also the SM stimulation allowed a significant recovery of EVA compared to the stim-off condition, but to a lesser extent compared to that obtained by AS stimulation. No appreciable effects were observed on motor response selection times by stimulation of either site. The movement initiation RTs were reduced compared to the stim-off condition only by stimulation of the SM part of the STN.

Conclusions. Our results showed that in PD there is a weakening of the mechanisms underlying the top-down control of VA, which likely indirectly accounts also for the enhancement of AC. This finding is part of a more composite scenario of deficits, especially in otherwise stimulated patients, who undergo a milder drug treatment than pharmacologically treated patients, including slowing of the processes of movement initiation, and slowing of the processes of motor response selection.

Dopaminergic treatment proves to be effective not only in restoring movement initiation mechanisms, but also the top-down mechanisms of VA, suggesting an involvement of the dopaminergic pathways in this cognitive domain.

In parallel with the amelioration of the mechanisms of target selection, the observed enhancement of AC under dopaminergic treatment suggests that the dopaminergic pathways may be involved also in the mechanisms that compute salience of visual stimuli, or the bottom-up control of attention, although other interpretations are available.

The stimulation of the STN shows a similar effect to that obtained by dopaminergic treatment, establishing a direct involvement of the basal ganglia in VA control. In particular, our results strengthen the idea of a functional specialization of different sub-territories of the STN, and of the different cortico-basal ganglia loops in which they are integrated in relation to the top-down mechanisms of VA. As a matter of fact, two well distinct patterns seem to emerge depending on the stimulated region: SM stimulation produces marked effects on the movement initiation processes and appreciable positive effects on EVA mechanisms, while AS stimulation seems to be especially effective in improving the mechanisms of target selection. On the other

hand, no functional specialization of the sub-territories of STN in relation to the exogenous mechanisms of VA seems to emerge, suggesting that top-down and bottom-up mechanisms are supplied by different anatomical networks involving the cortico-basal-ganglia loops.

Résumé

Introduction. Plusieurs études suggèrent que les patients parkinsoniens sans démence pourraient présenter des déficits dans des tâches d'attention visuelle sélective qui nécessitent l'habilité a orienter volontairement leur attention vers un but (attention visuelle endogène, AVE) en ignorant tout autre stimuli non pertinents potentiellement sources d'interférences. En effet, les patients pourraient présenter une augmentation de la distractibilité en présence d'objets ou évènements saillants, qui ont la capacité de capturer l'attention du patient au cours d'un comportement dirigé vers un but, engendrant un coût suffisamment important en termes de temps de réaction et de précision (capture attentionnelle, CA), pour interférer avec les activités quotidiennes. Ces observations suggèrent une implication possible des ganglions de la base dans l'attention visuelle (AV), étant donné que les symptômes de la maladie sont principalement liés à un déficit striatal en dopamine. Jusqu'à présent, les éléments en faveur d'un rôle des boucles cortico-ganglions de la base dans la modulation des mécanismes de l'AV sont faibles et indirects.

Objectif. Évaluer le rôle des boucles cortico-ganglions de la base et des voies dopaminergiques sur les mécanismes sous-jacents à l'AVE et la CA, en utilisant deux traitements effectifs de la maladie de Parkinson (MP), que sont les traitements dopaminergiques et la stimulation du noyau subthalamique (NST).

Méthodes. Le principal instrument pour notre étude à été une tâche de CA, qui a été intégrée de façon appropriée avec une tâche de temps de réaction de choix et une autre tâche de temps de réaction motrice simple afin d'évaluer l'efficacité des mécanismes sous-jacents à la CA et à la sélection visuelle de la cible (AVE), ainsi que les mécanismes de sélection de réponse motrice et d'initiation de mouvement. Nous avons comparé les performances de deux groupes de patients parkinsonien sur ces tâches - un groupe étant évalué dans trois différentes conditions de stimulation électrique (sans stimulation, ou stimulation sélective de la partie sensorimotrice, SM, ou de la partie associative, AS, du NST), l'autre groupe étant évalué dans deux différentes conditions de traitement médical (avec ou sans traitement dopaminergique) - avec celles d'un groupe des sujets contrôles sains.

Résultats. Les patients évalués à jeun de traitement antiparkinsonien et après l'arrêt de

la stimulation (stim-off) ont montré une augmentation de la CA par rapport aux sujets sains. De même, les temps de sélection de la cible (AVE) et d'initiation de mouvement étaient augmentés dans les deux groupes de patients, alors que le temps de sélection de la réponse motrice n'augmentait de façon considérable que dans le groupe stimulé. Il convient de remarquer que le traitement dopaminergique habituel de patients autrement stimulés électriquement consistait en un dosage nettement plus faible que le groupe des patients autrement traités de manière pharmacologique.

Sous traitement dopaminergique habituel et sous stimulation des parties SM et AS du NST, les patients ont montré une augmentation comparable de la CA en termes de ΔRT (différence des temps de réaction entre les essais avec et sans distracteur de la tâche de CA). Le traitement dopaminergique et la stimulation de la partie AS du NST amélioraient l'AVE, en la ramenant au niveau des sujets de contrôle. De même, la stimulation de la partie SM du NST permettait une récupération considérable de l'AVE par rapport à la condition stim-off, mais dans une moindre mesure que celle obtenue par une stimulation de la partie AS. Aucun effet appréciable n'a été observé sur les temps de sélection de la réponse motrice par stimulation de l'un ou l'autre site.

Les temps de réaction motrice simple n'étaient réduits par rapport à la condition de stim-off que par la stimulation de la partie SM du NST.

Conclusions. Nos résultats suggèrent dans la MP, un affaiblissement des mécanismes « top-down » de contrôle de l'AV, ce qui pourrait aussi expliquer indirectement l'augmentation de la CA. Cette constatation s'inscrit dans le cadre d'un scénario plus composite des déficits, qui inclut le ralentissement des mécanismes d'initiation de mouvement, et le ralentissement des mécanismes de sélection de la réponse motrice, en particulier chez les patients stimulés électriquement qui sont soumis à un traitement dopaminergique plus faible que les malades traités seulement de manière pharmacologique.

Le traitement dopaminergique est efficace dans le rétablissement non seulement des mécanismes d'initiation de mouvement, mais également des mécanismes « top-down » de l'AV, suggérant une implication des voies dopaminergiques dans ce domaine cognitif. Parallèlement à l'amélioration des mécanismes de sélection de la cible, le renforcement observé de la CA sous traitement dopaminergique pourrait suggérer que la voie dopaminergique puisse également avoir un rôle dans les mécanismes

d’évaluation de saillance des stimuli visuels, ou le contrôle « bottom-up » de l’attention, bien que d’autres interprétations soient possibles.

La stimulation du NST a montré un effet similaire à celui obtenu par un traitement dopaminergique, en favour d’une implication directe des boucles cortico-ganglions de la base dans le contrôle de l’AV. En particulier, nos résultats ont mis en évidence une spécialisation fonctionnelle de différents sous-territoires du NST et des différentes boucles cortico-ganglions de la base dans lesquels ils sont intégrés en ce qui concerne les mécanismes de « top-down » de l’AV. En fait, deux modèles bien distincts semblent émerger selon le site stimulé: la stimulation de la partie SM produit des effets marqués sur les processus d’initiation de mouvement et des effets positifs appréciables sur les mécanismes de l’AVE, alors que la stimulation de la partie AS semble être plus particulièrement efficace dans l’amélioration des mécanismes de sélection de cible.

D’autre part, il semble y avoir aucune spécialisation fonctionelle des sous-territoires du NST par rapport aux mécanismes exogènes de l’AV, suggérant que les mécanismes « top-down » et « bottom-up » de l’AV soient fournis par des réseaux anatomiques différents, impliquant les boucles des ganglions de la base.

Riassunto

Introduzione. Alcuni studi suggeriscono che pazienti non-dementi affetti da Malattia di Parkinson (MP), possono presentare un'alterazione delle prestazioni durante l'esecuzione di compiti di attenzione visiva selettiva, che consiste nella capacità di focalizzare volontariamente l'attenzione su informazioni rilevanti (attenzione visiva endogena, AVE), ignorando nel contempo altri stimoli irrilevanti, che possono distogliere dall'obiettivo prefissato. Infatti, i pazienti possono presentare una spiccata distraibilità in presenza di oggetti/eventi salienti capaci di catturare l'attenzione durante l'esecuzione di un compito finalizzato (cattura attenzionale, CA), determinando un costo in termini di tempo di reazione e di accuratezza tale da interferire con le loro attività quotidiane.

Queste osservazioni suggeriscono un possibile coinvolgimento dei gangli della base nell'attenzione visiva (AV), poiché i sintomi della MP sono principalmente correlati a un deficit striatale dopaminergico. Ad oggi, la dimostrazione di un coinvolgimento dei circuiti cortico-sottocorticali nell'AV è parziale ed indiretta.

Obiettivi. Valutare il ruolo dei diversi circuiti cortico-sottocorticali passanti per i gangli della base e della via dopaminergica sui meccanismi che sottendono l'AVE e la CA, utilizzando due trattamenti efficaci nella malattia di Parkinson: la terapia dopaminergica e la stimolazione del nucleo subtalamico (NST).

Metodi. Il principale strumento impiegato nel nostro studio è stato un paradigma di CA opportunamente integrato con un paradigma di "choice reaction time" ed un altro di "simple motor reaction time". Questi tests hanno permesso di valutare l'efficacia sia dei meccanismi che sottendono la CA e la selezione visiva del target (AVE), sia di quelli di selezione della risposta motoria e di avvio del movimento. Con questi paradigmi, abbiamo confrontato le prestazioni di due gruppi di pazienti affetti da MP - uno valutato in differenti condizioni di stimolazione elettrica (senza stimolazione, con stimolazione selettiva dell'area sensorimotoria, SM, o di quella associativa, AS, del NST), l'altro in differenti condizioni terapeutiche (con o senza trattamento dopaminergico) - con quelle di un gruppo di soggetti sani di controllo.

Risultati. I pazienti valutati a digiuno di trattamento dopaminergico e dopo lo spegnimento della stimolazione (stim-off) evidenziavano un aumento della CA rispetto

ai soggetti sani. Inoltre, i tempi di selezione del target (AVE), e di avvio del movimento risultavano prolungati in entrambi i gruppi di pazienti, mentre il tempo di selezione della risposta motoria era significativamente aumentato soltanto nel gruppo degli stimolati. É rilevante notare che l'usuale trattamento dopaminergico del gruppo dei pazienti stimolati elettricamente era significativamente inferiore rispetto a quello del gruppo di pazienti trattato solo farmacologicamente.

Per effetto sia del trattamento dopaminergico abituale, sia della stimolazione delle aree SM e AS del NST, i pazienti evidenziavano un incremento simile della CA in termini di ΔRT (inteso come differenza nei tempi di reazione tra i trials con e senza distrattore del paradigma di CA). Il trattamento dopaminergico e la stimolazione dell'area AS del NST miglioravano l'AVE, riportandola al livello di quella dei soggetti di controllo. Anche la stimolazione dell'area SM consentiva di ottenere un miglioramento significativo dell'AVE rispetto alla condizione di stim-off, ma di entità inferiore rispetto a quello ottenuto per stimolazione dell'area AS. Per stimolazione di entrambe le aree del NST non si sono ottenuti modificazioni apprezzabili sui tempi di selezione della risposta motoria.

I tempi di avvio del movimento risultavano accorciati rispetto alla condizione di stim-off solo per stimolazione della parte SM del NST.

Conclusioni. I nostri risultati suggeriscono che nella MP vi è un indebolimento dei meccanismi top-down di controllo dell'AV, il che può spiegare, indirettamente, il parallelo incremento dell'AC osservato nelle medesime condizioni. Questo risultato è parte di un quadro variegato di deficit, in particolare nei pazienti stimolati elettricamente - i quali abitualmente assumono una quantità di terapia dopaminergica inferiore rispetto a quelli trattati solo farmacologicamente - che include il rallentamento dei processi di avvio del movimento, e il rallentamento dei processi di selezione della risposta motoria.

Il trattamento dopaminergico si è dimostrato efficace non solo nel migliorare i meccanismi d'avvio del movimento, ma anche nel ricondurre alla normalità i meccanismi top-down dell'AV, suggerendo un coinvolgimento della via dopaminergica in questa funzione della sfera cognitiva.

Parallelamente al miglioramento dei meccanismi di selezione del target, l'aumento della CA osservato per effetto del trattamento dopaminergico suggerisce che la via

dopaminergica possa avere un ruolo nei meccanismi di computazione della salienza degli stimoli visivi, o il controllo “bottom-up” dell’attenzione, sebbene altre interpretazioni siano possibili.

La stimolazione del NST ha evidenziato un quadro simile a quello ottenuto con il trattamento dopaminergico, indicando un coinvolgimento diretto dei gangli della base nel controllo dell’AV. In particolare, i nostri risultati rafforzano l’ipotesi di una specializzazione funzionale dei differenti sub-territori del NST, e dei diversi circuiti cortico-sottocorticali passanti per i gangli della base in cui essi sono integrati, nei meccanismi top-down dell’AV. In effetti, due quadri ben distinti sembrano emergere in funzione della regione stimolata: la stimolazione dell’area SM ha degli effetti pronunciati sui meccanismi d’avvio del movimento e un effetto positivo sui meccanismi dell’AVE, mentre la stimolazione AS sembra essere efficace soprattutto sui meccanismi di selezione del target. D’altra parte, non abbiamo evidenziato alcuna specializzazione funzionale dei differenti sub-territori del NST in rapporto ai meccanismi esogeni dell’AV. Ciò suggerisce che differenti circuiti neuronali, che coinvolgono i gangli della base, sottendono i meccanismi di top-down e bottom-up.

Abbreviations

AC: attentional capture
AS: associative
BDI-II: Beck Depression Inventory-II
DBS: deep brain stimulation
DBS-STN: deep brain stimulation of the subthalamic nucleus
DM: decision-making
EVA: endogenous visual attention
FAB: Frontal Assessment Battery
fMRI: functional magnetic resonance imaging
IE: inverse efficiency
MDRS: Mattis Dementia Rating Scale
MMSE: Mini-Mental State Examination
med-off: medication-off condition
med-off/ASstim-on: medication-off/associative stimulation-on condition
med-off/SMstim-on: medication-off/sensorimotor stimulation-on condition
med-off/stim-off: medication-off/stimulation-off condition
med-on: medication-on condition
PET: positron emission tomography
PD: Parkinson's disease
RT: reaction time
SAS: Starkstein Apathy Scale
SE: standard error mean
SM: sensorimotor
SRT: simple reaction time
STN: subthalamic nucleus
UPDRS III: Unified Parkinson Disease Rating Scale part III
V: voltage
V1: primary visual cortex
V2: visual area V2 or prestriate cortex
V3A: visual area V3A
V4: visual area V4

Background

Parkinson's disease (PD) affects 1.8% of people over 65 years. In rare cases, termed "early onset", sometimes of genetic origin, the disease begins between 18 and 40 years of age. PD is a gradually progressive neurodegenerative disorder. The main clinical signs are: tremor at rest, rigidity (hypertonia), bradykinesia (slowed and reduced voluntary and spontaneous movements), akinesia (difficulty to initiate movements), and postural disorders.[1-3]

Moreover, PD is known to be accompanied in many instances by a variety of cognitive deficits.[4] Generalized deficits in intellectual functions[5-7] have been reported, as well as more subtle and specific difficulties with visual-spatial perception,[8, 9] memory,[10, 11] language,[12] concept formation and behavioural regulation.[10, 13, 14]

Findings from several studies of PD patients suggest that this clinical population may have an attentional deficit. Poor concentration[15] and the inability to attend to more than one act at a time[16] have been reported in PD patients. In addition, these patients have been shown to exhibit difficult shifting from one set to another on the Wisconsin Card Sorting Test,[9, 14] to be unable to maintain a set against competing alternatives on the Odd-Man-Out choice discrimination task,[10] and are more prone to interference in the presence of a distactor stimulus than normal controls as measured on a dichotic listening task.[17]

Several behavioural studies indicate that PD patients with normal cognitive status may be impaired on visual attention tasks,[18-20] and more specifically on visual selective attention tasks.[21, 22] Besides, there is some evidence of an enhanced distractibility of PD patients in the presence of an irrelevant but salient stimulus, sufficient to interfere with their daily activity.[23-25]

Visual selective attention

One of the most severe problems of visual perception is information overload. Our capacity-limited brain is not equipped to deal with the vast amount of sensory information that more or less continuously is presented to us at any given time. Thus, it is important for the nervous system to make decisions which part of the available information needs to be selected for further, more detailed processing, and which

parts are to be discarded. Furthermore, the selected stimuli need to be prioritized, with the most relevant being processed first and the less important ones later, thus leading to a sequential treatment of different parts of the visual scene. This selection and ordering process is called *visual selective attention*.

Visual selective attention can be accomplished using one of two functionally different control mechanisms. *Endogenous or top–down* control refers to a voluntary mode of orienting that serves to keep attention directed at locations where behaviourally relevant stimuli are expected, regardless of the actual presence of stimuli.[26] Endogenous attention is said to be goal-directed when attentional priority is given to those events and objects that are in line with the current goals of the observer, personal history, and experiences. In contrast, *exogenous or bottom–up driven* control refers to a presumably automatic mechanism in which salient stimuli capture attention, without taking into account the internal state of the organism.[27-29]

A dramatic example of a stimulus that attracts attention using bottom-up mechanisms is a fire-cracker going off suddenly, while an example of top-down attention is the focusing onto difficult-to-find food items by an animal that is hungry, ignoring more "salient" stimuli.

According to the *biased competition model* of attention, as developed by Desimone and Duncan (1995), the competition among visual stimuli for neural representation occurs within visual cortex itself, and it can be biased by both top-down influences and bottom-up sensory-driven mechanisms. The stimulus that wins the competition for neural representation will have further access to memory systems for mnemonic encoding and retrieval and to motor systems for guiding action[30] (Fig.1)

Competition among visual stimuli biased by bottom-up mechanisms

Now, we have a fairly good understanding of how bottom-up sensory-driven mechanisms modulate the sensory interaction among multiple visual stimuli for neural representation, as revealed by the recording of single-cell activity, and hemodynamic events in neuroimaging studies. One way is by stimulus conspicuousness which occurs when an object has a unique feature (e.g. color, luminance, orientation, motion, size) that sets it apart from the rest of the image.[31] The term “pop-out” is often used to describe this capturing of attention through a bottom-up selection process.

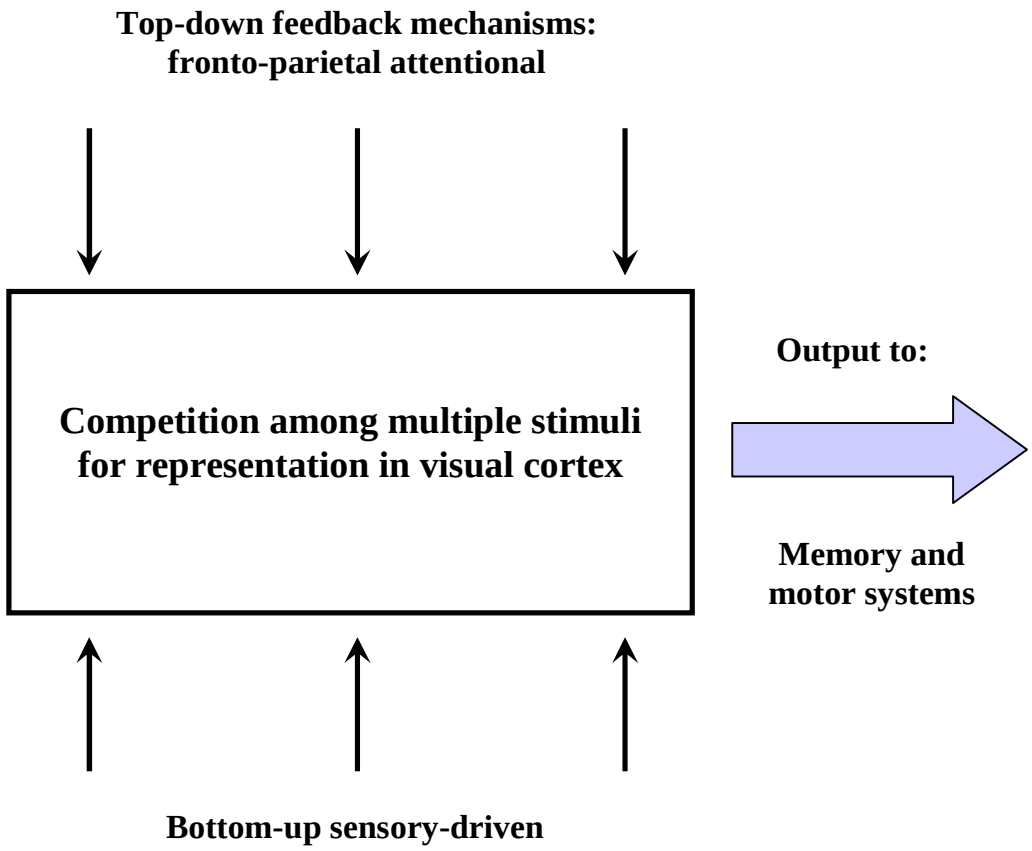

Fig.1 The biased competition model of visual attention.

Single-cell recording studies in the monkey have shed light on the neural correlates for competitive interactions among multiple objects in the visual field, by comparing responses to a single visual stimulus presented alone in a neuron's receptive field with the responses to the same stimulus when a second one is presented simultaneously within the same receptive fields.[32, 33] It has been shown that the responses to the paired stimuli within the receptive field were a weighted average of the responses to the individual stimuli when presented alone. For example, if a single effective stimulus elicited a high firing rate and a single ineffective stimulus elicited a low firing rate, the response to the paired stimuli was reduced compared to that elicited by the single effective stimulus. This result indicates that two stimuli present at the same time within a neuron's receptive field are not processed independently, for, if they were, then the responses to the two stimuli when presented together would

have summed. Rather, the reduced response to the paired stimuli suggests that the two stimuli within the receptive field interacted with each other in a mutually suppressive way. This sensory suppressive interaction among multiple stimuli has been interpreted as an expression of competition for neural representation. Sensory suppression among multiple stimuli present at the same time in the visual field has been found in several areas of the visual cortex, including extrastriate areas V2, V4, the middle temporal and medial superior temporal areas, and the inferior temporal cortex.[32-35]

Based on hypotheses derived from these monkey physiology studies, Kastner et al. (1998) examined competitive interactions among multiple stimuli in the human cortex using functional magnetic resonance imaging (fMRI).[36] In these studies, hemodynamic changes, as measured by fMRI, were used as indirect measures of neural activity. Complex, colourful visual stimuli, known to evoke robust responses in ventral stream visual areas of the monkey brain, were presented eccentrically in four nearby locations of the upper right quadrant of the visual field, while subjects maintained fixation. The stimuli were presented under two different presentation conditions, sequential and simultaneous. In the sequential presentation condition, a single stimulus appeared in one of the four locations, then another appeared in a different location, and so on, until each of the four stimuli had been presented in the four different locations. In the simultaneous presentation condition, the same four stimuli appeared in the same four locations, but they were presented together. Thus, integrated over time, the physical stimulation parameters were identical in each of the four locations in the two presentation conditions. However, sensory suppression among stimuli within receptive fields could take place only in the simultaneous, not in the sequential presentation condition, and in the correspondent brain areas seen for the monkeys. Importantly, the difference in activations between sequential and simultaneous presentations was smallest in V1 and increased in magnitude towards ventral extrastriate areas V4 and temporal-occipital area, and dorsal extrastriate areas V3A and middle temporal area. This increase in magnitude of the sensory suppressive effects across visual areas suggests that the sensory interactions were scaled to the increase in receptive field size of neurons within these areas. That is, the small receptive fields of neurons in V1 and V2 would encompass only a small portion of the visual display, whereas the larger receptive fields of neurons in V4, temporal-occipital

area, V3A and middle temporal area would encompass all four stimuli. Therefore, suppressive interactions among the stimuli within receptive fields could take place most effectively in these more anterior extrastriate visual areas.[31, 37]

Competition among visual stimuli modulated by top-down biasing signals

Several findings support the idea that unwanted distracting information is effectively filtered out by attention. Single-cell recording studies in the monkey have demonstrated that when a monkey directs attention to one of two competing stimuli within a receptive field in extrastriate areas V2 and V4, the response is similar to the response to that stimulus presented alone.[33] These findings imply that attention may resolve the competition among multiple stimuli by counteracting the suppressive influences of nearby stimuli, thereby enhancing information processing at the attended location. This may be an important mechanism by which attention filters out unwanted information from cluttered visual scenes.[30]

A similar mechanism operates in the human visual cortex, as revealed by fMRI studies, while subjects have to spatially direct attention on multiple competing visual stimuli in two different attentional conditions, that is either unattended or attended condition.[31, 36] During the unattended condition, attention was directed away from the visual display, while in the attended condition, subjects were instructed to maintain fixation and attend covertly (in an act of mentally focusing on one sensory stimulus, apart from eye movements) to the peripheral stimulus location closest to fixation in the display. In the attended condition the extent of activation of visual striate and extrastriate cortex areas increased significantly compared to the unattended condition. More importantly, and in accordance with prediction from monkey physiology, directed attention led to greater increases of fMRI signals to simultaneously presented stimuli than to sequentially presented stimuli. Additionally, the magnitude of the attentional effect scaled with the magnitude of the suppressive interactions among stimuli, with the strongest reduction of suppression occurring in ventral extrastriate areas V4 and temporal-ocipital area, suggesting that the effects scaled with receptive field size.

Visual attention paradigms to separately study top-down and bottom-up driven control

The most common experimental paradigm used to study visuospatial attention is the *Posner paradigm*.[26, 31, 38, 39] This experimental task revolves around cued visuospatial orientation that requires attentional activation. Subjects staring at a fixation point are usually presented with a cue that guides the individual toward a particular spatial location.[40, 41] This prepares the attentional system of the individual to anticipate and respond specifically to the corresponding target following the eliciting cue.

The cue and target are usually separated by relatively long intervals so that neural activation of attention can be assessed in the presence and absence of visual stimuli.[31] This helps to elucidate the neural mechanisms associated with attentional activation versus direct visual activation. A variation to this task increases visuospatial target unpredictability by using more randomly cued locations. This forces bottom-up pathway activation related to the stimulus-driven processes of visuospatial attention.[31, 40, 41]

The Posner's cueing paradigm includes slight variations, which allowed to elucidate the different pathways underlying endogenous and exogenous visual selective attention (i.e. top-down vs. bottom-up mechanisms), as reported in the next section.

In the endogenous orienting condition, a central cue (typically an arrow) points to a possible target location, thereby allowing the participants to focus their attention on that location. After cue presentation, the target will appear at the cued location (valid) in the majority of the trials, but will sometimes appear at an uncued location (invalid). The typical finding is that participants tend to respond faster and with higher accuracy to the target if it is presented at the cued location than when it is presented at the uncued location, revealing a benefit of location-cueing.

In an exogenous orienting condition, typically a brief peripheral onset cue is presented at one of the target locations. The cue does not predict the location of the subsequent target and it is assumed that the cue attracts attention automatically. Similar to central cueing, subjects are faster in responding to targets presented at the cued location than at the uncued location. However, unlike in central cueing, when the

stimulus onset asynchrony between cue and target exceeds approximately 250 ms, subjects respond more slowly to targets presented at the cued location.[39, 42] This phenomenon is called inhibition of return. Inhibition of return is believed to be the result of an automatic build-up of inhibition that occurs over time following the withdrawal of attention from the cued location.[39, 43]

Posner and colleagues' merit was to be able to assess in isolation the exogenous and endogenous components of visual attention by means of two variants of a very simple paradigm.

Top-down attentional control

Tract-tracing studies in monkeys have given insights into a distributed network of higher-order areas in frontal and parietal cortex that appears to be involved in the generation and control of attentional top-down feedback signals, as proposed by the biased competition model. In particular, these studies demonstrated direct feedback projections to extrastriate visual areas V4 and temporal-occipital area from parietal cortex and to anterior inferior temporal cortex from prefrontal cortex, as well as indirect feedback projections to areas V4 and temporal-occipital area from prefrontal cortex via parietal cortex[44, 45] (Fig.2).

The evidence that the top-down biasing signals generated in frontal and parietal areas produce a change within visual cortex derives from single-cell recording studies, which showed that spontaneous (baseline) firing rates were 30–40% higher for neurons in areas V2 and V4 when a monkey was cued to attend covertly to a location within the neuron's receptive field before the stimulus was presented there.[46] This increased baseline activity, termed the 'baseline shift', has been interpreted as a direct demonstration of a top-down signal that feeds back from higher-order control areas to lower-order processing areas. In the latter areas, stimuli at attended locations would be biased to 'win' the competition for processing resources at the expense of stimuli appearing at unattended locations.[30, 31, 47, 48]

Prefrontal cortex, namely the dorsolateral prefrontal cortex in humans, provides both inhibitory and excitatory input to distributed neural circuits required to support performance in diverse selective attention tasks.[49]

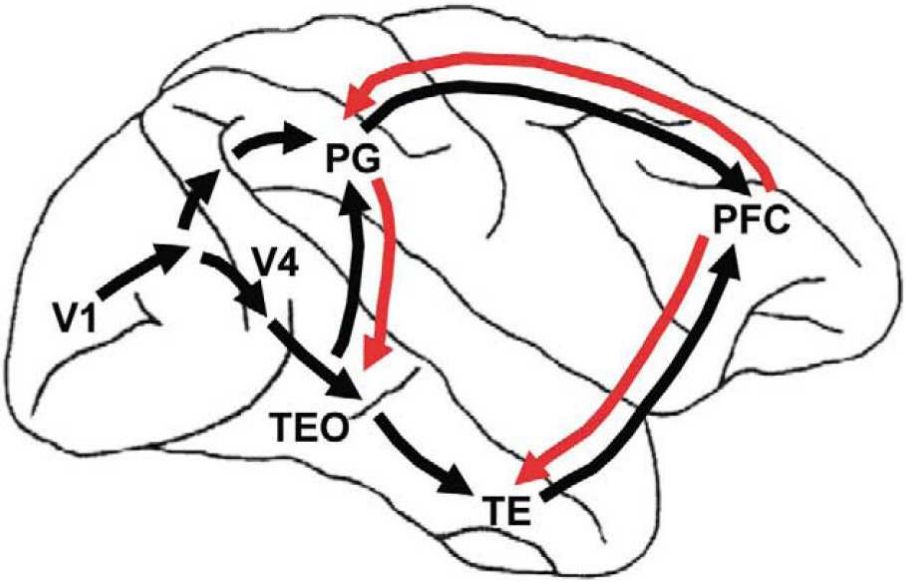

Fig.2 Anatomical substrate for top-down influences. Cortical visual processing, as outlined on a lateral view of a monkey brain, originates in the primary visual cortex (V1) and proceeds both ventrally and dorsally to temporal and parietal regions, respectively, before converging in prefrontal cortex. Red arrows indicate potential feedback connections that might provide the anatomical substrate for top-down attentional effects. Abbreviations: PFC, prefrontal cortex; PG, inferior parietal cortex; TE, anterior inferior temporal area; TEO, temporal-occipital area.[31]

The distractibility theory postulates that prefrontal patients are unable to suppress responses to irrelevant stimuli in a range of sensory and cognitive processes.[50] In particular, enhancements of primary auditory and somatosensory cortical responses to task-irrelevant distracters have been found in neurological patients with dorsolateral prefrontal damage[51] and in schizophrenic patients with prefrontal hypometabolism on positron emission tomography (PET) scanning.[52] This suggests that prefrontal damage disrupts inhibitory modulation of inputs to primary sensory cortex, perhaps through abnormalities in a prefrontal-thalamic sensory gating system, contributing to the attentional deficits observed in these patients. In addition to a critical role in inhibitory control of sensory flow to primary cortical regions, prefrontal cortex also exerts excitatory input to activity in multiple sub-regions of

secondary visual and auditory association cortex. Unilateral prefrontal damage results in multi-modal decreases in neural activity in posterior association cortex in the hemisphere ipsilateral to damage. This excitatory modulation is necessary to sustain neural activity during working memory.[49]

In humans, several studies provide evidence that a fronto-parietal attentional network may be the source of feedback that generates the top-down biasing signals modulating activity in visual cortex.[31] Interestingly, a fronto-parietal network of regions consisting of areas in the superior parietal lobule, the frontal eye field, and the supplementary eye field has been consistently activated in a variety of tasks involving visuospatial attention.[53-57] Other studies showed that directed attention in the absence of visual stimulation activated the same distributed network of areas as directed attention in the presence of visual stimulation and consisted of the frontal eye field, the supplementary eye field, and the superior parietal lobule. A time course analysis of the fMRI signals revealed that there was an increase in activity in these frontal and parietal areas during the expectation period (in the absence of visual input), with no further increase in activity evoked by the attended stimulus. These results suggest that the activity reflected the attentional operations of the task per se and not the effects of attention on visual processing. This conclusion is supported by the finding that, in the unattended condition, no significant visually evoked activity was observed in these frontal and parietal regions.[58, 59]

Additional evidence for a fronto-parietal network of regions involved in attentional control comes from another imaging study. By using an endogenous orienting condition similar to that of the Posner's paradigm, Corbetta et al. (2000) showed that the intraparietal sulcus was uniquely active when attention was directed toward and maintained at a relevant location (preceding target presentation), suggesting that the intraparietal sulcus is a top-down source of biasing signals observed in visual cortex.[60] Conversely, the exogenous orienting condition of Posner's paradigm, revealed right-hemisphere predominant activations, specifically encompassing regions in the temporal-parietal junction, anterior insula, and the ventral frontal cortex.

Corbetta and Shulman (2002) have recently proposed two anatomically segregated but interacting networks for spatial attention. According to their scheme, a

dorsal fronto-parietal system is involved in the generation of attentional sets associated with goal-directed stimulus-response selection. Key nodes within this largely bilateral network include the intraparietal sulcus/superior parietal lobule and the frontal eye field. A second, ventral system, which is strongly lateralized to the right hemisphere, is proposed to detect behaviourally relevant stimuli and to work as an alerting mechanism for the first system when these stimuli are detected outside the focus of attention. This latter network is thought to involve the temporo-parietal junction (at the intersection of the inferior parietal lobule and the superior temporal gyrus) and the middle and inferior frontal gyri. Overall, the dorsal and ventral networks can be thought of as subserving, respectively, endogenous and exogenous spatial attention functions.[54]

This fronto-parietal source of top-down biasing signals revealed by imaging studies exhibits great overlap with the set of regions implicated in visuospatial neglect in studies of patients with brain lesions affecting the right cerebral hemisphere.[31] Patients suffering of visuospatial neglect fail to detect stimuli on the side of space opposite the lesion, and they are not consciously aware of contralesional objects or parts of objects.[61] For example, a patient will read from one side of a book, apply make-up to only one half of her face, or eat from only one side of a plate. Patients with visuospatial neglect typically exhibit extinction. Detection reaction time (RT) in the contralesional field is not significantly slowed if a valid cue is given. When, however, a cue draws attention to the ispilesional field and the target subsequently appears in the opposite, contralesional field, then detection time is slowed dramatically. This pattern of results (i.e. extinction) is often interpreted as a deficit in one of the proposed elementary operations of attention,[62] namely, disengagement. Visuospatial neglect may follow unilateral lesions at very different sites, including the parietal lobe, especially its inferior part and the temporo-parietal junction ,[63] regions of the frontal lobe,[64] the anterior cingulate cortex,[65] the basal ganglia,[64] and the thalamus, in particular, the pulvinar.[66]

Saliency map

A remarkable attempt at understanding bottom-up attention and the underlying neural mechanisms was made by Koch and Ullman (1985).[67] They proposed that the

different visual features that contribute to attentive selection of a stimulus (colour, orientation, movement, etc.) are combined into one single topographically organized map, the *saliency map*, which integrates the information from the individual feature maps (each of which encodes contrast within a single feature dimension) into one global measure of conspicuity.[68-70] The bottom-up saliency is thus determined by how different a stimulus is from its surround, in many submodalities and at many scales. To quote from Koch and Ullman (1985), "saliency at a given location is determined primarily by how different this location is from its surround in colour, orientation, motion, depth etc".[67] Then, the saliency map is a topographically arranged map that represents visual saliency of a corresponding visual scene. These authors posited that the most salient location in a visual scene would be a good candidate for attentional selection. Once a topographic map of saliency is established, the attentional location is obtained by computing the position of the maximum in this map by a winner-take-all mechanism. After the selection is made, suppression of activity at the selected location leads to selection of the next location at the location of the second-highest value in the saliency map and a succession of these events generates a sequential scan of the visual scene.

The Koch and Ullman study was purely conceptual. The first actual implementation of a saliency map was described by Niebur and Koch (1996).[71] They applied their saliency map model which made use of colour, intensity, orientation and motion cues both to simplified visual input (as is typically used in psychophysical experiments) and to complex natural scenes and they demonstrated sequential scanning of the visual scene in order of decreasing salience (Fig.3).

Bottom-up mechanisms (and thus the saliency map) do not completely determine visual selective attention. In many cases, top-down influences play an important role and can override bottom-up saliency cues. Various mechanisms have been proposed to integrate top-down influences in the saliency map.[72] Activation in the salience map may be a function of feature weights, which are determined by the search goals. Visual conjunction search represents a type of task which shows clearly that top-down factors can influence visual selective attention. In the conjunction search paradigm, the target, which is embedded among irrelevant distracters, does not have a unique feature; instead, it is defined by a conjunction of features, as for example

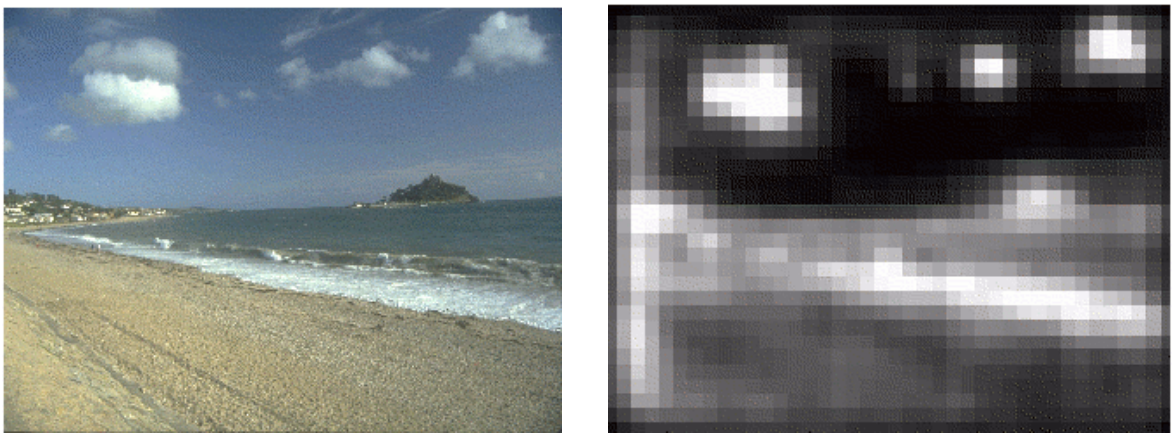

Fig.3. A visual scene on the left, with the corresponding saliency map to the right. The figure shows a complex visual scene and the corresponding saliency map, as computed from the algorithm in Niebur and Koch (1996). The scene is static so the motion component of the algorithm does not yield a contribution. The surf line is well-represented in the saliency map since it combines input from several feature maps: intensity, orientation and color all have substantial local contrast at several spatial scales in this area. The same is the case for the clouds and the island in the distance.

when a red T has to be found among red L's and green T's – here only the conjunction ''red + T" defines the target and not the features individually. The conjunction search requires serial search, in which the RTs increase linearly as the function of the number of elements in the display.[73] Egeth et al. (1984) had participants search for a red O between black O's and red N's, a typical conjunction search. They found that RT increased with increasing numbers of red elements in the display.[74] RT did not increase at all, however, when the number of black O's increased. Participants seemed able to ignore all black elements in the display, and restrict their search to the red ones. This experiment suggests that attentional selection can be influenced by top-down settings (e.g., to select only elements in the relevant dimension). This suggests that a mixture of bottom-up and top-down processes is likely at play during conjunction search: target features guide attention to the target, while subjects use the target feature information to form an attentional set to guide search in a top-down fashion.[47, 72, 75-77]

Thus, visual conjunction search paradigms are especially suitable to study the

interactions between top-down and bottom-up mechanisms of visual attention, more so than Posner's paradigms, which are instead suitable to study exogenous and endogenous orienting of attention in isolation.

The question where the saliency map is located in the brain arises thus quite naturally. Koch and Ullman (1985)[67] proposed that it may be located in the lateral geniculate nucleus of the thalamus, an area previously suggested as playing a major role in attentional control by Crick (1984).[78] Another thalamic nucleus, the pulvinar, is known to be involved in attention and has also been suggested as a candidate for housing the saliency map.[79] Another possibility is the superior colliculus (SC), likewise known to be involved in the control of attention.[80] Several neocortical areas have been suggested as well, including V1,[81] V4,[82] and posterior parietal cortex.[83]

The results of a series of experiments with monkeys performing visual search tasks have identified a population of frontal eye field visually responsive neurons that exhibit all of the characteristics of a visual salience map.[69] The frontal eye field is located in the rostral bank of the arcuate sulcus in the prefrontal cortex of macaques and is undeniably a part of the oculomotor system. Over the recent years, it has become rather obvious that neurons in frontal eye field not only are able to issue signals for oculomotor control, in particular for encoding the saccadic goal, but they also encode the location of a salient or otherwise relevant visual stimulus falling in the receptive field, indicating that they play a role in visual selection apart from and beyond the role in guiding gaze.[84] In fact, the frontal eye field is ideally positioned to contain a map of visual salience for guiding selective spatial attention. Frontal eye field is reciprocally connected with both the dorsal and ventral visual processing streams, and these connections are topographycally organized.[85] About half of the neurons in frontal eye field have visual responses with spatially defined visual receptive fields.[86] The visual cortex of primates is organized into functionally specialized areas that contain neurons that are tuned to one or a few feature dimensions.[87] The preattentive processing in these visual areas corresponds conceptually to the feature maps in the theoretical models of visual search.[68] The frontal eye field receives the signal from extrastriate visual cortex representing specific features such as form, color, and direction of motion. However, the frontal eye field visually responsive neurons do not exhibit selectivity for specific features;[88,

[89] instead they exhibit selective activation that is related to the overall behavioural relevance of stimuli, whether relevance is derived from the intrinsic properties of the stimuli or from the viewer's knowledge and goals. This selective activation in the frontal eye field is not in itself a motor command because the magnitude of activation reflects the relative behavioural significance of the different stimuli in the visual scene and occurs even when no saccade is made.[69]

In conclusion, there are a number of identified candidates which may correspond to different flavours of salience, perhaps more bottom-up driven in some area and more strongly modulated by behavioural goals in some other area.

Effects of time and space on visual selective attention

Most current accounts of visual perception suggest that there are two main stages of visual information processing: a low-level preattentive stage and high-level attentive stage.[47, 72, 76, 90] Preattentive processing occurs prior to the allocation of focal attention, has a large capacity and occurs in parallel fashion across the whole visual field. It has been suggested that one of the outcomes of preattentive processing is a salience map. The map location with the highest activation is then selected for further ''attentive" processing. Attentive processing has a small capacity and occurs only for a part of the visual field.[72]

Models of visual selection usually do not take into account the effect of time or space on selection.[47, 75-77, 90, 91] Theoretically, it is possible that early in processing, the salience map is computed from bottom-up factors alone, while top-down factors contribute late in processing.[27, 52, 92-96]

Another way in which the issue of top-down versus bottom-up control of selection could be resolved involves not time but space. Implicit in the idea of spatial attention is that some selected contiguous area in the visual field receives priority in information sampling. This area has been referred to as the ''attentional window" of observers.[97] Although spatial attention is mostly investigated in the context of selection of stimuli once they appear, observers probably use their expectations to limit spatial selection in advance of stimulus presentation. One way in which top-down settings might influence performance is that observers adjust the size of the attentional window according to their expectations of the task. This is precisely what

we can expect in Posner's paradigms, which are characterized by 50% of valid cues, with a consequent focusing of the attentional window. In particular, when observers expect an easy search, they presumably set their window so that it encompasses the entire display, and then pick the most salient element in it.[98] In case of a serial search task the window does not encompass the whole display. Instead, search elements are examined individually or in small clusters. If selection is limited to stimuli within the attentional window, setting the window size may provide a way for top-down control to influence selection from the bottom-up information.[72]

Attentional capture

Although the Posner's cueing paradigms are excellent tools to study the top-down and bottom-up driven processes of attention in isolation, their use in studying interactions between top-down and bottom-up driven processes are somewhat limited. In particular, one notable disadvantage of the cueing paradigm is that two different types of cues are used to modulate top-down versus bottom-up control of attention, making it hard to modulate these two forms of attention within the same framework.

A potentially better way to investigate the relation between top–down and bottom–up driven control is the attentional capture paradigm.[93]

Attentional capture, AC, refers to the phenomenon for which objects or events (which act as distracters) in visual space receive priority independent of the observer's goals, disrupting target search, and leading to slowed, incorrect and missing responses.[99] It can be considered as a measure of distractibility.

Scientific interest in AC has grown exponentially over the last 20 years.[100-102] A good part of this interest stems from the fact that modelling AC has the potential to provide fundamental insights into the nature of cognitive control.

To study the properties of AC, stimuli are typically used that are highly salient and ‘‘pop out’’ from the display (such as a red element surrounded by green elements), the so-called feature singletons. In the early 1990s, Theeuwes et al. developed a paradigm, referred to as the "irrelevant singleton" or "additional singleton" paradigm, which became a classical test to study AC.[92, 93, 100-103] In this paradigm, observers are asked to search a visual display and respond to a prespecified target defined by a particular feature value (usually a unique shape, color or onset element). This

condition is compared to a condition in which an irrelevant, yet salient non-target singleton item (object unique in a different dimension) may also be present (Fig.4). Critically, the presence of a salient distracter triggered a shift of attention to its location before attention was allocated to the target, increasing the time required to respond to the target.[92, 104, 105]

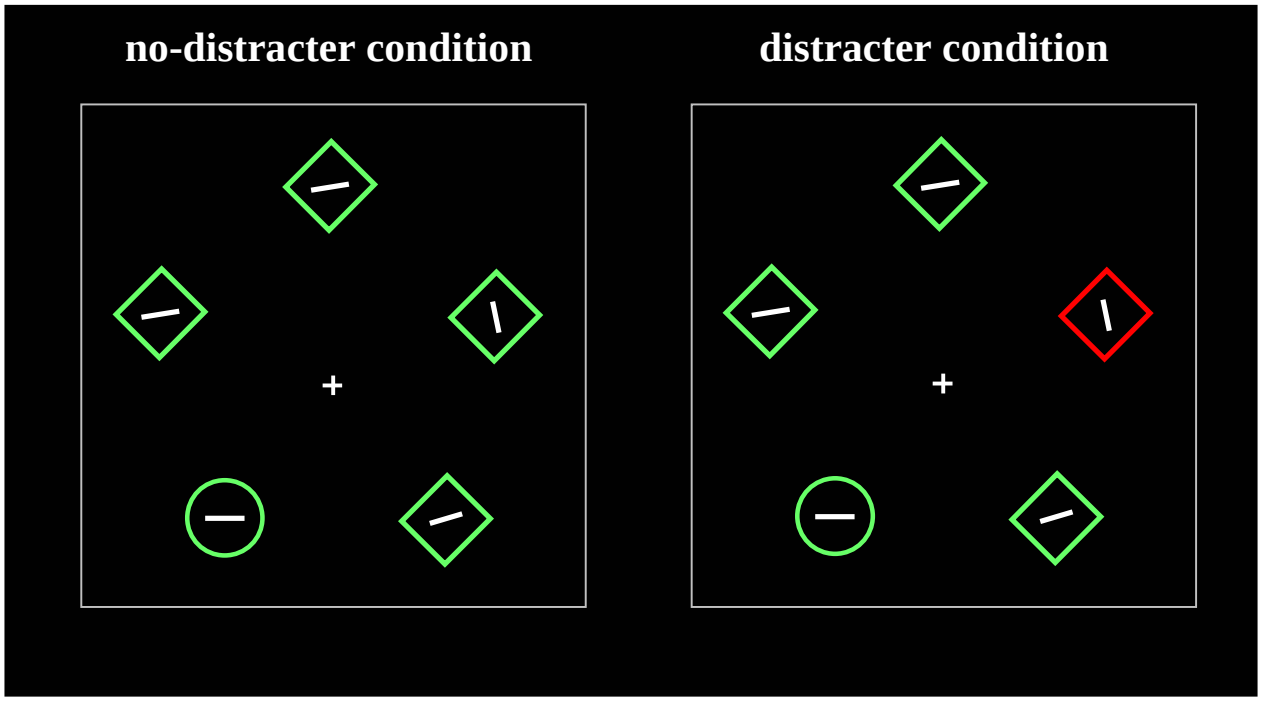

Fig.4 Example of trials of a classical attentional capture task referred to as the “irrelevant singleton” paradigm. In this case, in the no-distracter condition, the target is represented by the single green circle that contains a horizontal (but it could be vertical) oriented white line, surrounded by four green squares, which contain a white line tiled by 22,5 degrees. This condition is compared to a condition in which an irrelevant, yet salient non-target singleton (distracter) may also be present. In this case the distracter is represented by a red square.

Recently, this AC effect has been investigated by using event-related potentials.[106] In particular, as reported by Van der Stigchel et al. (2009), some studies have focused on a component of the event-related potentials called the ‘N2pc’ that is considered an index of the deployment of spatial attention.[72] The N2pc is defined as a

larger negative voltage at electrodes contralateral to an attended stimulus and is thought to reflect the attentional selection of an item via the suppression of surrounding items.[107] Hickey et al. (2006) investigated whether a salient colour singleton in the AC paradigm elicits an N2pc. When target and distracter were presented in opposite hemifields, an N2pc was observed for both stimuli, with the distracter-elicited N2pc preceding the target-elicited N2pc. This indicates that participants shifted their attention first to the distracter and then to the target, in line with the idea that irrelevant salient singletons capture attention independently of the top-down set.[106]

It is noteworthy that in the AC task the singleton is always irrelevant but salient, and nonetheless it is able to disrupt the target search, while in 50% of the trials of the exogenous orienting condition of Posner's paradigm the exogenous cue validly predicts the target. This suggests that the AC paradigm is more suitable than Posner's task to study the competition between top-down and bottom-up mechanisms of visual attention, and a distraction effect.

The RT cost due to the distracter led Theeuwes (1991, 1992) to argue that the colour singleton captured attention automatically because of its high level of saliency.[92, 103] The experiments described above can be interpreted with reference to a salience map.[72] Both the target and distracter objects are represented on the map, with the distracter having a larger activation than the target. If activation in the salience map is determined by top-down goals, there should have been no interference from the distracter, but there is. The presence of a salient distracter slows down the search for the target, and it can also reduce the target's detectability. On the basis of these findings, several authors have argued that AC is basically bottom-up and not subject to top-down control.[94, 104, 106, 108, 109] Importantly, the critical factor for the AC is the relative salience of the target and distracter: when the target was more salient than the irrelevant singleton, AC by the distracter was eliminated. [92, 93, 109]

According to another view, the ability of a stimulus to capture attention is contingent on whether an attentional-capturing stimulus is consistent with the top-down attentional setting; stimuli that do not match the top-down settings will be ignored.[110, 111] For instance, when searching for a red target, an irrelevant red cue that preceded the search display captures attention while an irrelevant onset has no effect

on performance.

Recently, Theeuwes (2004) suggested that the size of the attentional window[109] of observers could be one of the factors explaining why salient colour singletons fail to capture attention in some studies using a visual search task.[110, 112-114] As discussed earlier, observers may adjust the size of the attentional window according to their expectation of a search task. When the target is a unique object, as in the task used by Theeuwes (1992, 1994), the optimal strategy to find the target is to divide attention across the whole display.[92] As a consequence, the uniquely colored item that falls inside the attentional window is processed in parallel and captures attention. In case of a serial search task the window does not encompass the whole display. Instead, search elements are examined individually or in small clusters. This increases the chance that the unique element is not included in the initial salience computations and does not capture attention.[110, 111, 114] Therefore, as put forward by Van der Stigchel et al. (2009), changing the attentional window changes the set of objects that are attended.[72] Then, the size of an attentional window is a variable that needs to be considered when AC by a salient singleton is investigated. The only thing that is under top-down control seems to be the size of the attentional window. However, there is no top-down control within the attended window.

In conclusion, although both fMRI and event-related potential studies convincingly showed a possibility of top-down modulation of feature selective areas, the behavioural findings from AC paradigms suggest that this neural modulation does not necessarily influence initial selection.

The actual orienting of attention on the basis of bottom-up factors appears to depend on the conjoint activity of areas in the parietal and frontal networks.[29, 115]

Covert attention orienting

Selective attention can be directed to discrete locations in the visual field without saccades (covert attention), which improves perception at the attended location relative to nonattended locations.[69, 116] Recent research indicates that attention and eye movements are highly related, and they may be implemented via a common mechanism. According to the premotor theory of Rizzolatti et al. (1987) saccade programming in the frontal eye field and other oculomotor structures provides

the basis for covert orienting.[117]

In humans, functional imaging studies show that the frontal eye field is active during the allocation of attention with and without eye movements,[54, 118] and transcranial magnetic stimulation over the frontal eye field facilitates visual perception[119] and modulates performance in visual search tasks without saccades.[120] Recently, Moore et al. (2001, 2003) demonstrated that weak electrical stimulation of the frontal eye field below the threshold for producing saccades improves the perceptual abilities of monkeys,[121] and produces enhanced responses in extrastriate visual cortex that resembles the effects of directed spatial attention.[122]

The close relationship between covert attention and saccades suggests that the relative contribution of bottom-up and top-down control of selection can be investigated by recording eye movements. In particular, part of the evidence for the influence of timing on attentional selection comes from visual search experiments in which eye movements were recorded.[72, 96] In a variant of the AC paradigm, the so-called 'oculomotor capture' paradigm, observers viewed displays containing a number of grey circles positioned on an imaginary circle around a central fixation point.[95, 123] After a fixed period, all circles changed colour except one (the target circle). Upon the presentation of the target, on some trials an additional irrelevant red circle was presented with abrupt onset in the display. In 30–40% of trials in which the additional onset circle was presented, participants did not saccade to the target element, but made an eye movement to the onset distracter element: the eye was 'captured' by the onset distracter. Consistent with the idea that initial selection is stimulus-driven, latencies of the saccades directed to the irrelevant onset are generally shorter than the latencies directed to the target.

Visual selective attention and attentional capture in Parkinson's disease

Several behavioural studies indicate that non-demented PD patients may be impaired on tasks of visual selective attention. For example, PD patients demonstrate abnormal performance on the Stroop task, which requires subjects to attend selectively to the colour of the ink in which words are printed while ignoring the actual word itself.[21, 124] These patients are also impaired on visual search tasks that require subjects to attend selectively and localize targets among distracters.[21-24, 124] In

particular Deijen et al. (2006), studied the susceptibility to distracters in early stage PD, using an "oculomotor capture" task, like that described in the previous paragraph, and in which in half of the trials an irrelevant stimulus with sudden onset was added to the display.[23] They found a deficit in suppressing reflexive saccades to these stimuli in spite of the fact that they were entirely task-irrelevant. This important piece of work is very important for the purposes of our study because it allowes us to make some predictions on the relation between top–down and bottom–up driven control in PD patients. Indeed, it was the study of Deijen et al. which inspired our current study.

Maddox et al. (1996) found that a significantly larger proportion of a group of non-demented PD patients, as compared with a group of healthy subjects, were impaired in making perceptual judgements about a simple visual stimulus when it was presented with other irrelevant visual information.[125] However, the fact that nearly one third of the PD patients were able to attend selectively in an optimal fashion suggests that visual selective attention was not equally compromised in all PD patients. These results are consistent with the fact that PD can manifest itself with heterogeneous cognitive profiles.[5]

Some authors have argued that in visual search tasks PD patients are impaired in certain aspects of the build-up and maintenance of inhibition of the irrelevant stimuli over time.

Filoteo et al. (1997) studied the endogenous and exogenous shifts of attention in non-demented PD patients, using the tasks devised by Posner.[126] They showed that, like in healthy subjects, at longer stimulus onset asynchronies, the responses of PD patients in the cued condition relative to the responses in the uncued condition were delayed compared to the ones measured at short stimulus onset asynchronies, which has been interpreted in terms of inhibitory mechanisms.[43, 127] However, in both exogenous and endogenous conditions, namely following peripheral as well as central cues, the magnitude of this delay was lower for PD patients than for healthy controls. Therefore, the authors supposed that attentional deficits in PD patients were caused by a rapid decay of inhibitory mechanisms which, under physiological conditions, impede access of irrelevant information to the cognitive processing system. Thus, PD patients could be more vulnerable to distracting information than healthy controls. This idea has been supported by studies on *negative priming*.[128] Negative priming

refers to the phenomenon of delayed response latencies and increased error rates when participants have to respond to a target presented in a probe display that was ignored in a previously presented prime display (ignored-repetition condition). It has been assumed that negative priming is due to inhibition of the mental representation of the previously ignored stimulus.[129, 130] Before an appropriate response can be performed to the target of the probe display, this existing inhibition has to be overcome. Interestingly, clinical studies revealed that PD patients did not show negative priming,[131, 132] or show a reduction in the magnitude of the negative priming.[133] Also these findings suggest that attention-related inhibitory mechanisms are severely impaired in PD patients.

Cortico-basal ganglia loops

PD is a neurodegenerative and progressive disorder of the basal ganglia characterized by a selective loss of dopaminergic neurons, predominantly in the substantia nigra pars compacta.[134]

The basal ganglia can be viewed as components of functional circuits including thalamus and higher-level cortical areas.[135] Higher-level cortical areas send projections to the basal ganglia, which outputs project to the thalamus and back to the originating cortical areas.[136] Within the basal ganglia a direct pathway from the striatum to the globus pallidum internum and substantia nigra pars reticulata associated with excitation of motor actions, can be distinguished from an indirect pathway connecting the striatum and the globus pallidum internum/substantia nigra pars reticulata via external globus pallidus and the subthalamic nucleus (STN). This indirect pathway is associated with inhibition of action. The balance between these two pathways is moderated by the neurotransmitter dopamine which exerts an inhibitory or excitatory effect depending upon the postsynaptic receptor type, i.e. receptors of either the D1 or D2 receptor family. A third pathway connects directly the cortical motor and premotor areas to the STN (hyperdirect pathway),[137] and it mainly inhibits all motor programs in a reset-like fashion.[138] Considering that the entire cerebral cortex actually projects to the basal ganglia, a global subdivision of cortical activity into three functional territories referred to as sensorimotor (SM), associative (AS) and limbic was adopted.[137] These three functional cortical territories

project to different portions of the basal ganglia nuclei, the SM territory in the dorsolateral portions, the limbic territory in the ventromedial portions, and the AS territory in the central intermediate portions.[139-141] The basal ganglia system works as a device that receives a sample of the three specific functional aspects of cortical information and processes this information in a convergent manner. Moreover, a complex integration of cortical information takes place in each of the basal ganglia nuclei, that results in the elaboration of a completely new and specific output message that will be sent to the frontal cortex.

Thus, a deficit of the central dopaminergic activity can determine a functional impairment of the cortico-basal ganglia loops, explaining way in PD patients not only control of motor actions, but also cognitive functions, such as selective attention, are compromised.

Subthalamic nucleus

In spite of its small size, 12 × 5 × 3 millimetres, the STN seems to play a key role in modulating the output activity from the basal ganglia, in reason of its anatomo-functional organization, and its afferent and efferent connections with the cortical and subcortical structures.[138]

The role of the STN must be considered at different scales. At the macroscopic scale it works like a thermostat that would regulate the level of execution of cortical commands. In the normal state, with an appropriate level of activity, it enables normal execution of cortical commands. When hyperactive, it slows down all cortical programs, like in parkinsonian akinesia, which can be released by its inactivation by lesion[142] or high frequency stimulation.[143] At a territorial scale, considering its functional subdivision, the STN can process separately motor, AS, and limbic information.[144] Non motor effects, such as improvement of obsessive-compulsive disorders,[145] or production of a hypomanic state,[140, 146] as well as mirthful laughter[147] have been obtained by stimulation in the ventromedial, likely limbic part of the nucleus. At the neuronal scale, STN assures a much finer neuronal representation of limbic, AS and motor cortical commands, which are distributed in a medio-lateral gradient without any clear-cut segregation between different territories. In this sense, the whole nucleus has to be considered an integrator of emotional and motor aspects

of behaviour.[140, 148]

Striatal dopamine depletion, the hallmark of PD, is associated with an abnormal activity of STN.[149] Inactivation of the STN has thus been proposed as an alternative therapy to dopaminergic treatments in Parkinsonism.[142]

Current treatments in Parkinson's disease

Current treatment options for PD patients include levodopa and dopamine agonists. However, levodopa principally causes motor complications after long-term treatment (i.e., wearing-off and dyskinesia) and dopamine agonists may cause non-motor complications, such as excessive sedation, cardiac valve damage, psychosis and dopamine dysregulation syndrome.[150]

Very little is known, however, about the capacity of levodopa and dopamine agonists to improve cognitive deficits in PD. In the early 1970s, many studies suggested a positive effect of levodopa on cognitive signs.[151] Downes et al. (1989) have noticed an elevated sensitivity of the non-medicated PD patients to distractibility, thus suggesting that the attentional deficit could be corrected at least partly by levodopa therapy.[152] Later on, the influence of levodopa on cognitive functions has been assessed in patients subjected to controlled withdrawal. Data showed that certain, but not all, aspects of the cognitive functions were altered, emphasizing putative dopaminergic control on frontal lobe related functions such as working memory or executive functions.[153]

Therefore, the cognitive effect of levodopa might not depend on a neuropsychological specificity of the drug or the severity and progression of the disease, but, more likely, may be a function of dopaminergic depletion in the different parts of the basal ganglia and prefrontal cortex, since improvement or impairment of cognitive function with dopaminergic treatment is partial and task-related. In fact, the effects of levodopa on cognitive functions have been reported as beneficial as well as deleterious.[154-156] In a recent paper, Cools et al. (2001)[157] studied the effects of levodopa administration in PD on behavioral tasks associated with the different components of corticostriatal circuits described by Alexander et al. (1986).[135] The data showed that switching between two tasks, which requires high level of attentional control and involves the dorsolateral part of prefrontal cortex and parietal cortex, is

improved by levodopa treatment, whereas probabilistic reversal learning, associated with the orbitofrontal loops, is impaired. Consequently, it can be speculated that doses of levodopa necessary to improve motor aspects of PD also contribute to facilitate dopamine transmission in dorsolateral-parietal cortical areas, but may "overdose any area where dopamine regions are relatively intact", such as the orbitofrontal cortical areas.[157] Such a view is reinforced by the data by Weder et al. (1999), showing that working memory and directed attention deficits correlate at subcortical levels with a specific decrease in dopaminergic innervation at the level of the caudate nucleus and not at the level of the putamen.[158]

During the last two decades, deep brain stimulation (DBS) has revolutionized the treatment of advanced PD, becoming a routine method.[159-161] The main indication for DBS in PD is advanced PD with motor complications with relevant disability or therapy-resistant parkinsonian tremor. The ultimate goal of the DBS surgical procedure is the precise implantation of a stimulation quadripolar electrode in the targeted brain area and the connection of this electrode to a programmable pulse generator usually located subcutaneously in the subclavicular area (Fig.5). The stimulation is accomplished via one or more of the four contacts on its distal end. The pulse generator settings can be adjusted post-operatively by telemetry with respect to electrode configuration, voltage, amplitude, pulse width, and frequency. The implantation of the electrode is done by a stereotactic procedure in the awake patient in the medication-off state after 12-h drug withdrawal. Prior to the operation, the target is predetermined by means of stereotactic imaging procedures such as MRI, computed tomography or ventriculography. Many reports documenting significant and long-term benefit in PD with DBS surgery have been reported so far.[162-164] In particular, STN-DBS has been shown to improve to a great extent all the levodopa-responsive parkinsonian signs and levodopa-induced dyskinesia, and significantly reduced the need for daily anti-PD drugs.

In STN-DBS, the literature regarding neuropsychological outcome reports mixed results. In carefully selected patients, most groups have reported relatively little cognitive morbidity[162, 165, 166] with improvements in some areas.[167-169] In contrast, other studies have reported declines. The most robust finding across studies appears to be a decline in word fluency.[139, 166, 170] However, a minority of studies have

documented declines in verbal memory and selected measures of executive function.[170-172]

From a scientific point of view, since DBS modulates basal ganglia activity, it represents a rare opportunity to study the involvement of basal ganglia in motor, behavioural and cognitive functions.

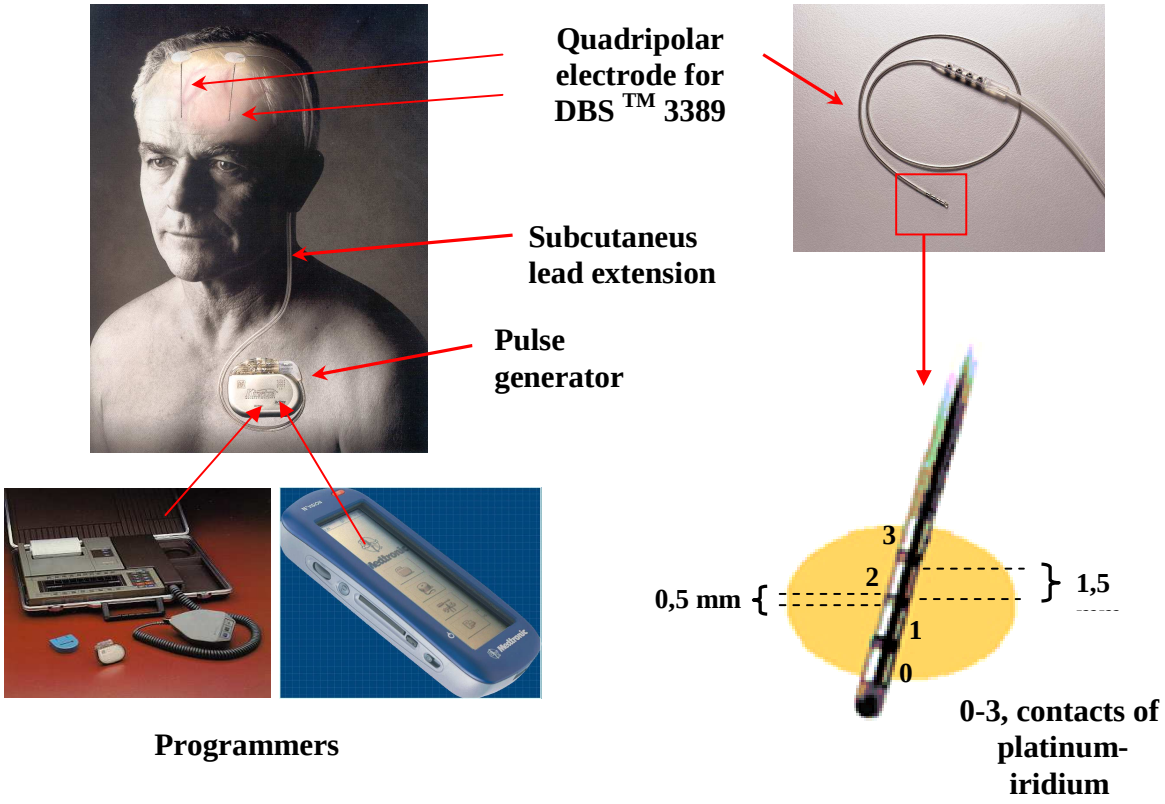

Fig.5 The deep brain stimulation system.

Involvement of the cortico-basal ganglia loops in visual attention

In animals, there is some evidence for the assumption that the basal ganglia, and in particular central dopaminergic activity, plays an important role in visual attention.

Baunez et al. (2007) studied the effects of high frequency stimulation of the

STN in rats performing a visual attentional task.[173] They demonstrated that the stimulation administered to control (non dopamino-depleted) rats impaired performance in the visual task. The same results had already been observed as a consequence of STN lesions.[174]

Considering the interconnections of the basal ganglia with the cortical areas, the selective attention deficits may be the result of dysfunction in other brain regions secondary to basal ganglia damage. For example, it is possible that dysfunction in the prefrontal cortex results in PD patients' selective attention deficits. Post-mortem examination of Parkinson brains has revealed a depletion of dopamine in the mesocortico-limbic projection.[175] The depletion of dopamine in these pathways has been implicated in the mediation of attentional processes in animals. In rats and monkeys, localised lesions of the ascending dopaminergic projection to the prefrontal association cortex caused an attention deficit as measured by a visual selective attentional task.[176, 177] The deficit produced by these lesions in monkeys was almost as severe as that caused by direct lesion of the prefrontal cortex and could be partially reversed by dopamine agonists.

The putative contribution of the dopaminergic neurons in the regulation of attention was also examined in a series of experiments consisting in recording dopaminergic neuronal activity directly at the mesencepahlic level or from neurons in the target area of the dopaminergic terminals. By this technique, it was shown that the typical electrocortical rhythms associated with attentive behaviour was suppressed either by the lesion of mesencephalic dopaminergic neurons[178] or injections of neuroleptics.[179] In contrast, these rhythms were shown amplified by dopaminergic precursors. Moreover, the neuronal discharge of the dopaminergic neurons recorded at mesencephalic level in behaving animals correlated with attentional processes.[178] Schultz (1994) showed that in primates dopaminergic neurons responded to unexpected events, then representing an alerting signal which interrupted the ongoing behaviour, allowing an adaptive reaction.[180] The suppression of the dopaminergic neurons could thus result in loss of the adaptive capacities of behaviour, as shown in Parkinsonism.

Chudasama et al. (2003) using a disconnection procedure, showed that rats with disconnected lesions of the medial prefrontal cortex and STN were impaired in a test

of visual attention.[181] This study provides direct evidence that performance in tasks that require optimal attentional and executive control relies on a corticosubthalamic interaction within the neural circuitry of the basal ganglia.

The SC is part of a network of brain areas, that directs saccadic eye movements. In particular, it receives inhibitory input from the frontal eye field via the caudate nucleus and the substantia nigra pars reticulata.[182] Muller et al. (2005) showed that microstimulation of a specific location in the SC spatial map would enhance visual performance at the corresponding region of space.[183] This data provides direct evidence that the SC contributes to the control of covert spatial attention. Then, dysfunction within the frontal lobes or the basal ganglia could determine a deficit in visual spatial attention.

In humans, the demonstrations of an involvement of the cortico-basal ganglia loops in visual attention are poor and indirect. In a study with normal subjects, PET has identified hypermetabolism within the basal ganglia during the administration of selective attention tasks.[184]

Applying PET, Volkow et al. reported a positive relationship between dopaminergic activity in the striatum and performance on the Stroop Test.[185] As regards this test, in PD patients treated by STN-DBS, some authors pointed out an increase of the errors during the stimulation.[168, 186, 187]

Summary of the introduction

Our capacity-limited brain is not equipped to deal with the vast amount of sensory information that is presented to us at any given time. Visual selective attention is the basic cognitive faculty that allows us to filter out irrelevant sensory information in favour of the relevant input. It is now well accepted that visual selective attention may be accomplished using two different anatomically segregated but interacting networks, endogenous or top-down (goal-directed), and exogenous or bottom-up (automatic) mechanisms, as demonstrated by a number of lesional, neurphysiological, behavioural, and functional MRI and PET studies in animals, as well as in humans.

In humans, several studies provide evidence that the dorsolateral prefrontal cortex and a fronto-parietal attentional network, may be the source of feedback that generates the top-down biasing signals modulating activity in visual cortex, while a second ventral cortical network, including the temporo-parietal junction and the middle and inferior frontal gyri is thought of as subserving the exogenous spatial attention functions.

Essential for the understanding of the bottom-up attention is the concept of saliency map, which is a topographically arranged brain map that represents visual saliency of a corresponding visual scene.

Different paradigms have been developed by several researchers during the last decades to measure visual attention processes. This is, for example, the case with the Posner's cueing paradigms which allow to study in isolation bottom-up from top-down mechanisms. In the AC paradigm, observers have to respond to a prespecified target, but in a number of trials their search may be disrupted by the appearance of a salient but irrelevant element, the distracter, which determines a cost in terms of reaction time and accuracy (AC phenomenon) of the goal-directed behaviour. This task proves to be suitable to study the competition between top-down and bottom-up mechanisms of visual attention, and it represents a useful tool to measure the degree of distractibility. Several experiments suggest that AC is basically bottom-up and not subject to top-down control. But this is controversial and other studies indicate the involvement of the top-down system. Further work is therefore required to clarify this issue.

Numerous neuropsychological tests have been used to study visual attention in PD. One of the most widely used the Stroop test which assesses among other parameters visual selective attention. The Posner's cueing paradigms have also been tested in PD patients.

Several lines of evidence suggest that attentional deficits in PD are caused by diminished inhibitory mechanisms. Moreover, PD patients could be more vulnerable to distracting information than healthy controls.

In animals, there is some evidence for the assumption that the basal ganglia, and in particular central dopaminergic activity, play an important role in visual attention.

Conversely, in humans, the evidence for a role of the cortico-basal-ganglia loops and dopaminergic pathways in modulating visual attention mechanisms is poor, controversial and indirect.

The STN-DBS, which is one of the most effective treatments in PD, represents a rare mean to directly study the possible role of basal ganglia in several brain functions. Indeed, this therapy allows to modulate the neuronal signals conveyed into the cortico-basal ganglia loops passing across the STN.

Objectives

Main Objectives:

1) to assess the effects of PD on visual selective attention and AC.
2) to study the effects of dopaminergic stimulation and the neuromodulation of the STN on visual attention performances in PD, assessing directly a possible involvement of the cortico-basal ganglia loops in these cognitive functions.

Secondary Objectives: from a clinical and neurophysiological point of view to study the respective role of the dopaminergic pathways and the SM and AS cortico-basal ganglia loops passing through the STN in visual attention performances.

Subjects, material and methods

Subjects

Three groups of subjects participated to this study:

group #1: pharmacologically-treated PD patients;
group #2: PD patients treated by STN-DBS;
group #3: healthy controls.

PD patients were selected among those treated at the Movement Disorder Unit of the Neurological Department of the University Hospital Centre (CHU) of Grenoble and at the Department of Neurological, Neuropsychological, Morphological, and Movement Sciences of the University of Verona (Italy). They were evaluated during their usual follow-up admissions.

As regards the surgical procedure for the implantation of electrodes in the STN-DBS treated patients, it was carried out as already reported by the Grenoble team,[188] but with some differences in the preoperative targeting (3T non-stereotactic MRI fused with 1T stereotactic MRI instead of ventriculography), and during the intraoperative neurophysiological exploration (2 or 3 trajectories instead of the usual 5) for the Verona team. Correct placement of the electrodes in both STNs was strongly suggested by the efficacy of the neurosurgical procedure, confirmed by

postoperative MR images, and by the clinical outcome. A few days after implantation of the electrodes, a double-channel programmable pulse generator (Kinetra model 7428, Medtronic, Minneapolis, Minnesota, USA) was placed in the subclavicular area and connected to the electrodes. All patients were implanted bilaterally with quadripolar electrodes (DBS-3389, Medtronic). The postoperative effects of stimulation were assessed through each of the four contacts to identify the one providing the best therapeutic window, defined as the difference between the current intensity threshold for the first adverse effect, and the current intensity to obtain the obtimal motor benefit by DBS. This contact was used for chronic stimulation.

Healthy controls were selected among patient family circle, the staff of CHU as well as the staff of the University of Verona.

Before entering the study, all participants underwent physical, neurological and neuropsychological examinations to ensure that they fulfilled the criteria set by the protocol.

The motor state of PD patients was evaluated by the Unified Parkinson Disease Rating Scale part III, UPDRS III, which is part of a composite scale used to measure the severity of the disease.[189] The maximum score on the UPDRS III is 108, with a higher score denoting greater motor impairment. This scale is generally used to quantify the motor disability of PD patients in different conditions of evaluation, for example under dopaminergic treatment (medication-on condition, med-on), or 12 h after a withdrawal of antiparkinsonian drugs (medication-off condition, med-off). The motor scores were obtained by a trained neurologist.

The cognitive profile of PD patients was assessed by the Mattis Dementia Rating Scale, MDRS,[190] a widely used tool, which measures overall cognitive functioning on five subscales: attention, initiation, construction, conceptualization, memory. The maximum score on MDRS is 144, and a score of less than or equal to 130 is considered diagnostic of mild dementia. The cognitive functioning of healthy subjects was assessed by the Mini-Mental State Examination (MMSE),[191] which is a brief 30-point questionnaire. In the time span of about 10 min it samples various functions including arithmetic, memory and orientation. A score of less than or equal to 24 is considered diagnostic of mild cognitive impairment.

The frontal lobe functions in PD patients as well as in healthy subjects were

assessed by the Frontal Assessment Battery, FAB,[192] which is a short bedside cognitive and behavioural battery. It is usually performed in approximately 10 min, and it consists of six subsets exploring: conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. The maximum score on FAB is 18, while a score below 13 is considered diagnostic of a mild or severe impairment on the executive functions.

The behavioural state in PD patients as well as in healthy subjects was assessed by the Beck Depression Inventory-II, BDI-II,[193] and Starkstein Apathy scale, SAS. In particular, depression was rated with the BDI-II, a 21 items questionnaire, revised form according to the definition of depression in the Diagnostic and Statistical Manual of Mental Disorders (IV revision). It is widely accepted and validated also in patients with PD. The maximum score on the BDI-II is 63, and a score more than 20 was considered diagnostic of mild or severe depression.

The SAS[194] is one of the most widely used questionnaires to assess apathy and has been validated in patients with PD. It comprises 14 questions, each one scored from 0 to 3 (maximum 42 points). Higher levels indicate more severe apathy. A cut-off at 14 points has been chosen to separate apathetic from non-apathetic subjects.

To assess the dominance of participants' hand in everyday activities, we used the Edinburgh Handedness Inventory,[195] which is a self-reporting questionnaire. A score above +40 indicates right-handedness.

Since the computerized tests used in our study essentially consisted in the presentation of red and green stimuli on a computer monitor, the screening to enter our protocol included also the desatured D-15 Lanthony test (Luneau, Paris), which is a colour vision test designed to indicate mild color deficiency quickly and easily.[196] This test contains a reference disc and fifteen faded (unsaturated) colored numbered discs (back numbered) which make up an incomplete color circle. Following a subject's attempt to sequentially arrange the discs, the evaluation determines colour perception or defects in deutan, protan, or triatan axis discrimination. This test is widely used to assess acquired deficits in colour discrimination both in healthy subjects and especially in PD patients.[197-201] Considering that our participants' mean age was expected to be over 50 years, and 2/3 of them would have been PD patients in an advanced stage of the disease, the desatured D-15 Lanthony test was performed to

ensure that participants did not suffer from significant deficiencies in red-green colour perception, as well as to exclude possible colour discrimination changes related to different conditions of dopaminergic treatment. For this purpose, our patients of group #1 underwent twice the colour vision test, i.e., in med-off and med-on (under dopaminergic stimulation). A score below 32 corresponds to minor errors.[200, 202]

Inclusion criteria

Participants had to be over 20 years-old, right-handed, neurologically healthy subjects, apart from PD. They had to self-declare normal or corrected to normal vision, and they should not to show of significant deficiencies in red-green color perception.

Patients had to be clinically diagnosed with idiopathic Parkinson's disease according to UK British Brain Bank Criteria for PD, and at a disease's stage characterized by motor complications, such as motor fluctuations and dyskinesia related to long-term pulsatile dopaminergic treatment. Their levodopa response, computed as percentage of motor state improvement after a levodopa challenge with respect to the med-off, should be more than 30%.

Since the protocol study included a prolonged evaluation in med-off for group #1, and an evaluation without medication and stimulation (med-off/stim-off condition, med-off/stim-off) for group #2, which implied the reappearance of parkinsonian signs, only patients able to tolerate these conditions, and who accepted this mild discomfort were selected. However, it should be considered that med-off and med-off/stim-off represent usual conditions of assessment during the follow-up of PD patients.

Patients of group #2 entered the study at least 3 months after surgery. This represents the mean elapse of time necessary for the disappearance of any possible microtraumatic effect due to the implantation procedure, which might interfere with a correct conduct of the study, and to obtain a fair control of parkinsonian symptoms by STN-DBS.

To study the respective role of the SM and AS cortico-basal ganglia loops in visual attention, only stimulated PD patients with at least one contact lead in the SM part and another contact in the AS part of the STN entered the protocol. The precise anatomical lead contacts localization with respect to the subdivisions of the STN was possible by fitting the images of a three-dimensional atlas developed from

immunohistochimical and MRI data to the postoperative MRIs of the patients.[200, 202-204] The anatomical contacts localization was possible thanks to the collaboration with Prof. J. Yelnik, and took place in his laboratory at the Hopital de la Salpêtrière, Paris. (Fig.6)

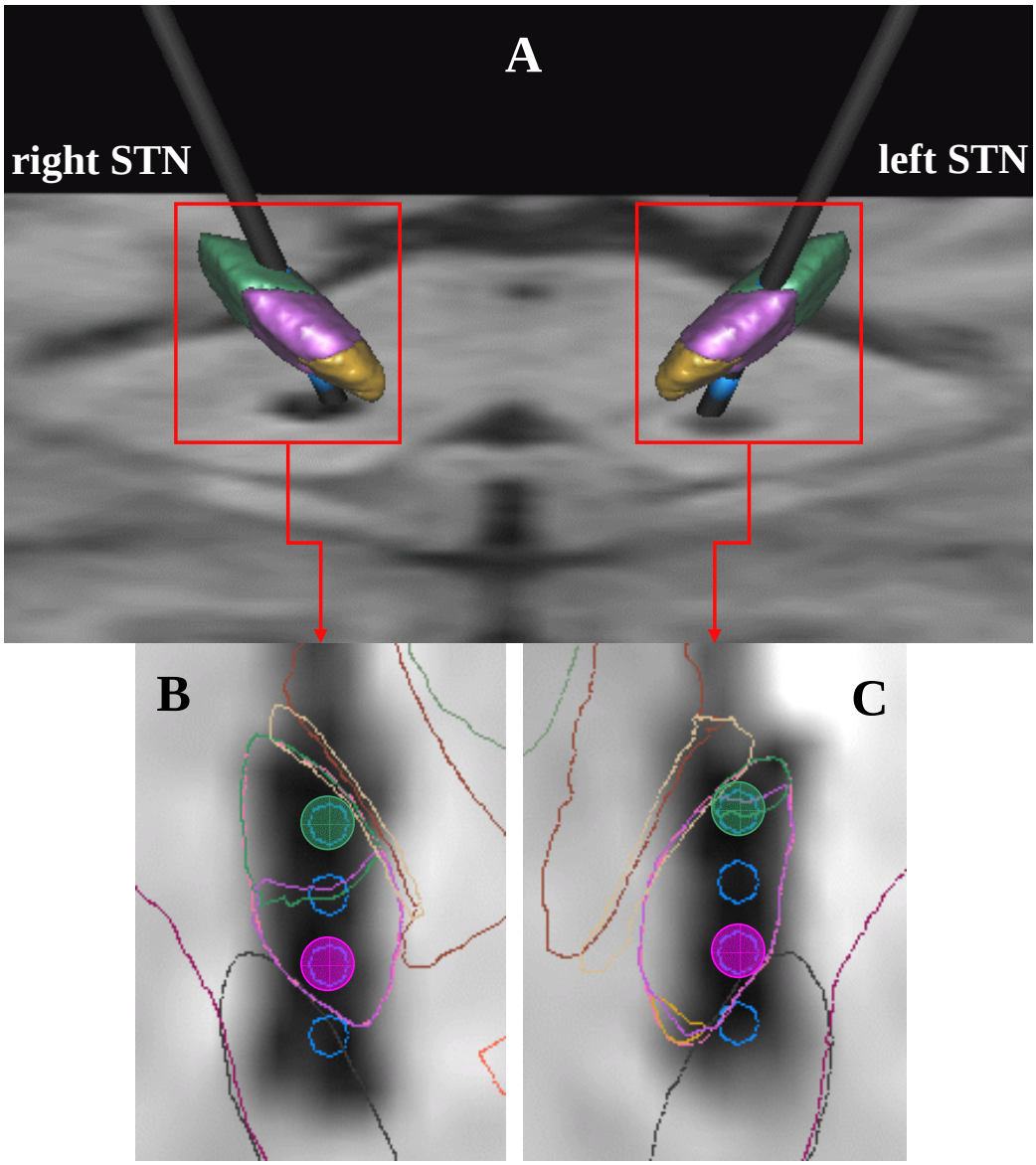

Fig.6 Lead contacts localization with respect to the subdivisions of the STN in patient #12. A) In green, violet and yellow, respectively the sensorimotor, associative, and limbic subdivisions of the STN. In B) and C), the green circles represent the contact used to predominantly stimulate the sensorimotor part of the STN, while the violet circles represent the contacts to predominantly stimulate the associative part of the nucleus.

Exclusion criteria

Exclusion criteria were represented by mild/severe cognitive impairment (dementia and dysexecutive syndrome) as well as behavioural disorders (depression, and apathy), according to the cut-off values defined in the battery of neuropsychological tests. Also, current psychosis represented a contraindication to enter our study. Psychotropic or neurotropic drug intake was not tolerated, except for short half-life benzodiazepe or similar drugs, but with the last intake going back at least 12 h. Participants should not have a history of drug or alcohol addiction. Moreover, PD patients should not complain of any other medical or psychological problem, in addition to those mentioned above, which could interfere with a smooth and accurate conduction of the study protocol (i.e., a marked tremor of head and upper limbs in med-off, disabling dyskinesias, levodopa induced disorders of alertness and attention, and side effects induced by STN-DBS which can interfere with the computerized task performances).

Participants were matched for age (± 5 years), sex, and education.

Patients were also matched for disease severity, according to the UPDRS III score in med-off condition.

All subjects had to be naive to the purpose of the experiment.

All subjects gave written informed consent to the research protocol, which was approved by the local ethical committee of the two Universities where the study took place.

Subject characteristics are listed in Table 1.

	GROUP #1 mean (±SE)	**GROUP #2** mean (±SE)	**GROUP #3** mean (±SE)	**p**
N. Subjects	12	12	12	
Sex	M:F=7:5	M:F=7:5	M:F=7:5	
Age	57.1 (±2.3)	55.5 (±2.7)	56.1 (±2.6)	N.S.
Education	13.6 (±1.1)	13.7 (±0.9)	13.7 (±1.0)	N.S.
MMSE			29.4 (±0.3)	
MDRS	140.8 (±0.6)	139.4 (±0.8)		N.S.
FAB	16.7 (±0.3)	16.0 (±0.4)	16.9 (±0.3)	N.S.
BDI-II	8.0 (±1.5)	6.3 (±0.9)	5.8 (±0.9)	N.S.
SAS	6.8 (±1.2)	8.1 (±0.9)	7.6 (±1.0)	N.S.
Disease severity	37.5 (±2.4)	42.6 (±2.6)		N.S.
Disease duration	13.9 (±2.1) y	11.9 (±1.2) y		N.S.
Edinburgh Inventory Scale	88.7 (±4.3)	86.3 (±5.1)	89.4 (±5.3)	N.S.
Levodopa therapy length	7.7 (±1.5) y	9.1 (±1.6) y		N.S.
LEDD	804.4 (±81.1)	392.9 (±74.6)		**< 0.001**
Lanthony test, right eye	med-off: 4.6 (±2.0) med-on: 3.0 (±1.6)	6.6 (±2.5)	3.0 (±1.6)	N.S. N.S.
Lanthony test, left eye	med-off 3.3 (±1.8) med-on: 4.0 (±1.8)	5.0 (±1.8)	3.1 (±2.1)	N.S. N.S.

Tab.1 Subject characteristics.

Disease severity was expressed as the motor score obtained in off-phase according to the the Unified Parkinson's Disease Rating Scale (UPDRS) part III. The maximum score on the UPDRS III is 108, with a higher score denoting greater motor impairment. Disease duration was estimated on the basis of the patients' subjective estimate of the time of occurrence of the first symptoms of Parkinson's disease. Antiparkinsonian drugs were expressed as levodopa equivalent daily dose, LEDD, in mg/die[205] y = years

N.S. = non significant

Study Protocol

Computerized tasks

The main instrument used in our experimental protocol was a computerized AC task, which was suitably combined with a choice reaction time task in order to assess the effectiveness of bottom-up and top-down mechanisms in visual attention (see below). By combining the choice reaction time task with a simple reaction time task, we could also obtain precious information about the effectiveness of the mechanisms of response selection and initiation of motor response.

All these tasks have been developed in the Laboratories of the Department of Neurological, Neuropsychological, Morphological, and Movement Sciences, Section of Physiology and Psychology, University of Verona, under the supervision of Prof. L. Chelazzi.

Apparatus

The computerized tasks have been created and run with the E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA), on a compatible Compaq 6715s Hp Computer. The stimuli appeared on a 17-in. CRT monitor (Samsung SyncMaster 753DF-T/T, resolution 1024 × 768), which was connected to the computer. The display stimuli consisted of green (CIE x,y chromaticity coordinates of 0.288/0.609) or red (coordinates of 0.633/0.334) geometrical elements matched for luminance (18.4 cd/m^2). The fixation cross was presented in white (78.0 cd/m^2) on a black background (0.0 cd/m^2). The colorimetric and photometric measurements were carried out by means of a photo-radio-colorimeter (J17 LumaColor^{TM} Photometer, Tektronix Inc., Wilsonville, USA). The detector head of this device was directed toward the color patches used in this experiment, which were displayed at the centre of the computer screen.

The “1” and “2” adjacent keys (1.7 × 1.7 cm) of a numeric keypad (Manhattan model 176354 numeric keypad), connected to the computer by a USB port, were used as response buttons.

Subject was tested in a quiet and dimly lit room, seated on a comfortable and adjustable armchair, with his/her head resting on a chinrest to hold the viewing

centred on the monitor at a 57 cm constant distance.

Attentional Capture Task

In our protocol study, we used an AC task developed starting from the classical and validated tests pioneered by Theeuwes et al. (1992, 1994).[23, 92, 93] There are different accepted versions of this test, which was variously modified by some authors according to the aims of their study.

In our AC task, subjects received two conditions. In the so-called no-distracter condition (control trial), they were instructed to search for a target element embedded among irrelevant stimuli, in a goal-directed manner, according to previous instruction. In the so-called distracter condition, which occurred in 1/3 of the trials, simultaneous with the presentation of the target, a distracter appeared on the display, replacing one of the other irrelevant stimuli. We included such a low percentage of distracter trials in our AC task because it is known that the capture grows stronger as the frequency of distracter presentation is lower.[206]

We conjectured that the original Theeuwues's AC task could be too difficult for our patients, especially with regard to the identification of the target, represented, in the original study, by a vertical or horizontal line contained in an outline circle or square. Then, we made some little changes to the original version of the test, making it simpler for the PD patients.

Stimuli and procedure. The sequence of events was as follows. Initially, a white fixation cross (0.5°) was presented at the centre of the visual field against the black background together with a warning sound for 300 ms. Then, a stimulus display consisting of 6 diamonds (1.2° on a side) all of the same colour (green or red), equally spaced around the fixation cross on an imaginary circle whose radius was 3.6°, appeared on the monitor. After 700 ms, one of the 6 diamonds was abruptly cut on the upper or lower tip (0.6° on a side), changing into a pentagon-shaped element, i.e. the target, respectively with the base upward or downward. This represented the target display in the no-distracter condition. It lasted only 200 ms to prevent eye movements,[207] and subjects had to focus their attention on the up or down location of the cut, while ignoring the other elements. In the so-called distracter condition, simultaneous with the target presentation, one of the other 5 diamonds changed colour

(red instead of green or vice versa) as well as orientation (45° rotation, becoming a square), therefore becoming a singleton. This element represented the irrelevant but salient stimulus (distracter) which was able to disrupt the target search.

Subjects were instructed to respond to the orientation of the pentagon-shaped target by pressing key “1” of the numeric keypad if the base of the pentagon was upward or key “2” if it was downward, respectively using their right hand forefinger or middle finger, which were resting on the response keys. Following the disappearance of the target display the screen went black and subjects had 2300 ms more to give their response, (thus, the maximal response emission time was 2500 ms). The inter-trial interval was 1500 ms (screen black). An exemplar of the typical no-distracter and distracter condition of the AC task are shown in figure 7.

On the whole, subjects performed 360 randomly mixed trials consisting of 240 no-distracter trials and 120 distracter trials. Along the task, both the target (in its two forms: pointing up or down) as well as the salient distracter appeared equally often in each of the 6 display positions, otherwise occupied by the irrelevant diamonds. The positions of the target and the distracter were randomized from trial to trial. Moreover, the target appeared equally often in red or green so as to prevent consistent mapping.

To ensure an optimal level of attention throughout the whole experimental session, while avoiding excessive fatigue, the total trials were presented in 6 blocks, each consisting of 60 trials, separated by breaks, each one lasting no more than 3-4 min, at subject’s discretion. During stimuli presentation, subjects were requested to maintain fixation at the centre of the display, stressing that a steady fixation would reduce RT and make the task easier. Both speed and accuracy were emphasized.

The AC task as a whole took about 24 min (without breaks).

Before the first experimental session, subjects practiced the task at least in two blocks, each of 60 trials, and anyway the training session continued until an accuracy of 70% or more was achieved. For the following experimental sessions, only a practice block was required.

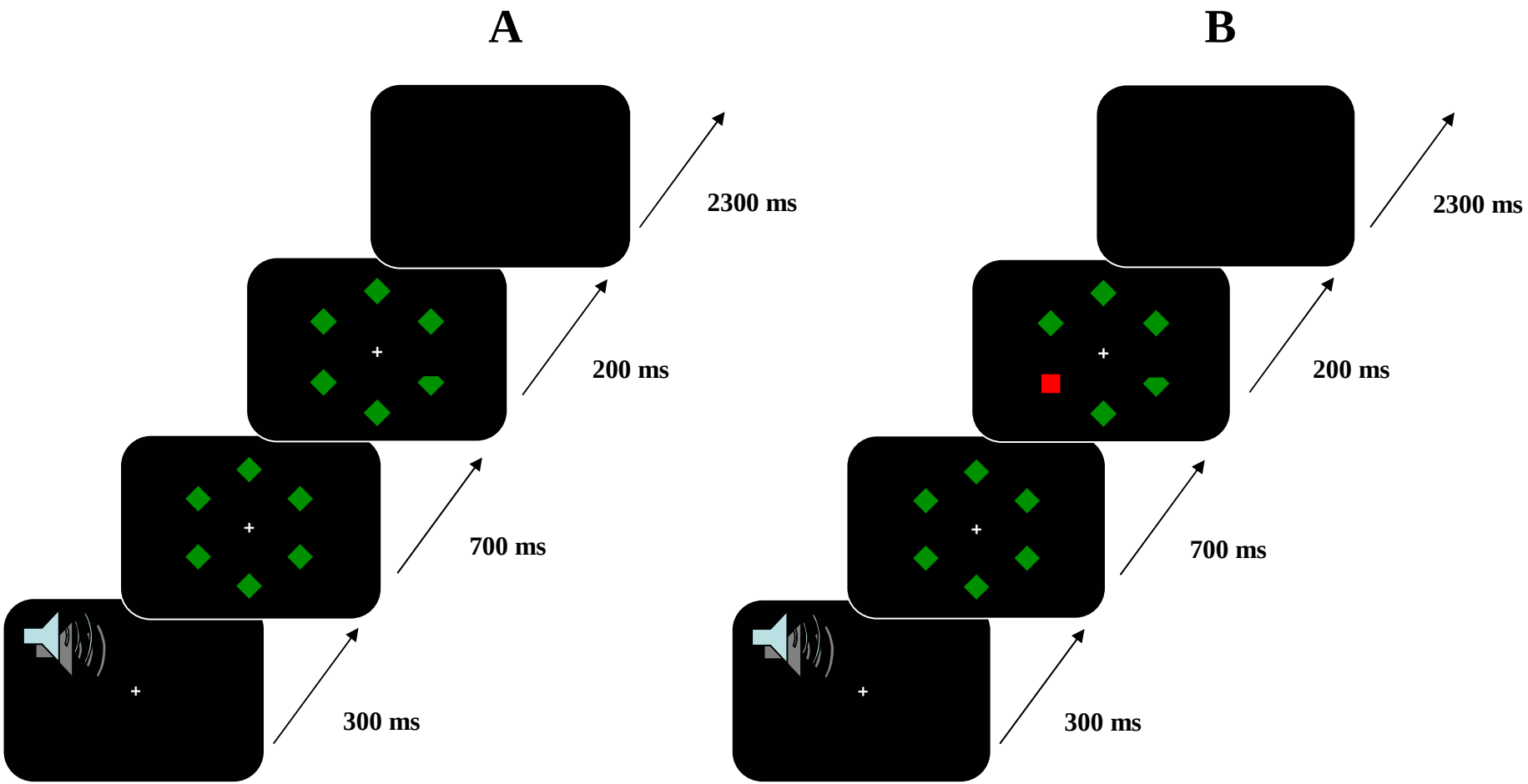

Fig.7 Graphic illustration of a no-distracter (A) and a distracter (B) condition of the attentional capture task.

Choice Reaction Time Task

It is evident that different brain mechanisms could contribute to the emitted response in a trial of the AC task. In a no-distracter trial we could conjecture the involvement of mechanisms of target selection, mechanisms of response selection and mechanisms of initiation of the motor response. In particular, under the term of target selection different cognitive processes may be probably included, that is low level pre-attentive processes, depending on specific primitive properties of the stimulus array, mechanisms of endogenous visual attention (EVA), which guided the selection of the relevant target in a goal-directed manner, and also bottom-up selection mechanisms, considering that the target was defined by the abrupt cut on the upper or lower tip of one diamond element, which could contribute to some extent to exogenous AC.

We tried to isolate the perceptual-attentional mechanisms of target selection from the other components of the whole response by comparing the performance in a no-distracter trial of the AC task with that of a choice reaction time task.

This task is a version of the classical and validated choice reaction time test, [208] adapted to the purposes of our study.

Stimuli and procedure: a typical trial was similar to that described for the no-distracter trial of the AC task, except for a single diamond element (red or green) presented on the display in one of the 6 eccentric positions occupied by the stimuli of the previous task. This element abruptly was replaced by a pentagon-shaped target (of the same colour) with the base up or down. Subjects gave the response according to the instructions specified for the AC task. (Fig.8)

Therefore, a typical trial of the choice reaction time task was characterized by a component of perceptual discrimination (which allowed to identify the target and its orientation), by a component of response selection (which key to press depending on the target orientation), and initiation of the motor response. As a consequence, the difference in RT between the no-distracter trial of the AC task and the choice reaction time task allowed us to isolate the time necessary to select the target within an array of irrelevant stimuli. Different perceptual and selective attentional components contributed to this time, including an exogenous attentional component. Nonetheless, in our study we were able to assess in isolation the bottom-up selection mechanisms,

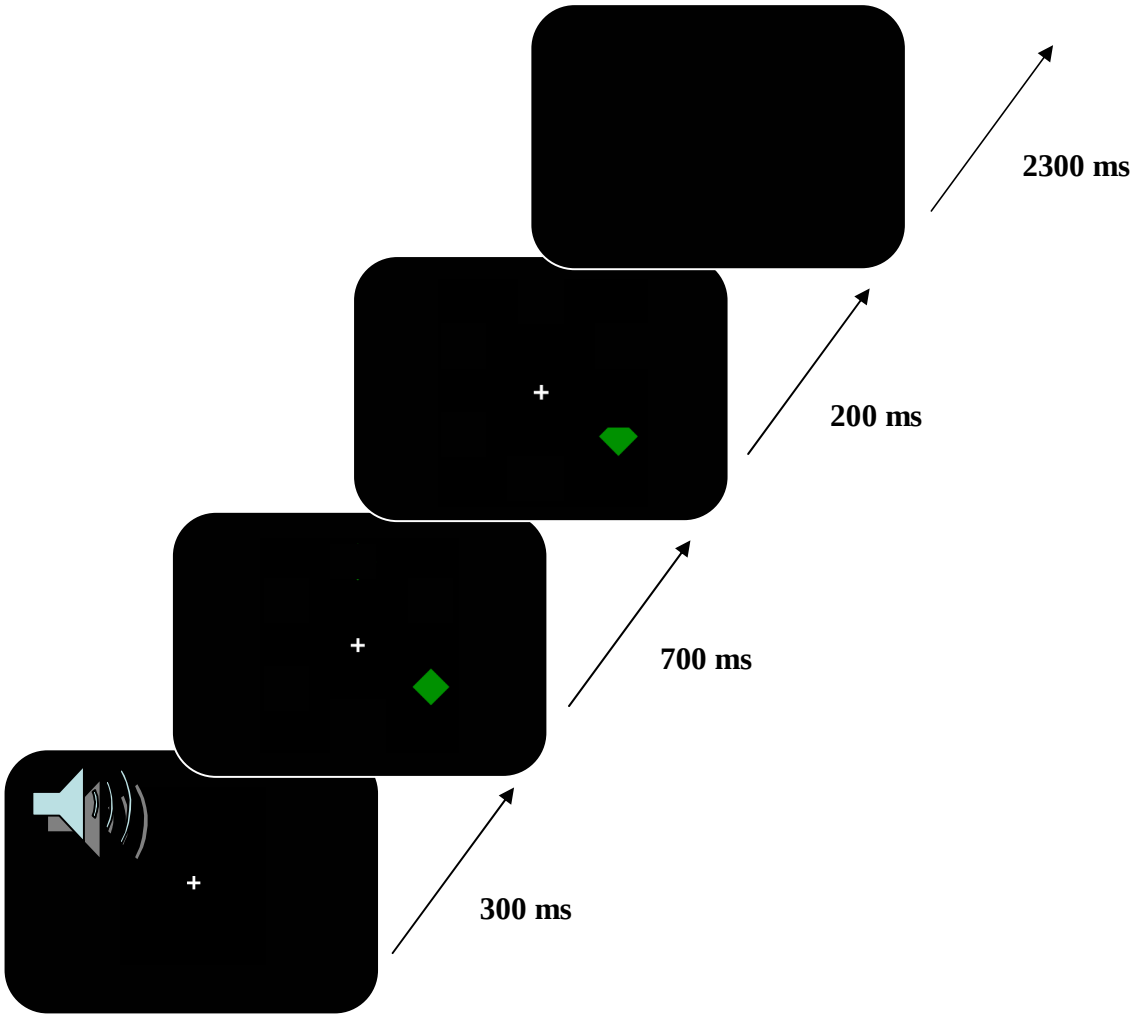

Fig.8 Graphic illustration of a choice reaction time trial.

by comparing the performances in trials with and without distracter of the AC task. Thus, we can assume that the time necessary to select the target mainly represented the functioning of the perceptual-endogenous attention (EVA) component. On the whole, in the choice reaction time task, the subjects performed 72 randomly mixed trials consisting of 36 trials with the target upward and 36 trials with the target downward. The target appeared equally often in red or green, and in each of the 6 eccentric positions of the array.

As a whole the task took about 5 min.

At the beginning of the first experimental session, subjects practiced the experimental task in one block of 36 trials. If an accuracy of 80% or more was achieved, the actual experiment was run, otherwise the practice block was repeated. The following experimental sessions started with 10 training trials.

Simple Reaction Time Task

A simple reaction time test was introduced in our experimental setting to assess the mechanisms of motor response initiation. This task was a version of the classical simple reaction time test, adapted for the purposes of the study.[209]

Stimuli and procedure: initially, a white fixation cross was presented at the centre of the visual field on a black background together with a warning sound. In all the trials, after a variable delay from onset of the cross (delays between 400 and 2000 ms), a diamond element (red or green) appeared on the monitor, for 200 ms, in one of the 6 eccentric positions occupied by the stimuli in the AC task. Subjects had to respond as fast as possible to the diamond onset, pressing the key "1". (Fig.9)

Therefore, this task allowed us to estimate the amount of time required to initiate a simple motor response on the basis of a very low level visual information (the detection of the stimulus onset). This task could be especially useful in our experimental setting to uncover possible variations in motor performance in the different studied groups as well as the different conditions of medication and stimulation in which PD patients were evaluated.

In a typical trial of this task there were no components of perceptual discrimination and selection of the motor response like those involved for the choice reaction time task. As a consequence, the difference in RT between the trials of these two tasks allowed us to isolate the time necessary to select the motor response on the basis of a discriminative visual analysis. This was a decision making (DM) component representative of the functioning of the mechanisms of motor response selection. Then, the computation of this difference in RT could enable us to uncover if our patients' performance in the AC task was affected by possible decision-making deficits, as reported by some authors in PD patients.[210-213]

On the whole, in the simple reaction time task, subjects performed 60 randomly mixed trials, in which the target appeared equally often in red or green, and in each of

the 6 possible eccentric positions of the array. The task was presented in 2 blocks, each consisting of 30 trials. In one block the subject responded with the index, while on the other block with the middle finger. The inter-trial interval was 1500 ms.

This test as a whole took about 5 min.

At the beginning of the first experimental session, subjects practiced the task in one block of 30 trials. If an accuracy of 80% or more was achieved, the actual experiment was run, otherwise the practice block was repeated. The following experimental sessions started with 10 training trials.

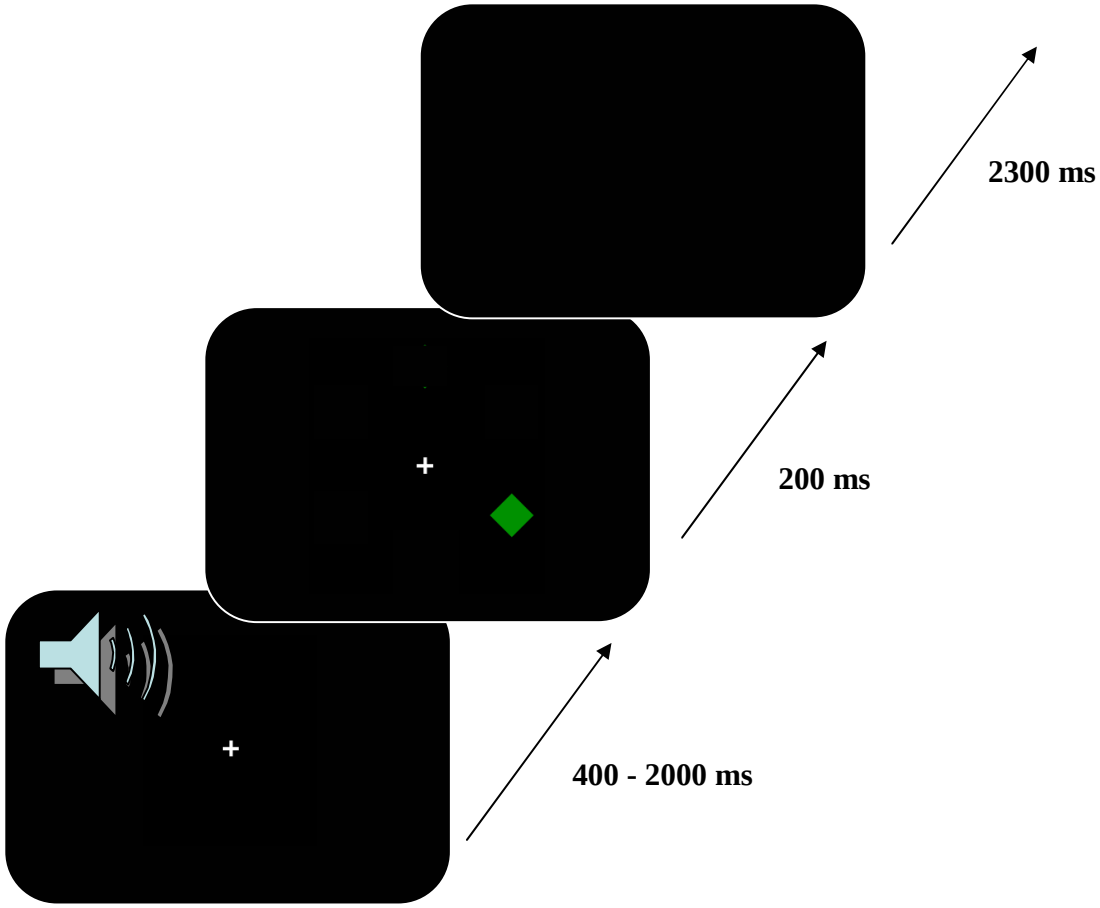

Fig.9 Graphic illustration of a simple reaction time trial.

Procedure and development of the experimental session

Each participant of the 3 groups underwent more than one experimental session.

PD patients of group #1 performed two experimental sessions in different conditions of medication: med-off and medication-on (med-on, corresponding to the best clinical state after their usual first dopaminergic dose intake in the morning). These sessions were performed on different days within the same week, and the conditions of evaluation were randomized. Each session began with the motor state evaluation scored by the UPDRS III, followed by the performance of the 3 computerized tasks, which were presented in a randomized order and counterbalanced to obtain the same number of patients beginning with the med-off or the med-on. At the end of each session, the patients' motor state was scored again to uncover possible changes in the global motor score during the experimental session. As a whole, each evaluation session took about 1h.

Patients of group #2 were evaluated in 3 different conditions at least 12 h after a withdrawal of antiparkinsonian drugs: 1) med-off/stim-off, 2) med-off/SM stimulation-on (med-off/SMstim-on, stimulating through the lead contacts localized in the SM part of the STN, as it usually would occur during chronic stimulation), 3) med-off/AS stim-on (med-off/ASstim-on, stimulating through lead contacts localized in the AS part of the STN, using a contact generally located one or two contacts more ventral than the one located in the SM part of the STN). The more distant were the used stimulation contacts from each other, the greater was the possibility for a selective stimulation of the SM and AS areas of STN, avoiding any overlapping effect due to the spread of electrical current. The parameters of stimulation were as close as possible to the ones used for chronic stimulation, while avoiding side effects. On each side, we stimulated both STN sites with the same electrical parameters, in order to activate the same volume of tissue (Table 2).

Also for this group, the experimental sessions were performed in different days within the same week, and the conditions of evaluation were randomized and counterbalanced. In med-off/stim-off, the patient started the experimental evaluation after having the stimulation turned-off for about 30 min. In each med-off/stim-on condition, firstly the stimulation was turned-off for about half an hour, then it was turned-on for half an hour, and at last the experimental evaluation started. Each expe-

	right STN			left STN		
Subject	**SM contact**	**AS contact**	**Voltage (V)**	**SM contact**	**AS contact**	**Voltage**
#1	2	0	2.4	3	1	2.2
#2	2	0	3.0	3	1	2.5
#3	3	1	2.5	2	0	3.3
#4	2	0	2.5	3	1	2.5
#5	3	1	2.4	3	1	2.7
#6	3	1	2.7	2	1	2.5
#7	2	0	3.0	3	1	3.0
#8	2	0	3.3	3	2	2.8
#9	3	1	2.0	3	1	2.4
#10	3	1	2.2	3	1	2.4
#11	2	0	2.6	2	0	2.4
#12	3	1	1.8	3	1	2.8
			mean value **2.5 ± 0.4**			mean value **2.6 ± 0.2**

Tab.2 Contacts and parameters of stimulation in the experimetal sessions for each patient. The four contacts of each electrode were numbered 0 to 3 from bottom to top. SM contact and AS contact: contacts used to stimulate the SM and AS part of the subthalamic nucleus, respectively. V = volt. The mean voltage was not significantly different between the two sides of stimulation (p = 1.0). The pulse width and frequency of stimulation were set to 60 µs and 130 Hz, respectively, for each side. STN = subthalamic nucleus.

mental evaluation was run in the same way as described for group #1. Therefore, in med-off/stim-off, stimulation was turned-off as a whole for about 1h 30 min, whereas in each med-off/stim-on condition, either we maintained the stimulation parameters

used for chronic treatment or we changed them as little as possible for no more than 1h 30 min.

Healthy controls (group #3) were evaluated twice to assess possible learning effects on the computerized tasks. These evaluations occurred in different days within the same week, and in each session the 3 computerized tasks were performed in a randomized order.

Statistical analysis

Variables measured

To pursue the objectives of this study, the main variables assessed were RT and error rate in performing the 3 computerized tasks, comparing the results among groups and conditions.

RT was the time between the presentation of the target stimuli on the display and the onset of the subjects' response. Statistical analyses were performed on RTs for trials with correct responses. We excluded from analyses trials on which the RT fell outside ±2.5 SDs from the mean value for each subject and each experimental condition.

Error rate was computed as the percentage of the omitted and wrong responses in the AC task and in the choice reaction time task, while error rate was the percentage of the omitted and anticipated responses in the simple reaction time task.

The *AC* effect was measured as the difference (Δ) in RTs and error rates between the distracter and no-distracter trials of the AC task.

To investigate any potential speed-accuracy trade-off related to the different conditions, we also calculated the *inverse efficiency* (IE) scores for the AC task. IE scores are a standard way to combine RT and accuracy data into a single performance measure, computed as mean RT divided by the proportion of correct trials for a given condition, and expressed as adjusted mean RT.[214-216] Higher values represent worse performances.

In an attempt to isolate components of the cognitive operations underlying the response given in a no-distracter trial of the AC task (such as EVA, DM, and motor initiation), albeit with some degree of approximation, we have adopted the subtraction

method of Donders.[217] The Donders' approach was based on the assumption that mental processing takes time, therefore inserting a specific computation into a RT paradigm will lenghten the behavioural response times by a certain amount compared to those obtained in the original RT paradigm, without affecting the other components of the test. Even if Donders' work paved the way for future research in mental chronometry tests, it was not without some drawbacks. In particular, the assumption that the incremental effect on RT was strictly additive did not hold up to later experimental tests,[209, 218] which showed that the insertions may interact with other aspects of the RT paradigm. Despite this aritmetical limit, Donders' method represents one of the core paradigms in psychometric psychology, having the potential to elucidate a lot of mechanisms underlying cognitive processing, at least at a conceptual level. In this sense, we have used this method, especially to infer the impairment of some components of cognitive-behavioral control in PD, and the effects of dopaminergic and electrical stimulation on them.

In particular, the *EVA* component was computed as the difference between the mean RT in no-distracter trials of the AC task and the mean RT in the choice reaction time task. Lower values of EVA suggest more efficient mechanisms of selection of the target within an array of irrelevant stimuli, and therefore they seem to indicate a strengthening of the endogenous attention mechanisms.

The *DM* component was defined as the difference between the mean RT in the choice reaction time task and the simple reaction time task.

Data analyses

Collected data underwent statistical analyses using SPSS (version 12.0, inc. Chicago, USA).

Separate analyses of variance (ANOVAs) were carried out in relation to the different computerized tasks (AC task, choice reaction time task, simple reaction time task) to compare different performance indices (RT, error rate, AC, EVA, DM) between groups (#1 versus #2 versus #3) and in different conditions of evaluation (with or without drug, with or without stimulation, stimulation of different parts of the STN).

In detail, the following evaluation criteria and analyses were adopted:

1) Effectiveness of the tasks and effects of session. Preliminary analyses in the group of healthy controls were run in order to assess both the effectiveness of our AC task, and the feasibility of applying the subtraction method of Donders to the results obtained in the other computerized tasks. Moreover, we verified possible learning effects due to the mere repetition of the experimental session. For this purpose, RT, error rate and IE in the AC task have been analyzed by means of repeated measures ANOVA with the type of trial (no-distracter versus distracter trials) and session (session-I versus session-II) as within-subjects factors. Similar analyses have been carried out for RTs and error rates in relation to the other computerized tasks, as well as for the other performance indices (EVA and DM), the session being the within-subject factor.

2) Effects of disease. To address the first objective in the present study, i.e. the effects of PD on visual selective attention and AC, we compared the performance on the computerized tasks of PD patients in med-off (group #1) and in med-off/stim-off (group #2) with that of the healthy controls (group #3). We ran a repeated measures ANOVA on RTs, error rates and IEs of the AC task, with the type of trial (no-distracter versus distracter trials) as within-subjects factor, while the group as between-subjects factor. The RTs and error rates obtained in the other computerized tasks, as well as the other performance indices (EVA and DM) were analyzed by one-way ANOVAs, with group as between-subjects factor.

3) Effects of dopaminergic treatment. To study the effects of the dopaminergic treatment on visual selective attention and AC, we made an evaluation within group #1, comparing the performances in med-off with that in med-on. For this purpose we made an analysis of variance (ANOVA) with the condition of evaluation (med-off versus med-on) and the type of trial of the AC task (no-distracter and distracter condition) as within-subjects factors, and the RTs, error rates, and IEs as dependent variables. The data obtained in the other computerized tasks, as well as the performance indices computed by the subtraction method were analyzed by means of

paired samples t-tests, comparing the results obtained in the two different conditions of evaluation.

4) Effects of STN-DBS. To study the effects of neuromodulation of the STN on visual selective attention and AC, we made an evaluation within group #2, comparing the performances in med-off/stim-off with that in med-off/SMstim-on and med-off/ASstim-on. Moreover, this type of evaluation enabled us also to directly assess the involvement of the cortico-basal ganglia loops in the mechanisms underlying visual attention, and the respective role of the SM and AS parts of STN in modulating these mechanisms. Then, we performed an analysis of variance (ANOVA), with the conditions of evaluation (med-off/stim-off, med-off/SMstim-on, med-off/ASstim-on), and the type of trial of the AC task (no-distracter and distracter condition) as within-subjects factors, and the RTs, error rates, and IEs as dependent variables. The RTs and error rates obtained in the other computerized tasks, as well as the other performance indices (EVA and DM) were analyzed by means of repeated measures ANOVA with the condition of evaluation as within-subjects factor.

5) Comparison between the effects due to dopaminergic and STN stimulation. A comparison between groups addressing the effect of different treatments allowed to analyze the respective role of the dopaminergic pathways and the cortico-basal ganglia loops passing through the STN in the bottom-up and top-down mechanisms of visual attention. To this end, we computed for each variable the difference between the mean value obtained in off condition with that in med-on (Δ med-off – med-on), as well as in med-off/SMstim-on (Δ med-off/stim-off – med-off/SMstim-on) or in med-off/ASstim-on (Δ med-off/stim-off – med-off/ASstim-on). In this way, we obtained a measure of the possible gain or detriment of the patients' performance due to the specific treatment with respect to the off condition.

On the basis of these differences, two separate statistical analyses were carried out applying the t-tests for independent samples. In one of them we compared the effects of medication with those of stimulation of the SM part of the STN, while in the other we compared the effect of medication with those of stimulation of the AS part of the STN.

6) Effects of dopaminergic and STN stimulation with respect to the control condition. At last, we also investigated whether medication and/or stimulation of the two STN sites could restore patients' performance to the normal level. To this end we carried out three separate analyses using the t-test for independent samples, comparing the performances of healthy subjects with those of group #1 in med-on, and group #2 in med-off/SMstim-on or med-off/ASstim-on. Again these comparisons were carried out for all the variables measured in the study.

Whenever a main effect of a factor (group, condition of evaluation or type of trial) was found, we performed comparisons between the levels of this factor by means of pairwise comparisons among the estimated means of the evaluated levels, with Bonferroni adjustment for multiple comparisons.

Post-hoc analyses of significant interactions were carried out by means of t-tests with Bonferroni's correction for multiple comparisons where necessary.

Unless otherwise specified, significant values have been considered for $p \leq 0.05$.

Computation of groups' size

We computed the groups' size on the main tool of our research, the AC task, and on the group #2 (that is, the group in which participants underwent the maximum number of evaluations), according to an α risk < 0.05 and a powerful = 90% (β risk < 0.10).

As every patient of the group #2 performed the experimental session in 3 different conditions of stimulation, to fulfil the criteria of randomization for sequence a minimum of 6 cases were required.

Statistical analysis comprised a within group evaluation, and a study of the interaction between group and condition, according to the criteria and the methodology described above.

As regards the within group evaluation, supposing that RTs would be distributed according to $N(\mu . \sigma)$, and if Cohen's d =1, we would expect to need 13 patients.

Referring to the paper of Deijen et al. (2006),[23] from which we started to devised our AC task, they found that in PD patients the mean RTs (±SD) in the no-distracter and distracter condition were respectively: 1080 (±193) ms and 1320 (±298) ms. These values correspond to Cohen's d = 1.2. If so, 10 cases would have been required. During a pilot study, carried out on 8 healthy volunteers to test the effectiveness of our AC task, we found that the mean RTs (±SD) in no-distracter and distracter trials were respectively: 523.4 (±64.7) ms and 625.6 (±80.8) ms. The mean ΔRTs was: 102.2 (±41.3) ms. A paired samples t-test of the mean RTs in no-distracter and distracter trials showed a significant difference (p = 0.006). These mean RTs lead to Cohen's d = 2.4, and if so 7 cases would have been required.

We decided to increase the group size to 12 subjects in order to obtain an equivalent distribution of the different evaluation condition sequences due to the randomization of the stimulation conditions.

As regards the interaction between group (PD patients versus healthy controls) and the type of trial of the AC task (no-distracter and distracter trials), we referred again to the work of Deijen et al. (2006), in which a sample of 12 healthy controls and 11 PD patients proved to be sufficient to obtain a significant interaction effect (p = 0.04) with respect to RT. Moreover, as regards the accuracy, Deijen et al. (2006) found a significant interaction effect between groups and the type of trial (p = 0.007). The number of the correct responses was reduced in the presence of the distracter, the reduction being larger in the patients.

To sum up, 24 PD patients (12 for the group #1, and 12 for the group #2) and 12 healthy controls took part to our protocol.

Results

Effectiveness of the tasks and effects of session

The percentage of trials excluded from analyses, because their RT fell outside ±2.5 SDs from the mean value, were 2.2%, 2.1%, and 2.4% respectively in the AC, choice reaction time, and simple reaction time tasks.

A first qualitative inspection of the data in the AC task showed that the mean (±SE) RT of healthy subjects in the no-distracter condition was to 541.2 (±17.8) ms and 534.8 (±15.7) ms, respectively in the first and second experimental session, while the mean cost in terms of Δ RT was of about 100 ms in the distracter condition, respectively 98.2 (±5.3) ms and 96.1 (±4.2) ms in the first and second session (Fig.10A). More in detail, analysis of RTs in the AC task revealed a significant effect of the type of trial [$F(1,11) = 560.12$, $p < 0.001$], due to faster RTs in the no-distracter condition (538 ±16.6 ms) compared with the distracter condition (635.2 ±18.6 ms). The factor session and the interaction type of trial × session were not significant ($p = 0.206$ and $p = 0.677$, respectively).

Analogous results were obtained by analyzing error rates in the AC task (Fig.10B). In detail, a significant effect of the distracter [$F(1,11) = 55.23$, $p < 0.001$] was found on error rates, due to more errors in the distracter condition (4.04 ±0.4%) than in no-distracter condition (1.04 ±0.2%), in both experimental sessions. The factor session and the interaction type of trial × session were not significant ($p = 0.698$ and $p = 0.840$, respectively).

A single measure of performance in the AC task, by the IE score, again revealed a significant effect of the distracter [$F(1,11) = 733.2$, $p < 0.001$], with higher IE values in the distracter condition (662.0 ±19.4 ms) than in the no distracter condition (543.3 ±16.4 ms), (Fig.11). The factor session and the interaction type of trial × session again were not significant ($p = 0.135$ and $p = 0.544$, respectively).

On the whole, these results showed that our AC task was an effective means to assess AC, and that performances were not affected by learning effects due to the mere repetition of the experimental session.

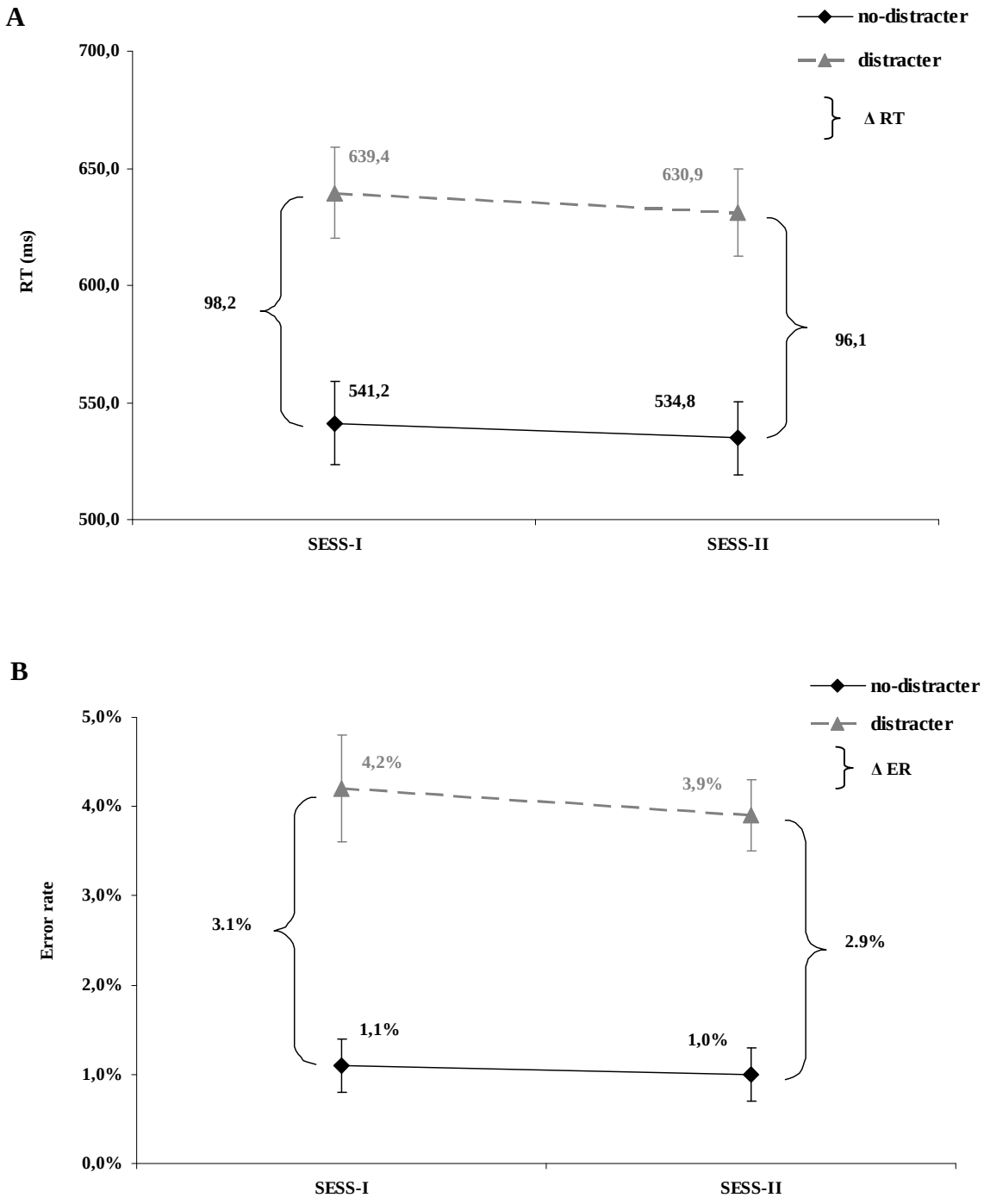

Fig.10 Healthy subjects: comparison of mean reaction time, RT (in A), and error rate, ER (in B), in the no-distracter and distracter conditions of the attentional capture task, in two consecutive experimental sessions (SESS). Δ RT and Δ ER = attentional capture in terms of Δ RT and Δ ER, respectively.

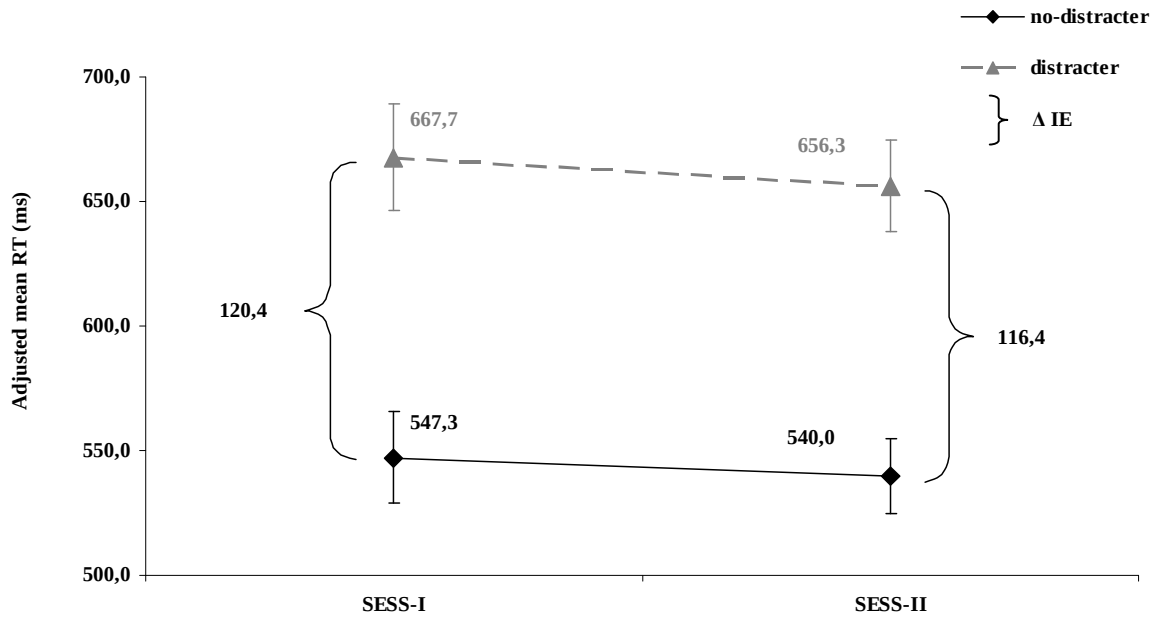

Fig.11 Healthy subjects: comparison of inverse efficiency (IE) score, expressed as adjusted mean RT, in the no-distracter and distracter conditions of the attentional capture task, in two consecutive experimental sessions (SESS). Δ IE = attentional capture in terms of Δ IE.

Comparing the data obtained in the choice reaction time and simple reaction time tasks, we noted that more complex was the task, the longer was the mean RT (Fig.12). In detail, the mean RTs were 443.5 ±16.7 ms and 435.6 ±15.4 ms, respectively, in the first and second experimental session of the choice reaction time task, while they amounted to 305.1 ±9.4 ms and 296.3 ±9.2 ms respectively in the first and second experimental session of the simple reaction time task. Overall, these RTs were shorter than those obtained for the no-distracter condition of the AC task. These results suggested that the RT lengthened in parallel with the increasing complexity of the tasks, which allowed us to adopt the subtraction method of Donders to approximately enucleate the two cognitive processes underlying the responses given in the no-distracter condition of the AC task: that is EVA and DM. Indeed, mean EVA amounted to 97.7 ±5.8 ms and 99.2 ±6.2 ms, respectively, in the first and second

session, while DM amounted to 138.5 ±17.1 ms and 139.3 ±14.3 ms (Fig.12). The analyses of RTs and Δ RTs obtained by these two tasks revealed also that the factor session was not significant (for all comparisons $p > 0.149$), pointing out that even these measures of performance were not reliably influenced by learning.

Also the error rates in the two tasks (0.2 ±0.2% and 0.5 ±0.3%, respectively, in the first and second session of the choice reaction time task, and 1.0 ±0.3% and 0.7 ±0.3% for the simple reaction time task) were not influenced by the repetition of the task ($p = 0.438$ and $p = 0.443$, respectively, in the choice reaction time and simple reaction time task).

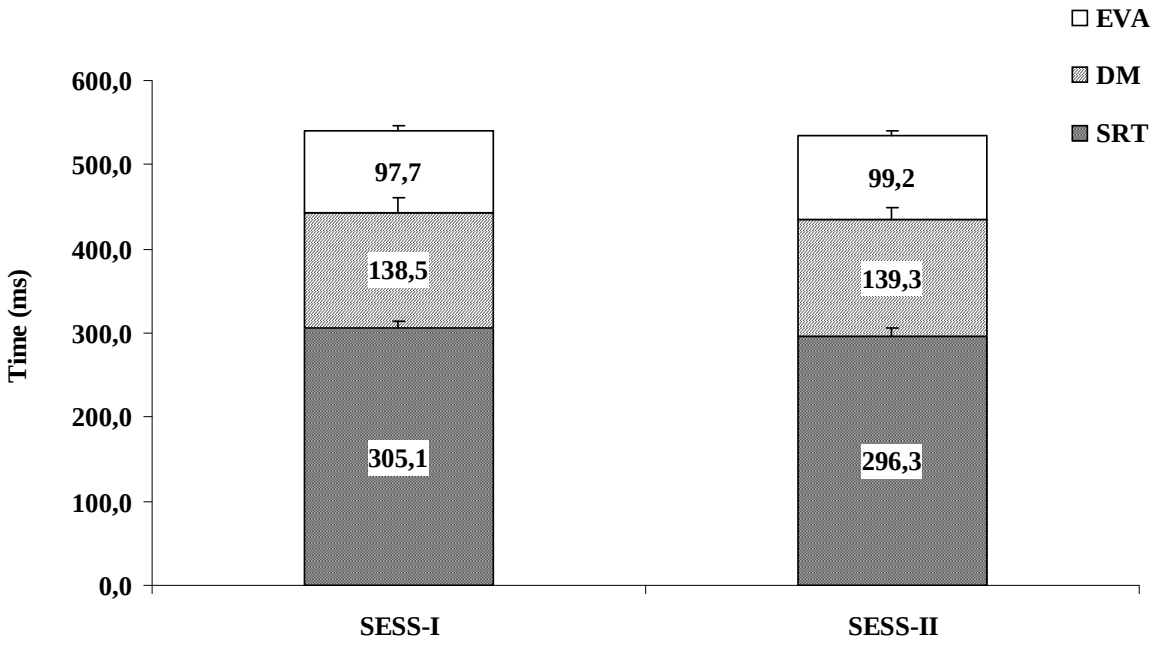

Fig.12 Healthy subjects: comparison of the mean times for movement initiation (simple reaction time, SRT), motor response selection (decision making, DM), and target selection (EVA, endogenous visual attention) in two consecutive experimental sessions (SESS). Note that SRT + DM = choice RT, while SRT + DM + EVA = RT in the no-distracter condition of the attentional capture task.

Effects of disease

The percentage of trials in med-off excluded from analyses, because their RT fell outside ±2.5 SDs from the mean value, were 2.5%, 2.6%, and 1.5%, respectively, in the AC, choice reaction time, and simple reaction time tasks. On the other hand, the percentage of outliers in med-off/stim-off were 2.5%, 2.0%, and 2.3%, respectively, in the AC, choice reaction time, and simple reaction time tasks.

At first glance, PD impaired performance with respect to healthy subjects by slowing down RT and increasing the error rate in the AC task (Fig.13A).

In detail, analysis of RTs in the AC task revealed a significant effect of the type of trial [$F(1,33) = 479.3$, $p < 0.001$], due to longer RTs (mean ±SE) in the distracter condition (769.0 ±18.7 ms) than the no-distracter condition (664.2 ±16.3 ms). The factor group was also significant [$F(2,33) = 16.0$, $p < 0.001$], due to longer RTs in med-off (738.4 ±30.2 ms) compared to control subjects (586.6 ±30.2 ms, $p = 0.003$), and med-off/stim-off (824.8 ±30.2 ms) compared to control subjects ($p < 0.001$). Otherwise, there was no reliable difference between the med-off and med-off/stim-off conditions ($p = 0.153$). The interaction type of trial × group was not significant ($p = 0.127$), although by looking at the AC effect, it was slightly, but non significantly, increased for the group in med-off (118.9 ±12.1 ms) with respect to the other two groups (med-off/stim-off: 98.2 ±6.5 ms, and healthy subjects: 97.2 ±4.1 ms), suggesting that the pathological condition, although slowing down the RTs, did not affect the mechanisms underlying AC.

A different pattern of results emerged from the analysis of error rate in the AC task (Fig.13B). In detail, a significant effect of the distracter [$F(1,33) = 67.0$, $p < 0.001$] was found on error rates, due to more errors committed by participants in the distracter condition (10.3 ±1.0%) than in no-distracter condition (2.5 ±0.2%). The factor group was also significant [$F(2,33) = 14.1$, $p < 0.001$)], due to higher error rates in med-off (8.3 ±0.9%) compared to healthy subjects (2.5% ±0.9, $p < 0.001$), and med-off/stim-off (8.2 ±0.9%) compared to healthy subjects ($p < 0.001$). Otherwise, no significant differences in error rates ($p = 1.0$) were found between the two groups of PD patients. The interaction of type of trial × group was significant [$F(2,33) = 6.3$, $p = 0.005$]. Post-hoc analysis revealed that the AC effect was larger in med-off (Δ error

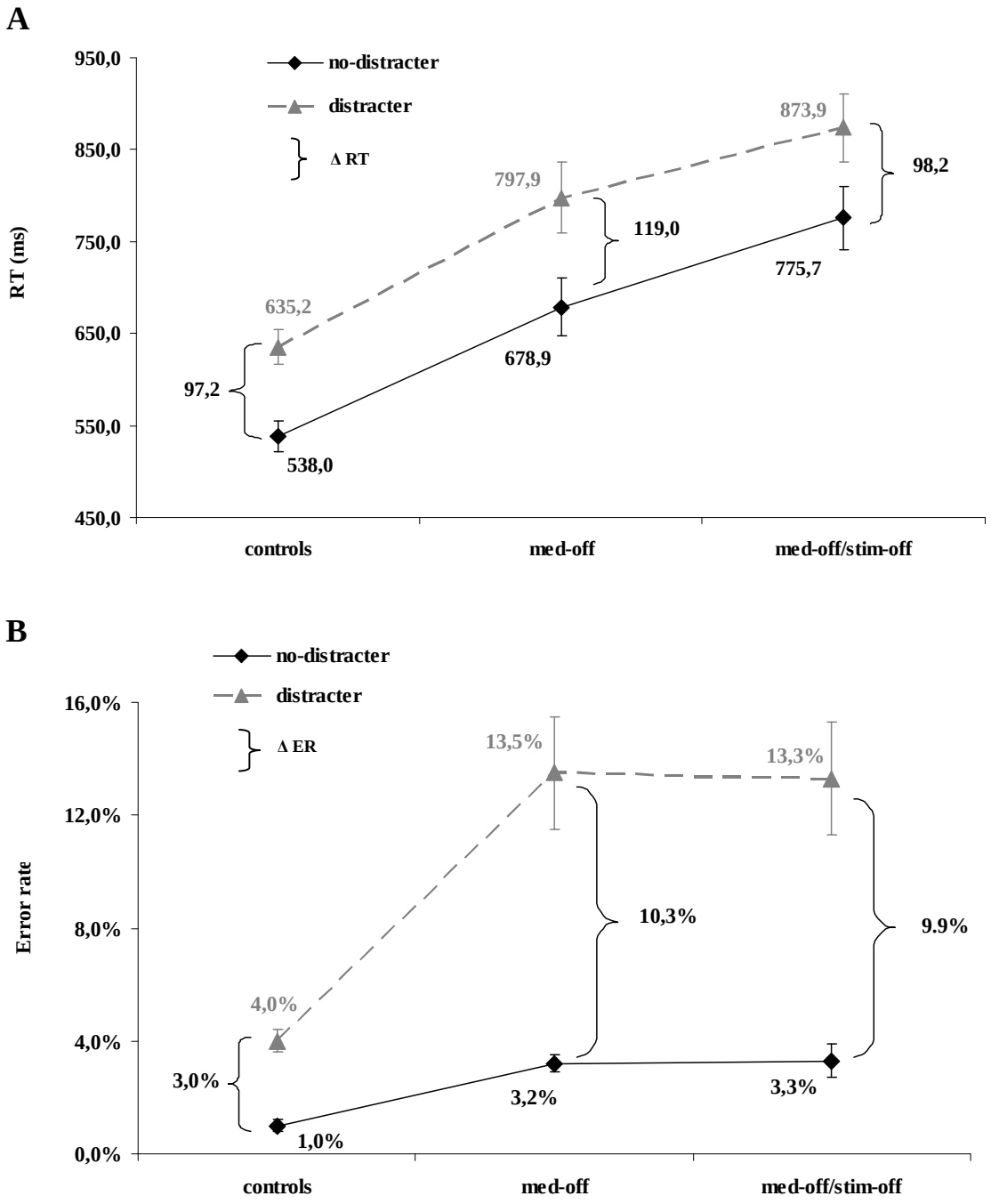

Fig.13 Comparison between the two groups of PD patients evaluated in off-condition (in med-off for the pharmacologically treated group, and in med-off/stim-off for the stimulation treated group) and healthy subjects in terms of reaction time, RT (in A), and error rate, ER (in B), obtained in the no-distracter and distracter conditions of the attentional capture task. Δ RT and Δ ER = attentional capture in terms of Δ RT and Δ ER.

rate: 10.3 ±2.0%) with respect to healthy subjects [Δ error rate: 3.0 ±0.4%, t(22) = -3.54, p = 0.002], and in med-off/stim-off (Δ error rate: 9.9 ±2.0%) with respect to healthy subjects [t(22) = -3.48, p = 0.002], suggesting enhanced AC in PD. Otherwise, no significant difference in Δ error rate [t(22) = -0.148, p = 0.884] was found between the two groups of PD patients.

Then, a discrepancy was apparent between the two measures representative of AC, i.e. Δ RT and Δ error rate. This result could be due to a potential speed-accuracy trade-off effect, related to different conditions of evaluation. To clarify this discrepancy, we calculated the IE scores (Fig.14).

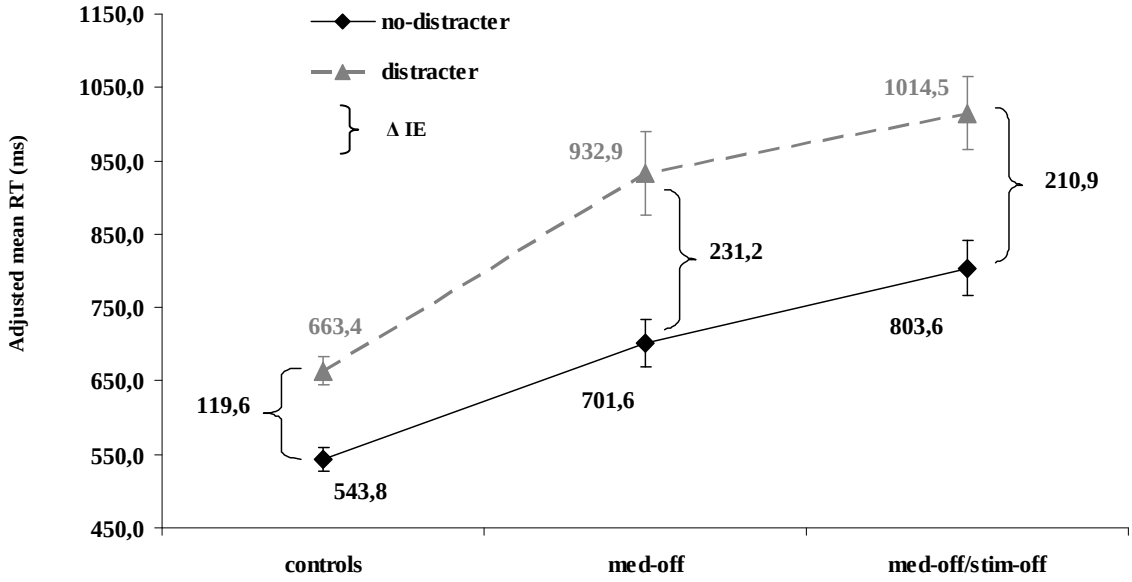

Fig.14 Comparison between the two groups of PD patients evaluated in off-condition (in med-off for the pharmacologically treated group, and in med-off/stim-off for the the stimulation treated group) and healthy subjects in terms of inverse efficiency (IE) score (expressed as adjusted mean RT), obtained in the no-distracter and distracter conditions of the attentional capture task. Δ IE = attentional capture in terms of Δ IE.

Firstly, this analysis revealed a significant effect of group [$F(2,33) = 18.6$, $p < 0.001$], due to higher IEs in med-off (817.2 ±36.3 ms,) than in control subjects (603.6 ±36.3 ms, $p = 0.001$), and in med-off/stim-off (909.1 ±36.3 ms) than in control subjects ($p < 0.001$), confirming that PD impaired performance in the AC task. Otherwise, there was no reliable difference between the med-off and med-off/stim-off conditions ($p = 0.248$). Moreover, a significant effect of the type of trial was observed [$F(1,33) = 167.6$, $p < 0.001$], due to higher IE in the distracter condition (870.3 ±26 ms) than in the no-distracter condition (683 ±17.5 ms). The interaction type of trial × group was significant [$F(2,33) = 5.6$, $p = 0.008$]. In particular, post-hoc analysis revealed that the AC effect was larger in the group of med-off patients (Δ IE: 231.2 ±33.3 ms) compared to healthy subjects [Δ IE: 119.6 ±4.3 ms, $t(22) = -3.32$, $p = 0.003$], and in the group of med-off/stim-off patients (Δ IE: 210.9 ±27.4 ms) compared to healthy subjects [$t(22) = -3.29$, $p = 0.003$]. Otherwise, no significant difference in Δ IE [$t(22) = 0.471$, $p = 0.642$] was found between the two groups of PD patients. Thus, these results suggested a behavioral homogeneity of our two groups of PD patients in terms of AC, which appeared enhanced by the pathological condition.

As regards the selection and initiation of motor responses, the analysis of RTs in the choice reaction time task revealed a significant effect of the factor group [$F(2,33) = 12.0$, $p < 0.001$]. In detail, we found longer RTs ($p < 0.001$) in the group #2 (med-off/stim-off: 613.9 ±30.8 ms) compared to healthy subjects (439.6 ±15.8 ms), whereas we obtained a p value very close to the significance ($p = 0.059$) by comparing PD patients in med-off (526.8 ±26.4 ms) with healthy subjects, as well as by comparing the two groups of PD patients in off-condition with each other.

Also the analysis of the RTs in the simple reaction time task pointed out that the factor group was significant [$F(2,33) = 10.4$, $p < 0.001$], due to faster RTs in healthy subjects (300.7 ±8.9 ms) than both groups of PD patients (med-off: 382.1 ±18.3 ms, $p < 0.013$; med-off/stim-off: 421.2 ±26.0 ms, $p < 0.001$), as we could expect by considering the akinesia typical of PD off-phase. No significant differences ($p = 0.468$) emerged by comparing the two groups of PD patients, suggesting a homogeneity in motor impairment between the two groups of patients (Fig.15).

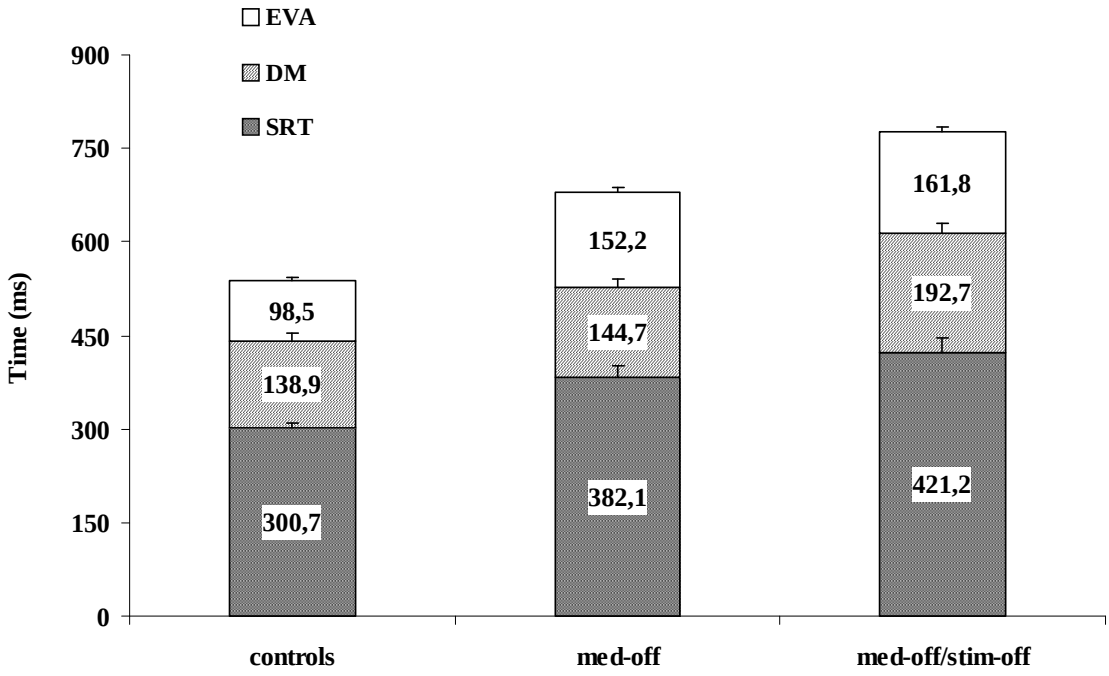

Fig.15 Comparison between the two groups of PD patients evaluated in off-condition (in med-off for the pharmacologically treated group, and in med-off/stim-off for the the stimulation treated group) and healthy subjects in terms of mean times for movement initiation (simple reaction time, SRT), motor response selection (decision making, DM), and target selection (EVA, endogenous visual attention). Note that SRT + DM = choice RT, while SRT + DM + EVA = RT in the no-distracter condition of the attentional capture task.

The error rates were not significantly different between the three groups in the choice reaction time task ($p = 0.292$) as well as in the simple reaction time task ($p = 0.140$). In Table 3, the mean (±SE) error rates for different groups and tasks are reported. The error rates in these two tasks were lower than those observed in the AC task, probably because the latter task was more difficult overall. Accordingly, when we consider these two tasks, the differences between PD patients and healthy subjects emerged mainly in the form of longer RTs than higher error rates.

	healthy subjects	med-off	med-off/stim-off
Choice reaction time task	0.4 ±0.2%	0.8 ±0.2%	0.5 ±0.3%
Simple reaction time task	0.8 ±0.2%	1.4 ±0.6%	2.6 ±0.9%

Tab.3 Mean (±SE) error rates in the choice and simple reaction time tasks for the three groups of participants.

Now, one might ask whether the larger increase of choice RTs observed for PD patients was due only to a mere motor impairment, or instead reflected a genuine impairment of the mechanisms of motor response selection. Analysis of DM revealed that the factor group was significant [$F(2,33) = 3.8$, $p = 0.032$]. This effect was due to larger Δ RTs in med-off/stim-off (192.7 ±16.8 ms) compared to control subjects (138.9 ±15.6 ms, $p = 0.050$), (Fig.15). Conversely, in med-off, we revealed only a slight increment in DM (144.7 ±12.5 ms, $p = 1.0$) compared to healthy subjects, and a tendency to a significant difference between med-off and med-off/stim-off ($p = 0.094$). These results showed that the mechanisms of motor response selection were potentially impaired only in the group of surgical treated PD patients. This observation suggested heterogeneity between our two PD groups, which could be related to some epidemiological or clinical parameter, as it will be pointed out in the discussion.

Analysis of EVA revealed that the factor group was significant [$F(2,33) = 17.5$, $p < 0.001$]. This effect was due to larger Δ RT in med-off (152.2 ±9.4 ms) compared to control subjects (98.5 ±5.7 ms, $p < 0.001$), and in med-off/stim-off (161.8 ±8.8 ms) compared to control subjects ($p < 0.001$), whereas no difference was found between the two PD groups ($p = 1.0$) (Fig.15). Thus, these results demonstrated that the time for display analysis and target selection were prolonged in both groups of PD patients, suggesting a weakening of the endogenous mechanisms of visual attention in PD.

On the whole, the analysis of the components of the response in no-distracter trials of the AC task showed that in med-off and in med-off/stim-off there was an impairment of the mechanisms of target selection and motor response initiation, while in med-off/stim-off only, there was also an involvement of the mechanisms of motor response selection.

Effects of dopaminergic treatment

The rate of outliers trials in med-on were 2.4%, 2.3%, and 2.4%, respectively in the AC, choice reaction time, and simple reaction time tasks.

A first qualitative inspection of the data showed that the dopaminergic treatment improved performances by decreasing RTs and the error rates in the AC task (Fig.16). More specifically, analysis of RTs revealed that the factor type of trial was significant [$F(1,11) = 113.8$, $p < 0.001$], due to longer RTs (mean ±SE) in the distracter condition (772.1 ±38.3 ms) than in no-distracter condition (642.3 ±29.7 ms). Moreover, the factor condition of evaluation was significant [$F(1,11) = 25.2$, $p < 0.001$], due to longer RTs in med-off (738.4 ±34.0 ms) compared to med-on (676.0 ±34.5 ms), thus indicating that the global performance was ameliorated by the pharmacological treatment. The interaction type of trial × condition of evaluation was also significant [$F(1,11) = 6.4$, $p = 0.028$]. In particular, the AC effect was larger under medical treatment (Δ RT: 140.6 ±13.7 ms) compared to med-off (Δ RT: 119.0 ±12.1 ms), suggesting that while the dopaminergic treatment speeded up the response times, it influenced also the mechanisms of visual attention (Fig.16A).

A different pattern of results emerged from the analysis of error rate in the AC task (Fig.16B). Indeed, while the factor type of trial was significant [$F(1,11) = 39.8$, $p < 0.001$], due to higher error rate in the distracter condition (12.5 ±1.4%) compared with the no-distracter condition (3.0 ±0.2%), the factor condition of evaluation, and the interaction condition of evaluation × type of trial were not significant ($p = 0.388$ and $p = 0.373$, respectively). Thus, these results seemed to point out that, contrary to what we saw for AC in terms of Δ RT, the dopaminergic treatment did not influence the mechanisms underlying the AC. To clarify this discrepancy, we calculated the IE scores (Fig.17).

In detail, this analysis showed a significant effect of the condition of evaluation [$F(1,11) = 11.1$, $p = 0.007$), due to a better global performance under dopaminergic treatment (736.9 ±41.7 ms) than in med-off (817.2 ±43.4 ms). Also the factor type of trial was significant [$F(1,11) = 58.9$, $p < 0.001$], due to higher IE values in the distracter (891.7 ±53.6 ms) than in the no-distracter (662.4 ±30.2 ms) condition.

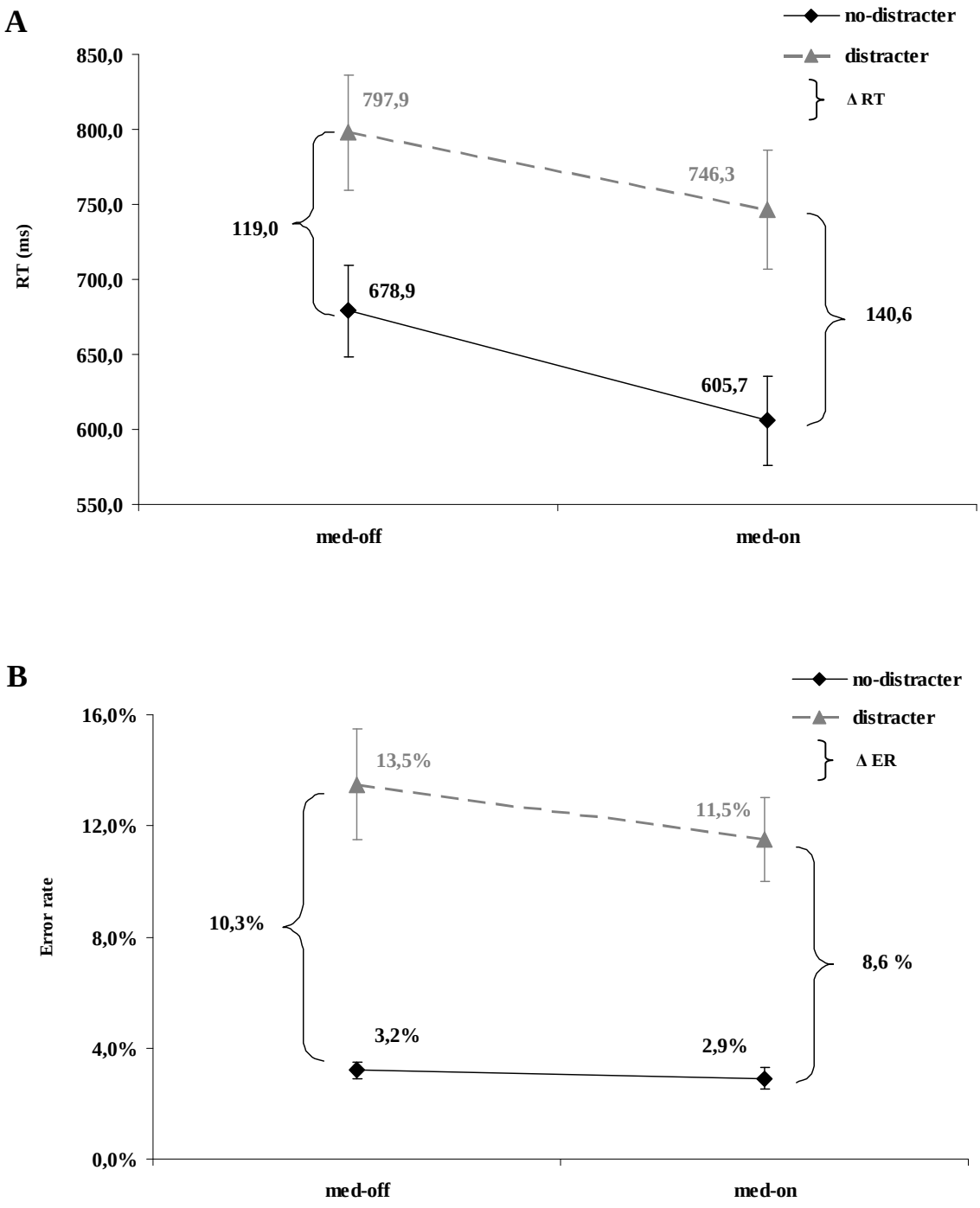

Fig.16 Comparison of mean reaction time, RT (in A), and error rate, ER (in B), obtained in the no-distracter and distracter conditions of the attentional capture task, by the group of pharmacologically treated patients, who were evaluated in med-off and med-on conditions. Δ RT and Δ ER = attentional capture in terms of Δ RT and Δ ER.

Conversely, the interaction type of trial × condition of evaluation was not significant (p = 0.893), as confirmed by the fact that no appreciable differences in Δ IE between the two conditions of evaluation (med-off: 231.2 ±33.3 ms; med-on: 227.3 ±32.8 ms) were observed, suggesting that the previous observed increment of AC in terms of Δ RT could be of unclear relevance.

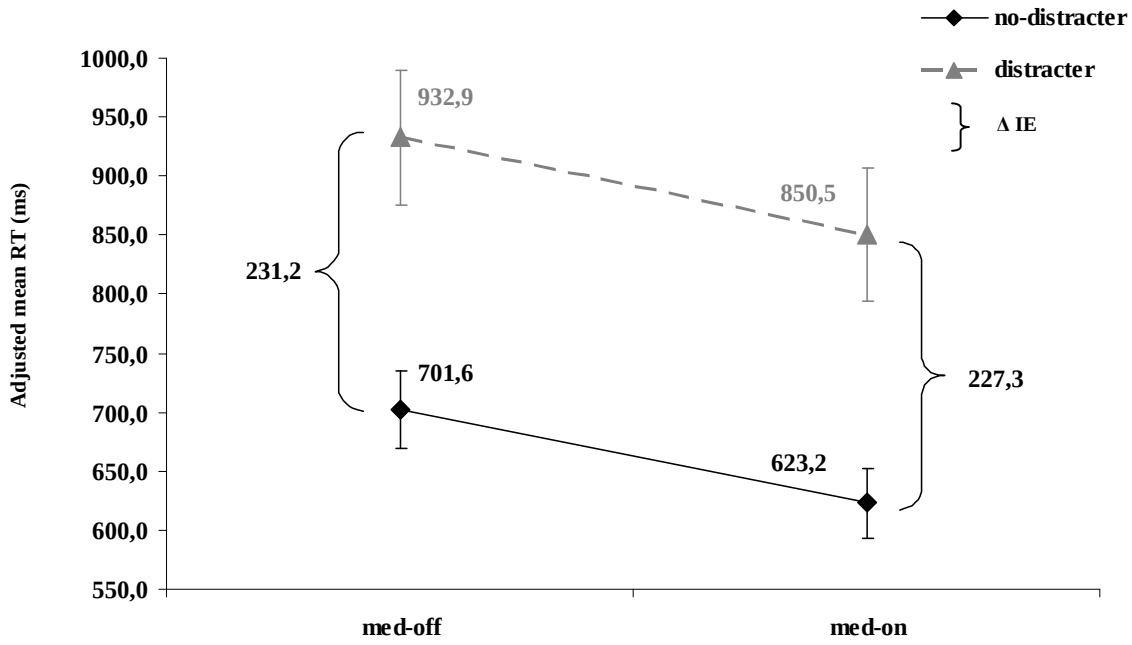

Fig.17 Comparison of the inverse efficiency (IE) score (expressed as adjusted mean RT), obtained in the no-distracter and distracter conditions of the attentional capture task by the group of medical treated patients, who were evaluated in med-off and med-on conditions. Δ IE = attentional capture in terms of Δ IE.

As described in a previous section, PD patients in med-off were slower than healthy subjects in performing the choice reaction time task and the simple reaction time task, even if the mean Δ RT between these two tasks (DM) was similar for both groups. Comparing the mean RTs in the same tasks for PD patients in med-off and med-on, we found that the factor condition of evaluation was not significant (p =

0.147) in the choice reaction time task (med-off: 526.7 ±26.4 ms; med-on: 506.9 ±27.3 ms), while it was significant [$t(11) = 5.7$, $p < 0.001$] in the simple reaction time task (med-off: 382.1 ±18.3 ms; med-on: 351.6 ±17.8 ms), suggesting that dopaminergic treatment could speed up the patients' motor responses, without consistently affecting the process of motor response selection (Fig.18).

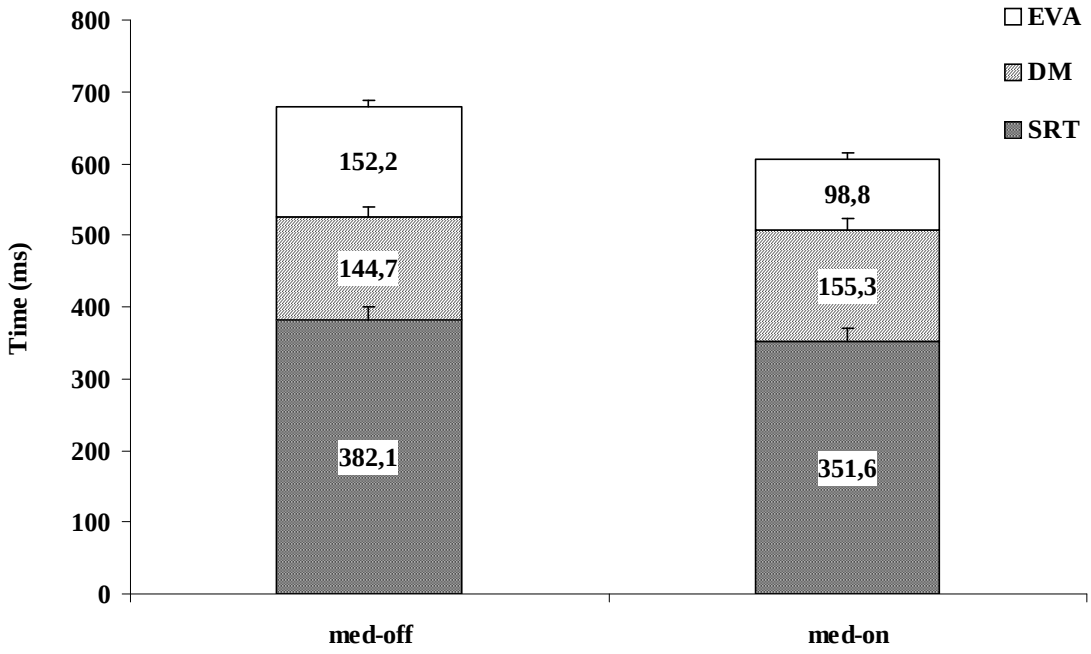

Fig.18 Comparison of the mean times for movement initiation (simple reaction time, SRT), motor response selection (decision making, DM), and target selection (EVA, endogenous visual attention) obtained by the group of pharmacologically treated patients, who were evaluated in med-off and med-on conditions. Note that SRT + DM = choice RT, while SRT + DM + EVA = RT in the no-distracter condition of the attentional capture task.

This lack of effect on motor response selection was confirmed by the analysis of DM, where no significant effect of condition of evaluation was found ($p = 0.435$). In particular, the DM component "diluted" the beneficial effect of the dopaminergic treatment obtained on motor response initiation, as revealed by the mild increment of DM in med-on (155.3 ±16.1 ms) compared with med-off (144.7 ±12.5 ms).

Analyses of error rates in the choice reaction time as well as the simple reaction time tasks revealed that there were no significant differences comparing the two conditions of evaluation ($p = 0.191$, and $p = 0.120$, respectively in the choice and simple reaction time task).

A beneficial effect on the mechanisms of target selection, due to dopaminergic treatment, seemed to emerge by the analysis of EVA. In detail, in med-on there a was significant [$t(11) = 7.8$, $p < 0.001$] reduction of EVA (98.8 ±8.7 ms) compared with med-off (152.2 ±9.4 ms), suggesting that the dopaminergic treatment might potentate the endogenous mechanisms of visual attention. If so, one might expect a reduction of the AC. Conversely, we observed an increase of AC in terms of Δ RTs, which could be explained by assuming that, under dopaminergic treatment, in parallel with the improvement of EVA mechanisms, there might be also an enhancement of the bottom-up mechanisms.

On the whole, the analysis of the components of the response in no-distracter trials of the AC task showed that under dopaminergic treatment there was an improvement of the mechanisms of target selection and motor response initiation, while there were no significant changes in the mechanisms of motor response selection.

Effects of deep brain stimulation of the subthalamic nucleus

The percentage of outliers excluded from analyses were 2.5%, 1.9%, and 2.8%, respectively, in the AC, choice reaction time, and simple reaction time tasks in med-off/SMstim-on, and 2.2%, 3.1%, 2.0% in med-off/ASstim-on.

A first qualitative inspection of the data obtained in the AC task showed that both conditions of stimulation, especially the med-off/SMstim-on reduced RTs, while no appreciable changes were evident in terms of error rates (Fig.19). In particular, the analysis of RTs in the AC task showed that the factor type of trial was significant [$F(1,11) = 281.9$, $p < 0.001$], due to longer RTs in the distracter condition (849.7 ±33.3 ms) than in the no-distracter condition (723.0 ±28.8 ms). The factor condition of evaluation was significant [$F(2,22) = 7.8$, $p = 0.003$], due to longer RTs in the med-

off/stim-off (824.8 ±35.5 ms, p = 0.009) compared with med-off/SMstim-on (753.6 ±27.0 ms). Otherwise, the RTs in med-off/ASstim-on (780.5 ±34.8 ms) did not differ significantly from med-off/stim-off (p = 0.092) and from med-off/SMstim-on (p = 0.488). The interaction type of trial × condition of evaluation was significant [$F(2,22) = 30.7$, $p < 0.001$]. Post-hoc analyses showed that the AC effect was larger under SM-stimulation (Δ RT: 143.2 ±10.0 ms) than in med-off/stim-off (98.2 ±6.5 ms, $t(11) = -7.49$, $p < 0.001$), as well as under AS-stimulation (Δ RT: 138.8 ±8.3 ms) than in med-off/stim-off [$t(11) = -6.76$, $p < 0.001$]. Otherwise, the two conditions of stimulation did not differ from one another in terms of AC [$t(11) = 0.641$, $p = 0.535$]. Therefore, under STN stimulation, there was an enhancement of the AC in terms of Δ RT, similarly to that seen under dopaminergic treatment.

Analysis of error rate showed that the factor type of trial was significant [$F(1,11) = 32.3$, $p < 0.001$], due to higher error rate in the distracter condition (13.9 ±1.7%) than the no-distracter condition (4.3 ±0.6%). The factor condition of evaluation and the interaction condition of evaluation × type of trial were not significant (p = 0.463 and p = 0.802, respectively). Therefore, in terms of error rate, STN stimulation did not seem to influence the mechanisms underlying AC, similarly to the dopaminergic treatment.

To clarify the discrepancy in the measures of AC, i.e. Δ RTs and Δ error rates, we computed the IE scores (Fig.20). This analysis showed that the factor type of trial was significant [$F(1,11) = 82.7$, $p < 0.001$], due to worse performances in the distracter trials (996.6 ±48.2 ms) than no-distracter trials (755.2 ±30.3 ms). Yet, under stimulation of both STN sites we obtained a partial amelioration of the global performances with respect to med-off/stim-off (909.1 ±41.8 ms), but without reaching significance: p = 0.134 in med-off/SMstim-on (847.6 ±35.6 ms), and p = 0.500 in med-off/ASstim-on (871.0 ±45.2 ms). Also the interaction condition of evaluation × type of trial was not significant (p = 0.179), as revealed by the lack of appreciable differences in the AC effect in terms of Δ IE between the three conditions of evaluation (med-off/stim-off: 210.9 ±27.4 ms; med-off/SMstim-on: 265.0 ±36.1 ms; med-off/ASstim-on: 248.3 ±29.7 ms), although a tendency to larger Δ IE emerged under stimulation.

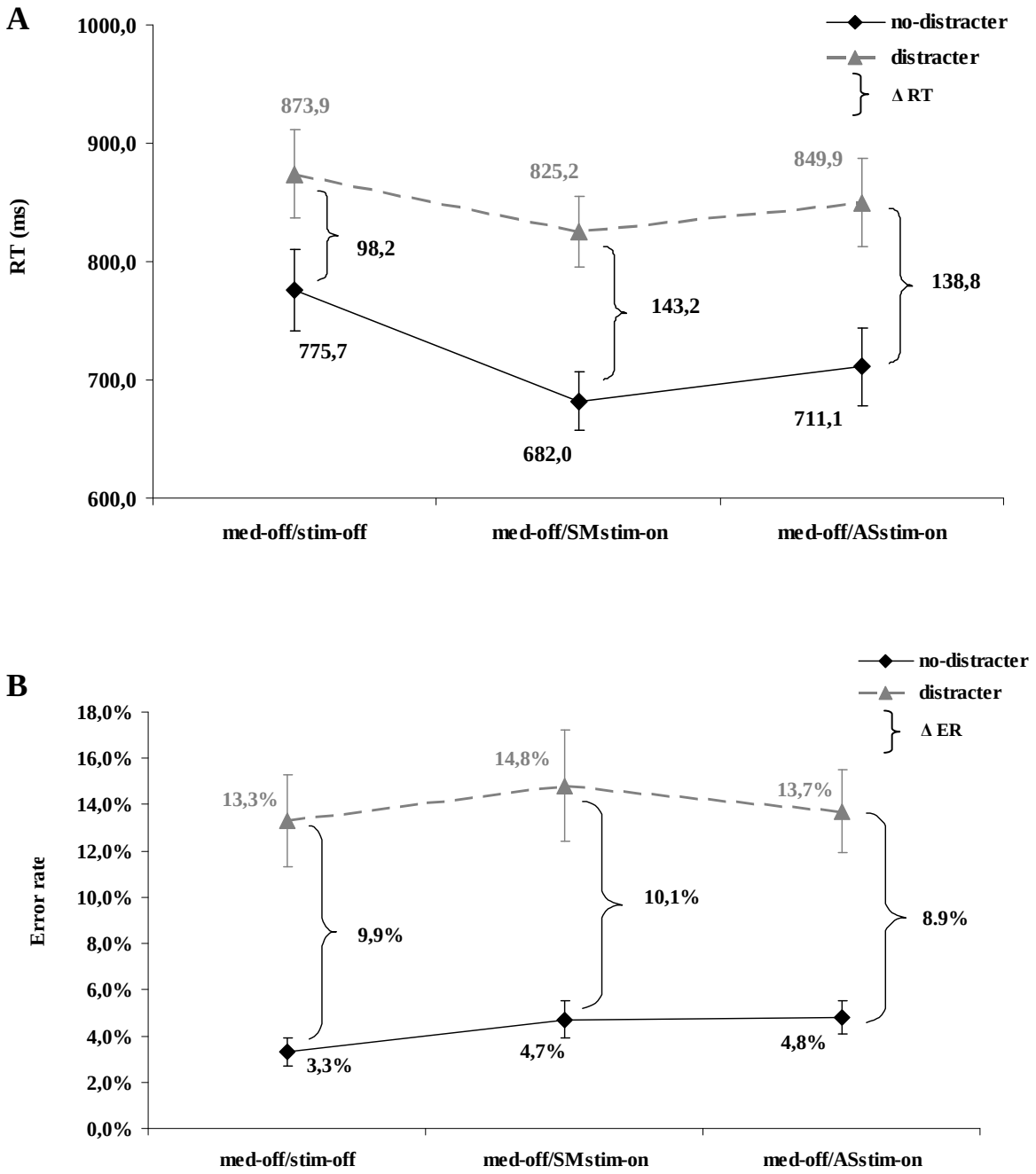

Fig.19 Comparison of mean reaction time, RT (in A), and error rate, ER (in B), obtained in the no-distracter and distracter conditions of the attentional capture task, by the group of stimulation treated patients, who were evaluated in med-off/stim-off, med-off/SMstim-on, and med-off/ASstim-on conditions. Δ RT and Δ ER = attentional capture in terms of Δ RT and Δ ER.

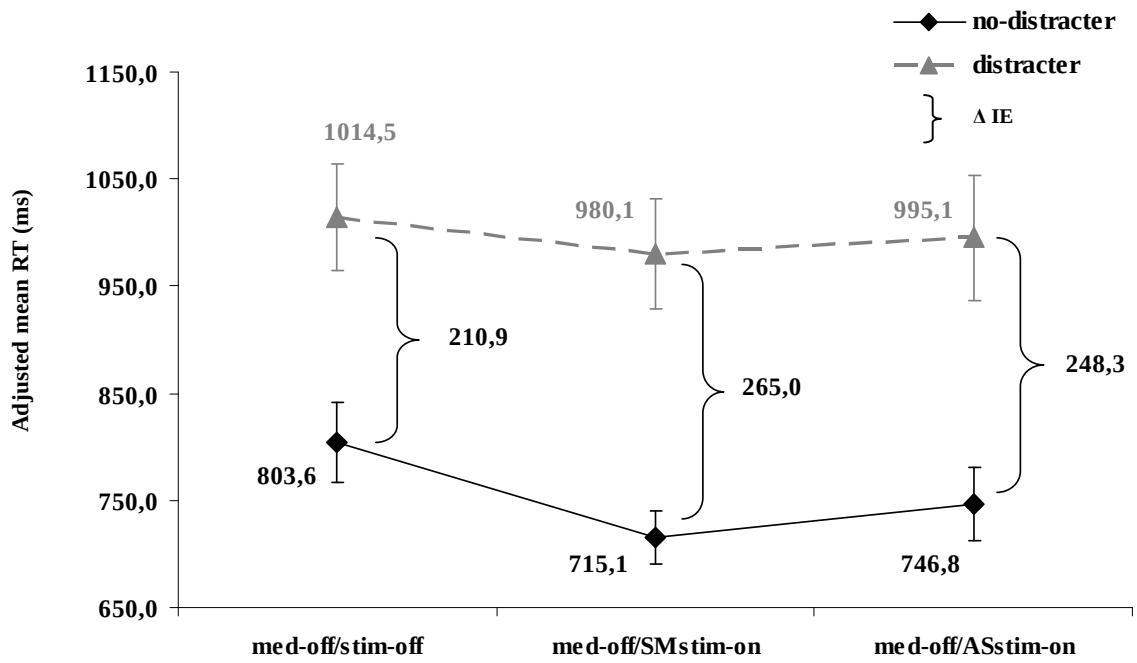

Fig.20 Comparison of the inverse efficiency (IE) score (expressed as adjusted mean RT), obtained in the no-distracter and distracter conditions of the attentional capture task by the group of stimulation treated patients, who were evaluated in med-off/stim-off, med-off/SMstim-on, and med-off/ASstim-on conditions. Δ IE = attentional capture in terms of Δ IE.

Therefore, like for dopaminergic treatment, the previously observed increment of AC in terms of Δ RT, occurring during stimulation, should be interpreted with caution because it might be a reflection of a potential speed-accuracy trade-off.

As regards the choice reaction time and simple reaction time tasks, on the whole the data suggest that only stimulation of SM part of the STN led to an improvement in task performance with respect to the pathological condition (med-off/stim-off), while no benefit was evident by stimulating the AS part of STN (Fig.21). In detail, analysis of RTs in the choice reaction time task revealed that the factor condition of evaluation was significant [$F(2,22) = 5.6$, $p = 0.011$]. This effect was due to longer RTs in med-off/stim-off (613.9 ±30.8 ms) compared to med-off/SMstim-on (558.8 ±21.9 ms, $p = 0.029$), whereas no significant difference emerged when comparing the RTs in med-off/stim-off with med-off/ASstim-on (608.8 ±32.4 ms, p =

1.0), and the two conditions of stimulation with one another (p = 0.072). Analysis of error rate revealed no significant effect (p = 0.143).

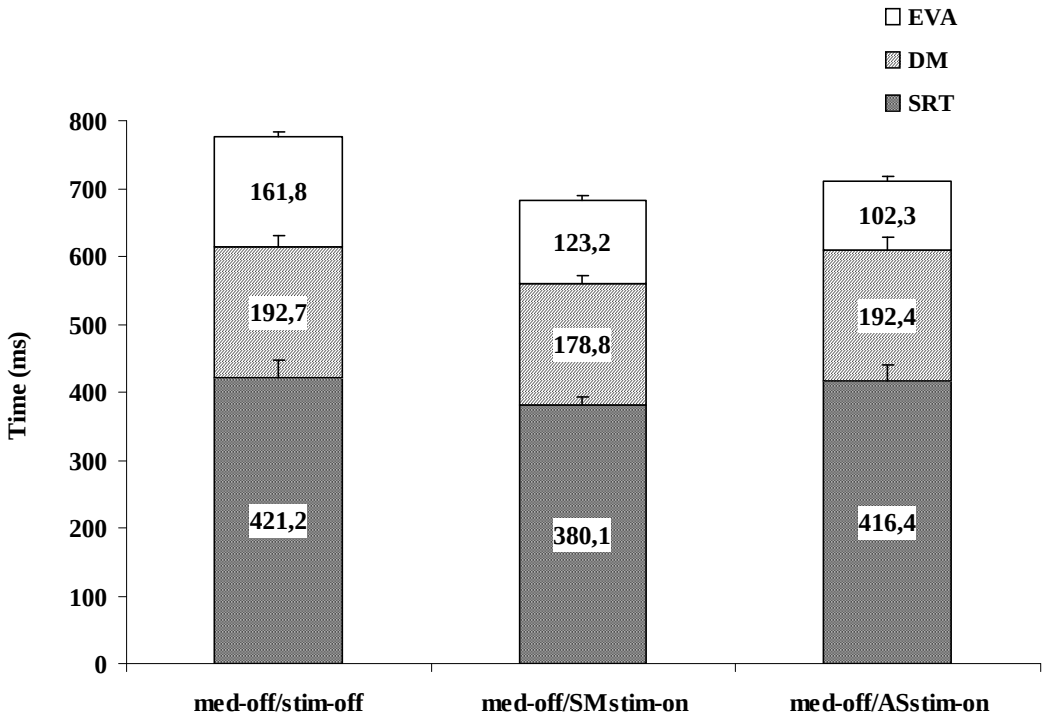

Fig.21 Comparison of the mean times for movement initiation (simple reaction time, SRT), motor response selection (decision making, DM), and target selection (EVA, endogenous visual attention) obtained by the group of stimulation treated patients, who were evaluated in med-off/stim-off, med-off/SMstim-on, and med-off/ASstim-on conditions. Note that SRT + DM = choice RT, while SRT + DM + EVA = RT in the no-distracter condition of the attentional capture task.

In the simple reaction time task, analysis of RTs showed that stimulation of the SM part of the STN led to faster RTs (380.1 ±13.1 ms), with a tendency to a significant effect, compared to the pathological condition (421.2 ±26 ms, p = 0.077), as well as compared to the stimulation of the AS part of the STN (416.4 ±23.5 ms, p = 0.058). No significant difference (p = 1.0) was found between med-off/ASstim-on and med-off/stim-off. Analysis of error rate revealed no significant effect (p = 0.217). Thus, the stimulation of the SM part of the STN seemed to be effective at improving the mechanisms of motor response initiation with respect to the pathological condition.

Analysis of DM revealed no significant effect of the factor condition of evaluation ($p = 0.513$) suggesting that stimulation, like dopaminergic treatment, did not interfere with the process of motor response selection (Fig.21). Nevertheless, a qualitative inspection of the data showed a trend towards an improvement of DM under stimulation of the SM part of the STN, contrary to what observed with dopaminergic treatment.

Conversely, stimulation seemed to have a great impact on the mechanisms underlying target selection, as showed by the analysis of EVA (Fig.21). This analysis showed that the factor condition of evaluation was significant [$F(2,22) = 75.2$, $p < 0.001$], due to shorter Δ RTs in med-off/SMstim-on (123.2 ±7.5 ms) and in med-off/ASstim-on (102.3 ±6.5 ms) compared with med-off/stim-off (161.8 ±8.8 ms) [for both comparisons $p < 0.001$]. Therefore, the aforementioned stimulation-induced enhancement of AC in terms of Δ RTs, might be explained by considering a potentation of the bottom-up mechanisms of visual attention, which occurred in parallel with the improvement of EVA, similar to what observed under dopaminergic treatment.

Moreover, we found that the time taken for target selection was significantly shorter by stimulating the AS part of the STN than the SM one ($p = 0.013$), suggesting a functional specialization of the AS part of the STN in the mechanisms of EVA control.

On the whole, the analysis of the components of the response in no-distracter trials of the AC task showed that under stimulation of the AS part of the STN there was an improvement of the mechanisms of target selection. Also the SM stimulation allowed a significant recovery of EVA compared to the stim-off condition, but to a lesser extent compared to that obtained by stimulation of the AS part. No appreciable effects were observed on motor response selection times by stimulation of either site. The movement initiation RTs were reduced compared to the stim-off condition only by stimulation of the SM part of the STN.

Comparison between the effects due to dopaminergic and STN stimulation

For these analyses the level of significance was set to $p \leq 0.025$ according to Bonferroni correction, since we compared the effect of dopaminergic treatment twice.

A) Dopaminergic versus SM-STN stimulation.

Overall, it appeared that dopaminergic and SM-STN stimulation did not determine significantly different effects compared with the off condition, as reported in detail in Table 4.

	Δ med-off – med-on	**Δ med-off/stim-off – med-off/ASstim-on**	**t; p (df = 22)**
Attentional capture task			
RT			
no-distracter condition	73.2 ±12.3 ms	93.7 ±19.6 ms	-0.886; 0.387
distracter condition	51.6 ±14.0 ms	48.7 ±18.7 ms	0.123; 0.903
Error rates			
no-distracter condition	0.3 ±0.5%	-1.3 ±0.6%	1.951; 0.064
distracter condition	2.0 ±2.1%	-1.5 ±1.9%	1.231; 0.231
Attentional Capture			
Δ RT	-21.7 ±8.6 ms	-45.1 ±6.0 ms	2.229; 0.038
Δ Error rate	1.8 ±1.9%	-0.2 ±1.8%	0.728; 0.474
Inverse Efficiency			
no-distracter condition	78.4 ±15.0 ms	88.5 ±21.1 ms	-0.391; 0.700
distracter condition	82.3 ±36.6 ms	34.4 ±37.7 ms	0.912; 0.372
attentional capture	3.9 ±28.4 ms	-54.1 ±28.0 ms	1.457; 0.159
Choice reaction time task			
RT	19.8 ±12.7 ms	55.1 ±17.7 ms	-1.623; 0.119
Error rate	0.4 ±0.3%	-0.4 ±0.4%	1.629; 0.365
Simple reaction time task			
RT	30.5 ±5.3 ms	41.2 ±16.0 ms	-0.635; 0.536
Error rate	-1.1 ±0.7%	1.3 ±0.9%	-2.195; 0.039
Decision Making	-10.7 ±13.2 ms	13.9 ±12.1 ms	-1.378; 0.182
Endogenous Visual Attention	53.4 ±6.9 ms	38.6 ±3.9 ms	1.871; 0.075

Tab.4 Mean (±SE) Δ RTs and Δ error rates in different tasks under pharmacological treatment and electrical stimulation of the sensorimotor part of the subthalamic nucleus. The t and p values obtained comparing the effects of the two treatments by t-tests are reported on the right column.

More precisely, the analysis of RTs in the AC task showed a similar improvement of performances by medical and electrical treatment in the no-distracter as well as in the distracter conditions. The analysis of AC in terms of Δ RT did not reveal significant differences in the increment of AC under dopaminergic and electrical stimulation, although a tendency to a larger Δ AC emerged under stimulation.

The analysis of errors revealed no significant difference, either in the no-distracter or in the distracter conditions. The analysis of AC in terms of Δ error rates confirmed that there was no significantly different effect when comparing the two treatments.

Analogously, the analysis of IE revealed no significant differences, either in the no-distracter or in the distracter conditions. Also the analysis of Δ AC computed on the IE scores did not show appreciable differences between the two treatments.
Finally, no significantly different effects due to pharmacological treatment and SM-STN stimulation were found in terms of RTs and error rates in the choice reaction time task, in the simple reaction time task, in terms of Δ DM, and Δ EVA.

B) Dopaminergic versus AS-STN stimulation.

Overall, we did not find reliable differences by comparing dopaminergic and AS-STN stimulation, as reported in Table 5. Only in the choice reaction time task, PD patients committed significantly more errors under stimulation than medication.

	Δ med-off – med-on	Δ med-off/stim-off – med-off/ASstim-on	t; p (df = 22)
Attentional capture task			
RT			
no-distracter condition	73.2 ±12.3 ms	64.6 ±18.2 ms	0.394; 0.697
distracter condition	51.6 ±14.0 ms	24.0 ±18.0 ms	1.208; 0.240
Error rates			
no-distracter condition	0.3 ±0.5%	-1.4 ±0.8%	1.784; 0.088
distracter condition	2.0 ±2.1%	-0.4±2.0%	0.832; 0.414
Attentional Capture			
Δ RT	-21.7 ±8.6 ms	-40.6 ±6.0 ms	1.805; 0.085
Δ Error rate	1.8 ±1.9%	1.0 ±1.9%	0.277; 0.784
Inverse Efficiency			
no-distracter condition	78.4 ±15.0 ms	56.8 ±20.3 ms	0.856; 0.401
distracter condition	82.3 ±36.6 ms	19.4 ±36.3 ms	1.220; 0.235
attentional capture	3.9 ±28.4 ms	-37.4 ±28.4 ms	1.029; 0.315
Choice reaction time task			
RT	19.8 ±12.7 ms	5.1 ±17.7 ms	0.675; 0.506
Error rate	0.4 ±0.3%	-0.8 ±0.3%	2.865; 0.009
Simple reaction time task			
RT	30.5 ±5.3 ms	4.8 ±11.8 ms	1.979; 0.060
Error rate	-1.1 ±0.7%	0.1 ±0.7%	-1.344; 0.193
Decision Making	-10.7 ±13.2 ms	0.3 ±14.3 ms	-0.564; 0.578
Endogenous Visual Attention	53.4 ±6.9 ms	59.5 ±4.9 ms	-0.720; 0.479

Tab.5 Mean (±SE) Δ RTs and Δ error rates in different tasks under pharmacological treatment and electrical stimulation of the associative part of the subthalamic nucleus. The t and p values obtained comparing the effects of the two treatments by t-tests are reported on the right column.

Effects of dopaminergic and STN stimulation with respect to the control condition

For these analyses the level of significance was set to $p \leq 0.017$ according to Bonferroni correction, since we compared three times the values obtained from controls.

At first glance, the dopaminergic treatment seemed to improve the patients' performance in our tasks more than the stimulation. Nonetheless, neither the medical

therapy, nor the electrical stimulation completely restored the patients' performance to the level of healthy subjects. A detailed data analysis is shown on Table 6.

More precisely, in the AC task, the RTs of patients under dopaminergic treatment were not significantly different from those of healthy subjects either in the no-distracter, or in the distracter condition. Conversely, the RTs of patients stimulated at the SM and AS parts of the STN differed from those of healthy subjects in the no-distracter as well as in the distracter condition (Fig.22A). These findings suggest that the dopaminergic treatment may be more effective than stimulation in restoring to normality the patients' performance in the AC task. Yet, we have seen that medical and electrical treatment had a comparable effect on the AC task performances. This discrepancy may be explained by considering that the two groups of PD patients were differently impaired in their performances in the AC task in off condition (even if without reaching a significance level), being the RTs of medically treated patients (med-off in the no-distracter: 678.9.1 ±30.9 ms, and in distracter condition: 797.9 ±38.0 ms) shorter than those of stimulated patients (med-off/stim-off in the no-distracter: 775.7 ±34.3 ms, and distracter condition: 873.9 ±37.1 ms). Therefore, in face of a comparable effect of the two treatments, the dopaminergic treatment seemed more effective in restoring the patients' performance to normality.

Dopaminergic and STN-stimulation (at both sites of stimulation), similarly influenced the mechanisms underlying the AC, by increasing the AC in terms of ΔRT compared to healthy subjects (Fig.22A).

Analysis of error rates in the AC task revealed that the error rates were higher for medically treated and stimulated patients compared with healthy subjects, both in no-distracter and in distracter conditions. Also AC in terms of Δ error rates showed a significant increase under medical and electrical treatment compared with that obtained in healthy subjects (Fig.22B).

Analysis of IE showed that, in the no-distracter condition, PD patients' performance in med-on was not significantly different from those of healthy subjects (Fig.23).

	med-on	med-off/ SMstim-on	med-off/ ASstim-on	controls	med-on vs controls **t**(df = 22)**;p**	SM-stimulation vs controls **t**(df = 22)**;p**	AS-stimulation vs controls **t**(df = 22)**;p**
Attentional capture task							
RT (ms)							
no-distracter condition	605.7 ±29.8	682.0 ±24.7	711.1 ±32.4	538.0 ±16.6	-1.983;0.060	-4.836;<0.001	-4.752;<0.001
distracter condition	746.3 ±39.8	825.2 ±30.0	849.9 ±37.5	635.2 ±18.6	-2.529;0.023	-5.380;<0.001	-5.130;<0.001
Error rates (%)							
no-distracter condition	2.9 ±0.4	4.7 ±0.8	4.8 ±0.7	1.0 ±0.2	-4.213;<0.001	-4.298;<0.001	-4.970;<0.001
distracter condition	11.5 ±1.5	14.8 ±2.4	13.7 ±1.8	4.0 ±0.4	-4.849;<0.001	-4.441;<0.001	-5.202;<0.001
Attentional Capture							
Δ RT (ms)	140.6 ±13.7	143.2 ±10.0	138.8 ±8.3	97.1 ±4.1	-3,049;0.006	-4.273;<0.001	-4.490;<0.001
Δ Error rate (%)	8.6 ±1.5	10.1 ±2.4	8.9 ±1.7	3.0 ±0.4	-3,677;0.001	-2.955;<0.007	-3.414;<0.002
Inverse Efficiency (ms)							
no-distracter condition	623.2 ±29.3	715.1 ±24.4	746.8 ±33.8	543.8 ±16.5	-2.361;0.028	-5.814;<0.001	-5.395;<0.001
distracter condition	850.5 ±56.2	980.1 ±50.8	995.1 ±58.1	663.4 ±19.5	-3.144;0.005	-5.816;<0.001	-5.408;<0.001
attentional capture	227.3 ±32.8	265.0 ±36.1	248.3 ±29.7	119.6 ±4.3	-3.252;0.004	-4.003;0.001	-4.283;<0.001
Choice reaction time task							
RT (ms)	506.9 ±27.3	558.8 ±21.9	608.8 ±32.4	439.6 ±15.8	-2.136;0.044	-4.418;<0.001	-4.689;<0.001
Error rate (%)	0.5 ±0.2	0.9 ±0.3	1.2 ±0.3	0.4 ±0.2	-0.456;0.653	-1.890;<0.072	-2.602;0.016
Simple reaction time task							
RT (ms)	351.6 ±17.8	380.1 ±13.1	416.4 ±23.5	300.7 ±8.9	-2.564;0.021	-5.031;<0.000	-4.605;<0.001
Error rate (%)	2.5 ±0.6	1.4 ±0.5	2.5 ±0.6	0.8 ±0.2	-2.563;0.023	-1.108;0.280	-2.681;0.014
Decision Making (ms)	155.3 ±16.1	178.8±13.1	192.4 ±18.6	138.9 ±15.6	-0.732;0,472	-1.955;<0.063	-2.199;0.039
Endogenous Visual Attention (ms)	98.8 ±8.7	123.2 ±7.5	102.3 ±6.5	98.5 ±5.7	-0.028;0.978	-2.613;0.016	-0.444;0.661

Tab.6 Mean ±SE performances indices obtained in different tasks by Parkinson's disease patients, under either dopaminergic treatment or electrical stimulation of the sensorimotor or associative part of the subthalamic nucleus, and by controls. The t and p values obtained by means of t-tests, comparing each performance index of patients under different treatments with that of controls are reported.

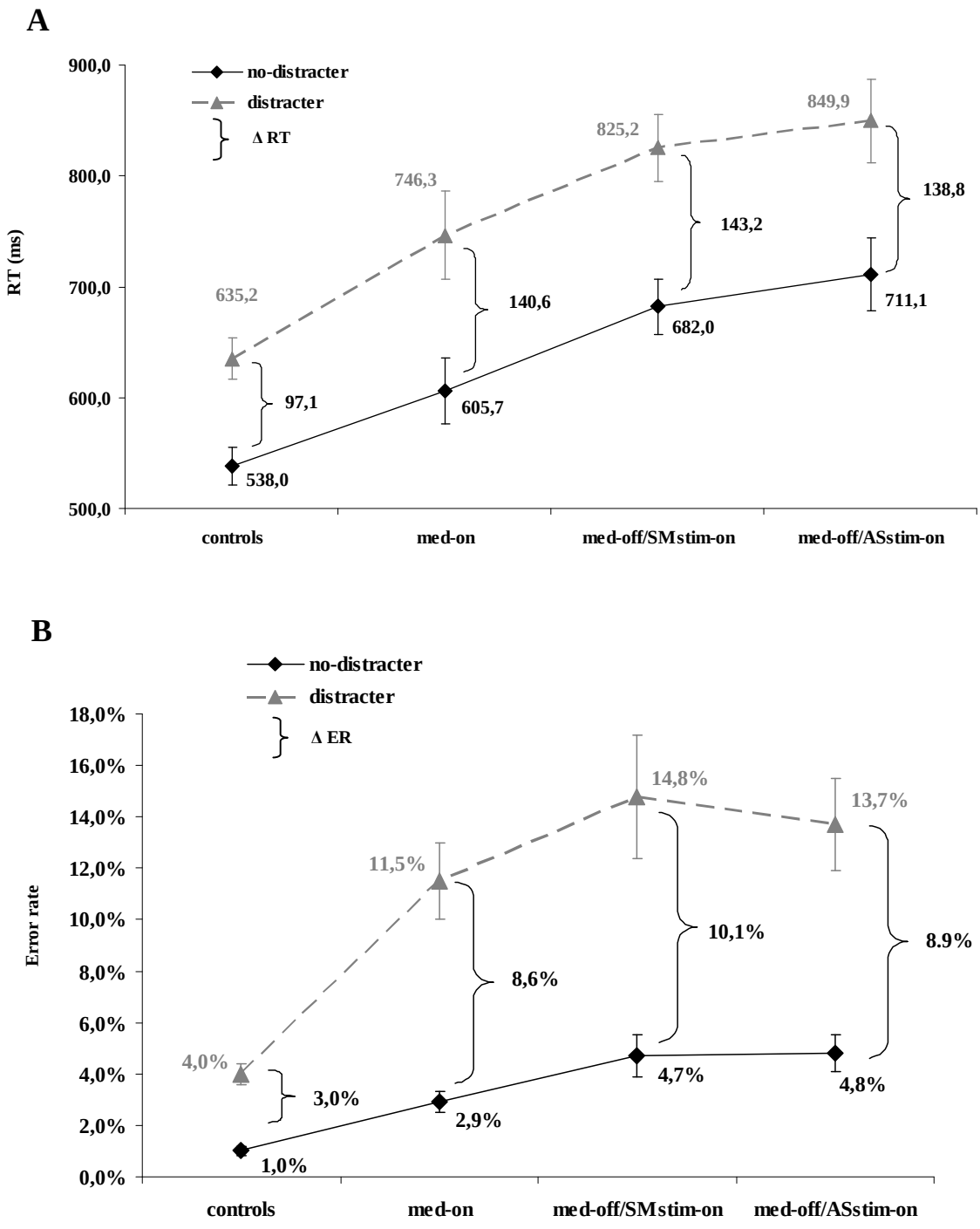

Fig.22 Comparison between the two groups of patients evaluated under treatment (in med-on for the pharmacologically treated group, and in med-off/SMstim-on and in med-off/ASstim-on for the stimulation treated group) and healthy subjects in terms of reaction time, RT (in A), and error rate, ER (in B), obtained in the no-distracter and distracter conditions of the attentional capture task. Δ RT and Δ ER = attentional capture in terms of Δ RT and Δ ER.

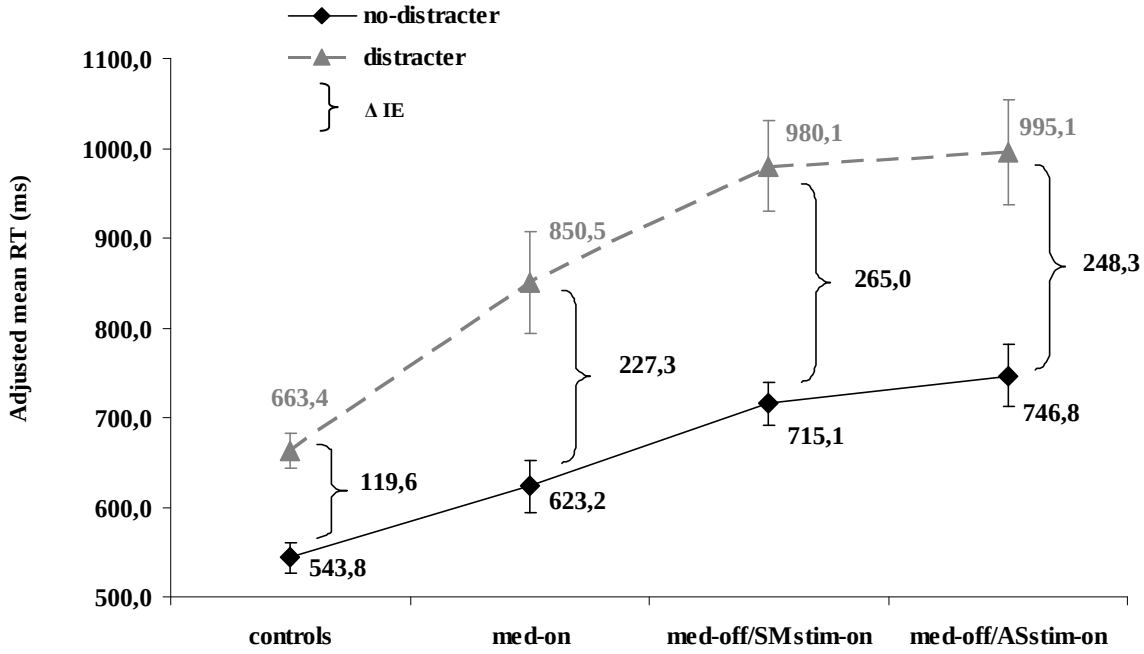

Fig.23 Comparison between the two groups of patients evaluated under treatment (in med-on for the medically treated group, and in med-off/SMstim-on and in med-off/ASstim-on for the stimulation treated group) and healthy subjects n terms of inverse efficiency (IE) score (expressed as adjusted mean RT), obtained in the no-distracter and distracter conditions of the attentional capture task. Δ IE = attentional capture in terms of Δ IE.

Conversely, under stimulation of the SM and AS parts of the STN the IE scores in the no-distracter condition were significantly higher than those of healthy subjects, suggesting that dopaminergic treatment was more effective than stimulation in restoring to normality these IE values.

However, this dopaminergic benefit was only partial, as revealed by the fact that in the distracter condition, PD patients had significantly higher IE scores under all types of treatment than healthy subjects. Also the AC computed on the IE scores resulted significantly increased compared with that of healthy subjects under dopaminergic as well as STN-stimulation of both sites.

Interestingly, while in med-off PD patients had longer RTs in the choice as well as in the simple reaction time tasks compared with healthy subjects, under

dopaminergic treatment they showed a substantial amelioration in their performances, as proved by the fact that the RTs on these tasks did not differ significantly from those of healthy subjects (Fig.24). Conversely, STN stimulation did not restore patients' RTs in these two tasks to normality.

Analysis of errors rates revealed a significant increase of errors only for stimulation of the AS part of the STN in both tasks (Table 6). Otherwise, no significant differences in error rates between healthy subjects and medically treated patients as well as healthy subjects and SM-stimulated patients were found.

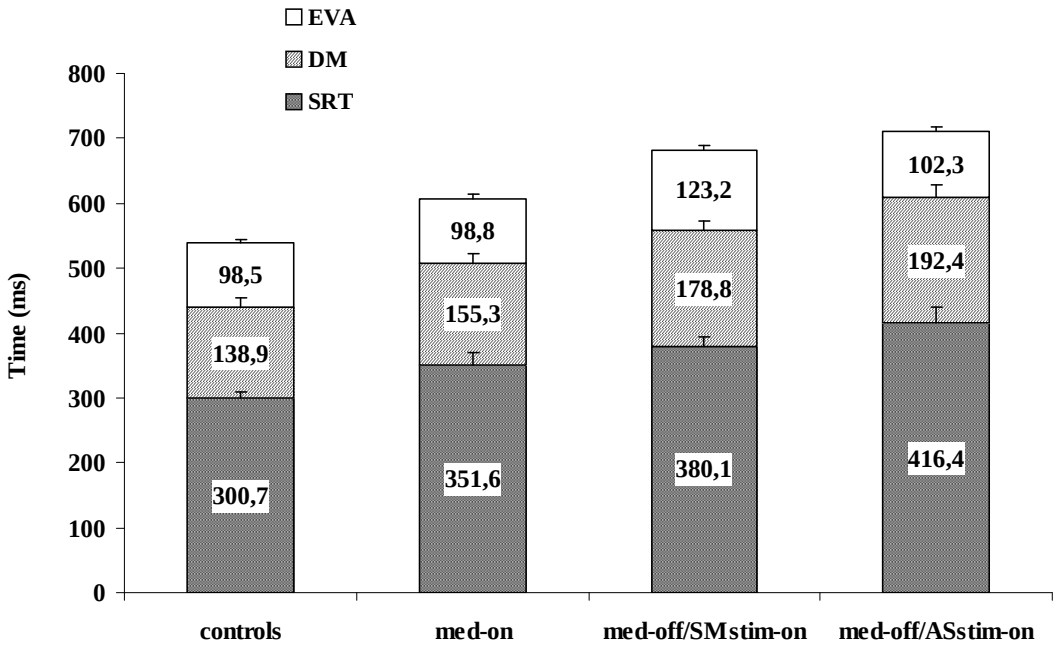

Fig.24 Comparison between the two groups of patients evaluated under treatment (in med-on for the medical treated group, and in med-off/SMstim-on and in med-off/ASstim-on for the stimulation treated group) and healthy subjects of the mean times for movement initiation (simple reaction time, SRT), motor response selection (decision making, DM), and target selection (EVA, endogenous visual attention). Note that SRT + DM = choice RT, while SRT + DM + EVA = RT in the no-distracter condition of the attentional capture task.

As regards the mechanisms of motor response selection, we found that under stimulation and medication the DM values did not significantly differ from those of healthy subjects (Fig.24). On the other hand, we have seen that in med-off/stim-off the mechanisms of motor response selection resulted impaired, without a significant amelioration under stimulation of both sites, while they were preserved in med-off. These results suggest that under STN stimulation, especially of the SM part, there is a tendency to an amelioration of the DM component of the response, even if it was not statistically significant. Conversely, the dopaminergic treatment seems to have no effect on DM.

Finally, and more interestingly, we found a different effect of dopaminergic and AS stimulation of the STN with respect to SM stimulation on EVA (Fig.24). More precisely, no significant differences were found between med-on and med-off/ASstim-on compared to healthy subjects, whereas med-off/SMstim-on differed from healthy subjects ($p = 0.016$). This result suggest that dopaminergic treatment as well as stimulation of the AS part of the STN can restore the mechanisms of EVA to normal value, while this is not the case for the SM-stimulation.

Discussion

The basal ganglia have long been implicated in the control of movement, and the anatomy of the basal ganglia is perfectely suited to selectively gate a desired motor plan to the motor cortex while simultaneously inhibiting competing motor plans.[219] Several studies have suggested that the role of the basal ganglia in selective gating is not limited to motor processes but extends to cognitive functions.[220]

In this work we aimed to investigate the possible role of cortico-basal ganglia loops and dopaminergic pathways in the mechanisms of top-down and bottom-up control of visual attention, by comparing the performances of PD patients in a variety of conditions, including under dopaminergic treatment, STN electrical stimulation and, finally, patients in off-phase condition. In summary the results of the present work indicated that PD patients assessed after withdrawal of dopaminergic treatment and after turning-off stimulation showed increased AC compared to healthy subjects. Also, target selection and movement initiation times were prolonged in both groups of patients, while motor response selection time was significantly increased only in the otherwise stimulated group. It is noteworthy that the usual dopaminergic treatment of otherwise electrically stimulated patients was at significantly lower dosage than that of the otherwise pharmacologically treated group.

Under usual dopaminergic treatment and stimulation of the SM as well as AS part of the STN, patients showed similarly increased AC in terms of ΔRT. Dopaminergic treatment and AS stimulation improved EVA, restoring it to the level of control subjects. Also the SM stimulation allowed a significant recovery of EVA compared to the stim-off condition, but to a lesser extent compared to that obtained by AS stimulation. No appreciable effects were observed on motor response selection times by stimulation of either site. The movement initiation RTs were reduced compared to the stim-off condition only by stimulation of the SM part of the STN.

Effectiveness of the tasks and effects of session

The main tool used in our protocol was an AC task, which was conveniently combined with two other tasks, the choice reaction time and simple reaction time tasks, to assess the effectiveness of the exogenous (bottom-up) and endogenous (top-

down) mechanisms of visual attention, as well as the mechanisms of selection and initiation of a motor response.

In our AC task, subjects received two conditions. In the so-called no-distracter condition (control trial), target selection was mainly guided by endogenous attentional mechanisms (in a top-down manner) because the subjects intentionally selected only the stimulus which was relevant to perform the task at hand (the unique pentagon-shaped element among 5 diamonds), although low-level pre-attentive processes, depending on specific primitive properties of the stimulus array, might have contributed to the target selection as well. Indeed, the target was not particularly salient among the non-targets, but nonetheless it was a unique element and therefore it benefited from bottom-up selection mechanisms. In the so-called distracter condition, an irrelevant, yet salient non-target singleton item (an object unique along two different dimensions: color and orientation), activated mechanisms of bottom-up selection, determining a cost in terms of reaction time (about 100 ms), and error rate (about 3%) in a group of healthy subjects. It is noteworthy that with similar irrelevant singleton paradigms, as developed by Theewues et al. (1991),[103] the AC in terms of ΔRT amounted to 120-150 ms. Thus, our AC task proved to be a powerful paradigm to assess AC, which arises from the conflict between bottom-up and top-down mechanisms of visual attention.

We observed that the performance of our healthy subjects in the various computerized tasks was not appreciably modified by learning effects occurring during the subsequent sessions of formal testing, likely because of the substantial training to which they were exposed before the experimental sessions. This result was essential to ensure that any difference in performance observed in PD patients, who were evaluated under different conditions of medication and stimulation, was really due to the evaluation condition, and not to a learning effect. However, to minimize the impact of any learning effect across experimental conditions, we applied a counterbalanced design in our study.

Effects of disease

Attentional capture in Parkinson's disease

Comparing the performances in the AC task of the two groups of PD patients,

evaluated in off-phase, with those of the healthy control subjects, we observed that overall the disease determined a slowing down of RTs, and an increase of error rates. At first glance, the longer RTs may be related to the akinesia typical of PD off-phase. Nevertheless, the higher rate of errors committed by patients than controls in both the no-distracter and distracter conditions of the AC task, with no significant differences in error rates between groups for the other two tasks, suggested a possible impairment of visual attention. In particular, the higher error rate observed in PD in the no-distracter condition suggests a defect in display analysis and target selection. This could be due to the weakening of the top-down mechanisms of attention. On the other hand, the higher error rate observed in patients in the distracter condition suggests a stronger withdrawal of attention from the target by the distracter itself, especially when the display duration is limited like in our task. This could be due to a disproportionate enhancement of the bottom-up mechanisms of attention in PD patients compare to controls. Concerning this, a study carried out in two monkeys, aiming at identifying the neural mechanisms necessary for visual attention, showed that restricted lesions in extrastriate cortical areas V4 and temporal-occipital area determined an increase in AC by strong stimuli, regardless of their behavioural relevance.[221]

The analyses of AC in terms of Δ RT suggested that the disease did not impair the mechanisms underlying AC, since there were no significant differences between groups. Only for patients of group #1 we observed a tendency to a higher value of Δ RT than the other two groups. This effect could be due to the significantly greater daily dopaminergic treatment of group #1 compared with that of group #2, which could leave slight traces in med-off. In this respect, it has been shown that dopaminergic stimulation correlates with the detection of salient stimuli in monkeys.[180] This means that our pharmacologically treated patients, althouh evaluated in med-off, could be more suscetible to a salient distracter than surgically treated patients.

Unlike what seen for Δ RT, AC poved to be significantly greater in terms of Δ error rates and IE scores in both groups of PD patients compared with controls, which pointed out that the mechanisms underlying this phenomenon might be actually affected by the pathological condition. Moreover, this increment in AC was

comparable between the two groups of patients, suggesting a behavioral homogeneity of our patients in terms of AC.

This finding is consistent with several studies carried out in PD patients, which showed an enhanced distractibility in the presence of irrelevant but salient stimuli.[19, 24, 25] In particular, in a controlled study carried out in medication-withdrawn PD patients, while performing a visuospatial memory task, behavioural and electro-encephalographic measures indicated that patients were impaired at filtering out distracters.[222] In another behavioural study, carried out by Deijen et al. (2006), PD patients showed an abnormal susceptibility to distracters in an oculomotor capture task.[23] Firstly, it is important to underscore that it is not clear to what extent evidence provided by that study may be interpreted in terms of covert attentional processing or overt motor behaviour, especially in the case of PD patients, who are known to have a central deficit in the motor demain, and in particular an impairment in the control of saccades.[223] This is the reason why for our study we devised an AC task in which we excluded eye movements altogether.

Nevertheless, the close relationship between covert attention and saccades, described in the introduction, allows to make some inferences about the relative contribution of bottom-up and top-down control of attentional selection also in the work of Deijen et al., and to make a comparison with our results. In particular, Deijen et al. showed that already at an early stage of disease (mean disease duration: 2.3 ±1.9 years), untreated PD patients presented a “capture effect” characterized by longer RTs and higher error rates in the distracter condition compared to the no-distracter condition. Conversely, in the no-distracter condition the performances of the patients were similar to those of the controls. This finding suggests that at an early stage of PD the top-down mechanisms of attention may be spared, and that the abnormal susceptibility to distracters may depend mainly on the enhancement of the bottom-up mechanisms or to a specific deficit to deal with distracting stimuli. Differently, we evaluated patients at an advanced stage of disease (mean disease duration: group #1, 13.9 ±2.1 years; group #2, 11.9 ±1.2 years), and the results seem to suggest that at this stage there is an impairment not only of bottom-up, but also of top-down mechanisms of attention.

Several studies have reported impairments in the inhibitory mechanisms of

visual selective attention, which usually impede access of irrelevant information to the cognitive processing system.[126, 131, 132] Thus, PD patients resulted more vulnerable to distracting information than healthy controls. However, these reports are not universally accepted.

For example, Posner et al. (1985)[224] and Kingstone et al. (2002)[225] reported intact inhibition of return in their respective PD groups. Briand et al. (2001)[43] further reported that participants with PD showed normal, faster response latencies for trials with short cue-target delays (facilitation) and normal, slowed response latencies (inhibition of return) for trials with longer cue-target delays.

Grande et al. (2006) examined inhibition of return (i.e., exogenously evoked inhibition) and negative priming (i.e., endogenously evoked inhibition) in a group of 14 patients with PD and 14 healthy controls).[133] Unlike the controls, who demonstrated significant inhibition in both tasks, PD demonstrated intact inhibition only in the inhibition of return task, which suggested that in PD patients only the neuronal network supporting endogenously evoked inhibition was disrupted. This study proposed a dissociation between exogenously and endogenously evoked inhibitory attentional mechanisms, analogously to the traditional accounts of set-shifting deficits in PD, which attribute them to problems with "internal" attentional control, leading to excessive guidance of behavior by "external cues".[13, 226] Specifically, several studies have indicated that PD patients exhibit greater difficulty with directing attention based on internal attentional sets than external attentional cues, not only in high-level cognitive tasks,[227] but also as measured with simple choice RT tasks and in the domain of movement.[228]

In particular, in their work, Grande et al. (2006) postulated that the impairment of endogenously evoked inhibition observed in the negative priming task might be related to dysfunction of the direct and indirect loops of basal ganglia.[133] In this respect the intralaminar nuclei of the thalamus, specifically the centromedian parafascicular nuclei, and their afferent and efferent connections to the frontal lobe, seem to play a critical role in selective attention.[229-231] The authors proposed that the observed differential impairment in exogenously and endogenously evoked inhibition is the direct result of the necessary involvement of intralaminar nuclei for endogenously evoked inhibition but not for exogenously evoked inhibition. Indeed,

they postulated that in the case of endogenously evoked inhibition, the intralaminar nuclei are underactive as a consequence of the disruption of the globus pallidum internum activity by dopamine depletion, while in the case of exogenously evoked inhibition, the intralaminar nuclei are activated via the superior colliculus, which functions normally in PD. Then, the globus pallidum internum seems to play an essential role in a circuit that is responsible for the inhibition of irrelevant information. This is consistent with the findings of a recent functional MRI study carried out on healthy subjects, which showed a greater activation in the left and right-middle frontal gyri and the left basal ganglia (especially the globus pallidus) when subjects attempted to avoid distracter stimuli.[232]

Mechanisms of target selection in PD

The Donders' approach allowed to highlight that the time needed for display analysis and target selection were prolonged in both our groups of PD patients. This suggests that PD patients could present a weakening of the endogenous mechanisms of visual attention. This is in agreement with Cools et al. (2009), who assumed that in PD patients there was a failure of the top-down mechanisms of attention,[227] with a consequent disproportionate bottom-up attentional control, as suggested by the principle of competitive interactions between top-down and bottom-up attentional control processes.[233] This could account for the enhanced AC observed in Cools et al.'s (2009) as well as in our study.

Neural correlates of top-down and bottom-up attentional control

It is still debated to what degree top-down and bottom-up attentional control processes are subserved by shared or by separate mechanisms. Separate loci within the parietal lobe have been identified as the neural source for goal-directed (superior parietal lobule) and stimulus-driven (temporo-parietal junction) attentional orienting.[58, 234, 235] In an investigation of neuropsy-chological patients with a lesion to one or the other of these distinct anatomical sites, the authors examined the relative contribution of superior parietal lobule and temporo-parietal junction for attentional orienting. Patients completed two tasks, one sensitive to stimulus-driven and the other to goal-directed attentional orienting. Based on the behavioural profiles obtained on

each task, patients were assigned to different groups and their lesion overlap explored. Patients, who exhibited difficulties with goal-directed attentional orienting and concurrently showed “hyper-capture”, presented with lesion overlap centered over superior portions of the parietal lobule. Patients who performed normally on the goal-directed orienting task, while remaining abnormally immune to AC, presented with lesion overlap centered over the inferior portions of the parietal lobule. As a result, patients with temporo-parietal junction damage performed better than controls (i.e., their accuracy was higher) by exhibiting reduced capture. Yet, superior parietal lobule and temporo-parietal junction systems are not entirely independent. This conclusion was supported by the finding that patients with superior parietal lobule damage showed a pattern of performance labelled “hyper-capture”, rather than showing the normal capture profile, which was expected if superior parietal lobule played no role in AC. It has been suggested that superior parietal lobule and temporo-parietal junction could interact in at least one of two possible ways. The first possibility is that temporo-parietal junction serves as an alerting system that detects behaviorally relevant stimuli but lacks high spatial resolution; thus, when a behaviorally relevant stimulus is detected, its precise location is supplied by the superior parietal lobule that stores finegrained spatial maps along with information about salient locations.[58, 235] A related possibility is that the capture mechanism (that includes temporo-parietal junction) acts as a circuit breaker of ongoing cognitive activity when a behaviorally relevant stimulus is presented.[54] The ‘‘hyper-capture’’ pattern of activity observed in patients with preserved temporo-parietal junction but lesioned superior parietal lobule provides further evidence for the hypothesis that temporo-parietal junction issues a control signal that terminates the task at hand, thus serving as a circuit breaker.[54, 236]

So far, only a limited number of studies have attempted to use the AC paradigm to investigate brain activations related to the interactions between top-down and bottom-up control of visual attention.

De Fockert et al. (2004) studied the neural correlates of AC using functional magnetic resonance imaging in human subjects during performance of Theeuwes’s visual task.[115] They found that the presence (vs. absence) of the color singleton distracter was associated with bilateral activation of the superior parietal lobule, and with activity in an area in the left lateral precentral gyrus of the frontal cortex

(anterior, inferior, and lateral to the frontal eye field). Moreover, a strong negative correlation between the neural signal in the frontal cortex and the magnitude of distracter interference effects on behaviour was found. This means that a greater activity in the left lateral frontal cortex is associated with reduced interference from irrelevant distracters. By contrast there was no significant correlation between activity in the superior parietal lobule and behavioural interference.

These findings imply that superior parietal lobule and frontal cortex serve different functions in AC. The activity in the superior parietal lobule may reflect shifts of attention towards the irrelevant distracter that occurs in a bottom-up, stimulus-driven manner. As such, attention may always be captured by the more salient distracter (with very little variation in the extent of attentional shifts and the strength of the associated signal in the superior parietal cortex, thus precluding any correlation with behavioural interference effects). On the contrary, the activity in the frontal cortex may reflect the extent to which this cortical region exerts top-down control in order to resolve the competition between the target and the irrelevant distracter. Supporting this hypothesis, an enhanced activity in the left lateral precentral gyrus of the frontal lobe has been previously associated with competition induced by stimuli that are incongruent (versus neutral or congruent) with the current response in Stroop-like tasks.[237-240] It should be noted that the model proposed by de Fockert is not consistent with the two-circuit model put forward by Corbetta and Shulman (2002).[54] Probably this discrepancy is due to a methodological issue: de Fockert used an AC task, which is well suited to study the interaction between the top-down and bottom-up control of attention, while Corbetta and Shulman used typical Posner-tasks to investigate separately these two mechanisms of attentional control.

Interactions between top-down and bottom-up attentional control mechanisms were also investigated using a rapid event-related fMRI design.[29] Healthy subjects performed an attentional search task in which, following a prestimulus mask, target stimuli (consisting of a letter C or a mirror image of the C, enclosed in a diamond outline) were presented either at one unique location among three non-target items (consisting of a random letter, enclosed in a circle outline; 50% probability), or at all four possible target locations (also 50% probability). On half the trials, irrelevant

colour singletons were presented, consisting of a colour change of one of the four prestimulus masks, just prior to target appearance. Participants were required to search for a target letter inside the diamond and report its orientation. Results indicate that, in addition to a common network of parietal areas, medial frontal cortex is uniquely involved in top-down orienting, whereas bottom–up control is mainly subserved by a network of occipital and parietal areas. Additionally, participants who were better able to suppress orienting to the colour singleton showed middle frontal gyrus activation, and the degree of top-down control correlated with left insular activity. These findings suggest that in addition to a common set of parietal areas, separate brain areas are involved in top-down and bottom-up driven attentional control, and that frontal areas play a role in the suppression of AC by an irrelevant colour singleton.

The aforementioned frontal areas are integrated in the cortio-basal ganglia loops,[135, 138] therefore an impairment of their normal function, as occurs in PD, may determine an enhanced AC.

Mechanisms of motor response selection and initiation in Parkinson' disease

Overall, in both groups of PD patients we observed longer RT than controls in the choice reaction time task. The subtraction method of Donders allowed us to appreciate that this deficit in both groups was due to the impairment of the mechanism of motor response initiation, typical of PD off-phase. In addition, only in the group of stimulated patients, we found a significant involvement of the mechanism of motor response selection, indicating a worsening of the DM component. This different pattern of motor response selection found in the two groups of PD patients might be due to their heterogeneity in terms of DM, as reported in the literature,[241] which may be explained by a more severe dopaminergic denervation or different non-dopaminergic lesions in the group of patients treated by stimulation compared with the medically treated group. Otherwise, this difference in the DM component could be explained as an effect of dopaminergic treatment, since the dopaminergic daily doses were higher in the pharmacologically treated patients than in the stimulated ones. This could mean a slight dopaminergic effect even in med-off, which could allow an improvement of DM in this condition.[242]

Effects of dopaminergic treatment

Our results suggest that the dopaminergic treatment, as indicated by the improvement of the response times observed in the no-distracter and distracter condition of the AC task, could affect the mechanisms of visual attention. Under drug, we found that the AC in terms of Δ RT was significantly greater than in med-off. This result unlikely depends on a reduced waking state of patients in relation to the dopaminergic intake, which in fact may be a side effect of this treatment.[156, 243] If so, there should have been a deterioration in overall performance, with an increase in error rate, but this was not the case. Actually, we observed a small reduction of errors committed especially in the distracter condition of the AC task compared with the med-off condition. Moreover, to avoid any potential side effect of the dopaminergic treatment, such as disorders of alertness, and disabling dyskinesias, which could interfere with a smooth performance in the experimental session, our patients were evaluated in their best clinical state after administration of their usual early morning dopaminergic intake, and not after a levodopa challenge, as usually done in many protocol studies.

A plausible explanation of the increase of AC in terms of Δ RT, observed in our patients under treatment, could be related to the effect of time on visual selection, since early in processing, the salience map is computed from buttom-up factors alone, while top-down factors contribute late in processing. This means that, critically, the presence of a salient distracter triggered a shift of attention to its location before attention was allocated to the target.[106] As a consequence, the faster the responses (as occurred under dopaminergic treatment), the greater could be the AC, due to a greater exposure to the bottom-up factors.

The analysis of IE scores showed that, under drug, despite the overall improvemement of performance compared with that in med-off, there was no enhancement of the AC. This observation suggests that the increment of AC in terms of Δ RT obtained under dopaminergic treatment should be interpreted with caution because it might reflect a form of speed-accuracy trade-off effect.

We found that under medication the times taken for display analysis and target selection (EVA) were shorter than in med-off, suggesting that the dopaminergic treatment might potentiate the endogenous mechanisms of visual attention.

Nonetheless, one could argue that this effect was spurious, and that the shorter EVA observed in med-on was simply due to fast responses in patients, leaving little opportunity for EVA computed by the subtraction method of Donders. But, for the same reason, one could expect longer EVA for slower responses. This is not consistent with the conspicuous reduction of EVA observed during stimulation of the AS part of the STN, a condition in which the responses of patients were not significantly shorter than those in off-phase, and therefore one should expect relatively long EVA.

Several neurophysiological and lesional studies carried out in animals showed that the dopaminergic pathway may play a crucial role in the mechanisms of top-down attentional control.[176-180] Therefore, an attentional deficit due to striatal dopamine depletion should be ameliorated by dopaminergic treatment, as in fact highlighted by some authors.[152, 158] In this respect, Kischka et al. (1996) reported that dopamine increased inhibition, or reduced interference, in a semantic priming task in healthy individuals.[244] It is possible, therefore, that inhibitory deficits of endogenous mechanisms of visual attention in patients with PD are lessened while they are on dopamine therapy.

Conversely, according to other authors, replacement of dopamine did not affect orienting of attention in PD patients, suggesting that other neurotrasmitters or modulators , especially noradrenaline and serotonin may be involved in the regulation of the top-down mechanisms of visual attention.[133, 157, 227, 245]

Indeed, there is evidence that different forms of attentional set shifting implicate distinct cortical and subcortical mechanisms. Specifically, it was emphasized that the striatum is active and required only for shifting between concrete stimulus exemplars but not for shifting between abstract rules.[220, 246] In a study using fMRI combined with nonliner dynamic causal modeling, Cools et al., (2010) demonstrated that the ventral striato-pallidum, activated by salient and unexpected events, modulated the top-down influences of the prefrontal cortex on stimulus-specific visual association areas in humans.[247] One mechanism by which salient stimuli might influence the activity of the ventral striato-pallidum is dopamine, which is released in the ventral striatum during salient events.[248, 249] This hypothesis is in line with suggestions that short latency dopamine signals mediate the shift of attention

to unexpected stimuli.[250, 251]

This correlation between dopamine-mediated neuronal activation and the detection of salient stimuli may also account for the increase of AC (in terms of Δ RT). In fact, the dopamine release in the ventral striatum in the presence of a salient event probably may result in a strengthening of the bottom-up mechanisms of visual attention, leading to increased perception of the salient distracter. In parallel, we have seen that the dopaminergic treatment may potentiate the endogenos mechanisms of visual attention. Thus, with reference to a saliency map, we may conjecture that the saliences of the target and the distracter were enhanced under dopaminergic drug, but relatively more for the distracter than the target. Consequently, this could result in a stronger withdrawal of attention from the target by the distracter itself, even if the mechanisms of top-down attention were potentiated by dopaminergic treatment.

In this respect, it was shown that dopamine hyperactivity can contribute to disrupt attentional processes to external stimuli, as shown, for example, in schizophrenic patients.[252] As noted by Sarter (1994), a hyperattention syndrome in schizophrenia would correspond to a failure "to disattend irrelevant stimuli including internally generated cues, impairment in filtering irrelevant stimuli, deficit in divided attention and inability to filter or to gate irrelevant information".[253]

As we could expect,[254] dopamine replacement allowed a significant improvement of akinesia, as suggested by the shortening of the RTs in the simple reaction time task compared with those in med-off condition.

The dopaminergic treatment apparently did not cause any significant amelioration of the mechanisms of motor responce selection (DM). However, this negative result could be biased by the daily doses of dopaminergic treatment taken by these patients, which could leave slight traces in med-off.

Effects of stimulation

There is ample evidence from animal studies,[255] assessment of patients with prefrontal lesion,[256, 257] and functional brain imaging[220, 232, 247] that the prefrontal cortex, basal ganglia, and their interconnections mediate attentional functions. Electrical stimulation of the STN, used to treat patients with PD, has proved to be a powerful and accurate means for testing directly the role of cortico-basal ganglia

circuits in non-motor functions,[203, 258, 259] because the functioning of the stimulated structure can be reversibly altered in a spatially and temporally controlled manner. Moreover, in this study, we used an interactive brain atlas to precisely localize each contact of the quadripolar electrodes in the STN of our stimulated patients, in order to assess whether there was a functional specialization of the different sub-territories of STN in the mechanisms underlying visual attention. In this respect, it was essential to selectively stimulate the SM and AS part of the STN, avoiding overlapping effects due to current spread. To this aim, in most cases (when it was possile, based on the anatomical location of the contacts), we chose two stimulating contacts centered on the SM and AS part of the STN, and interspaced by a contact (this means that in most cases the SM and AS contacts were 4 mm apart). Importantly, one would expect that the stimulating current diffused even less, on the order of 1 mm for a 2.5 V current.[260] This was in fact the mean current voltage used for stimulating both sides.

Overall, our results suggest that STN-DBS, in parallel with the improvement of the response times obtained in the AC task, which was more evident for SM-stimulation, could affect the mechianisms of visual attention. In particular, under stimulation, our patients resulted more distractible in terms of Δ RT than in med-off/stim-off. This similarity with attentional behaviour observed under dopaminergic treatment suggested that stimulation could potentatiate the bottom-up mechanisms of visual attention. Moreover, the increase of AC in terms of Δ RT was of a similar magnitude for both sites of stimulation, which suggested lack of functional specialization of the different sub-territories of STN in relation to AC mechanisms.

Nevertheless, the lack of significant changes in error rates committed in the AC task in different conditions of stimulation suggested that the increment of AC in terms of Δ RT, observed under stimulation, should be interpreted with caution because it might reflect a form of speed-accuracy trade-off effect. To confirm this, analysis of IE scores showed that, under different conditions of stimulation, there was neither improvement of overall perfomence, nor changes in AC.

On the other hand, our results showed that stimulation greatly improved the mechanisms underlying display analysis and target selection, just like we obseved under dopaminergic treatment. Interestingly, previous studies have reported that the effects of STN-DBS on a range of cognitive tests parallel those of levodopa.[139, 261]

The specific involvement of STN in visual attention processing is suggested by various studies carried out in animals using lesional[174, 181, 262] or stimulating procedures.[173] Moreover, several studies carried out in humans revealed that STN-DBS improves performance on tasks that require attentional set shifting.[187, 263, 264] On the basis of imaging results, it has been proposed that these attentional deficits in patients with PD are associated with underactivation of those prefrontal areas that are specifically coactivated with the striatum and overactivation of those prefrontal areas that are not coactivated with the striatum in controls.[265] DBS of the STN alters frontal activation[266, 267] and striato-frontal connectivity.[268] This alteration of frontal activation and striato-frontal connectivity with DBS of the STN is task specific, with increased activation observed during movement execution[266] and decreased activation during cognitive tasks requiring response selection under competition such as the Stroop task.[267] For instance, Schroeder et al. (2002), using PET, studied changes in regional cerebral blood flow associated with the Stroop task in Parkinson's disease patients ON and OFF bilateral STN stimulation.[267] They found that during STN stimulation, impaired task performance (prolonged reaction times) was associated with decreased activation in both right anterior cingulate cortex and right ventral striatum. On the other hand, a concomitant increased activation in left angular gyrus, indicative of ongoing word processing during stimulation, was consistent with an impairment to inhibit habitual responses. The anterior cingulate cortex and ventral striatum are part of the anterior cingulate cortex circuit associated with response conflict tasks. The decreased activation during STN stimulation in the ACC circuit, while response conflict processing worsened, provided direct evidence of STN modulating non-motor basal ganglia-thalamocortical circuitry.

We found that the stimulation of the AS part of STN potentiated the endogenous mechanisms of visual attention to a larger extent than the SM part. On the other hand, only the stimulation of the SM part of the STN led to an improvement of the mechanisms of movement initiation, as proved by the shortening of the RTs in the simple reaction time task compared with the med-off/stim-off condition. These results strengthen the idea of a functional specialization of different sub-territories of the STN, as already proved in humans.[203]

Interestingly, this result seems to contradict the aforementioned lack of

functional specialization of the sub-territories of STN in relation to the exogenous mechanisms of visual attention. This, actually, confirms that different mechanisms underlie the top-down and bottom-up attentional control processes. Probably, top-down and bottom-up mechanisms are supplied by different anatomical networks, which may be modulated in a similar way by dopaminergic and STN stimulation. Then, the beneficial effect of dopaminergic and electrical stimulation on the neural network controlling top-down mechanisms might simultaneously result in a detrimental effect on the network controlling the bottom-up mechanisms.

Concerning the DM component of the response, the stimulation of both STN sites did not lead to a significant improvement of motor response selection. In this sense, only a slight positive trend could be appreciated for stimulation of the SM part of the STN, as already reported.[254]

Comparison between different treatments and the control condition

Lastly, we compared the different treatments, and their effectiveness in restoring the normal functions.

Overall, the dopaminergic treatment was superior to electrical stimulation in improving most of the variables measured, even if it rarely restored patients' performance to normality.

For instance, the dopaminergic treatment allowed a significant amelioration of the response times in the no-distracter and distracter condition of AC task, in the choice and simple reaction time tasks, restoring them towards normality, while it was not the case for stimulation of both sites of STN. Yet, these data seem to contradict the general lack of significant differences obtained by comparing directly the treatments with one another. This inconsistency could be explained by keeping in mind that the two groups of PD patients showed a slightly different impairment in their performances in off condition. This could be a consequence of higher dopaminergic daily doses taken by the medically treated patients compared to the stimulated ones, which could leave slight traces in med-off. This means that, in off condition, the performances of the medically treated group could be better than those of the stimulated group. Therefore, it is possible that the direct comparison between medical and electrical treatment could understimate the actual effect of dopaminergic

treatment. Otherwise, we could assume that the different impairment in performances observed between the two groups of patients in off condition is actually related to a different degree of dopaminergic denervation or non-dopaminergic lesions.

Interestingly, dopaminergic treatment as well as the stimulation of the SM and AS parts of STN increased significantly, and to a comparable extent, the AC in terms of Δ RT, Δ error rate and Δ IE scores. This confirms that PD patients are more distractible than healthy subjects, and that the different treatments could potentatiate the bottom-up mechanisms of visual attention.

On the other hand, we have shown that dopaminergic treatment and AS stimulation can restore entirely the mechanisms of top-down visual attention, while this was not the case for the SM-stimulation. Nevertheless, we have to keep in mind that SM stimulation allowed a significant amelioration of the EVA mechanisms with respect to the med-off/stim-off.

Interestingly, despite the complete restoration of the top-down mechanisms by dopaminergic as well as AS-stimulation, the AC resulted enhanced in the same two conditions, which could be explained by a parallel potentiation of the mechanisms that compute salience of visual stimuli, or the bottom-up control of attention.

Lastly, we observed that under stimulation of the AS part of the STN, patients committed more errors in the choice reaction time and simple reaction time tasks than healthy subjects. This could be explained considering the close location of the AS stimulation contact to the limbic part of the STN, which could be activated by current spreading, in turn determining an impulsive behaviour.[140, 211, 269]

Conclusion

Our results showed that in PD there is a weakening of the mechanisms underlying the top-down control of visual attention, which likely indirectly accounts also for the enhancement of AC. This finding is part of a more composite scenario of deficits, especially in otherwise stimulated patients, who undergo a milder drug treatment than pharmacologically treated patients, including slowing of the processes of movement initiation, and slowing of the processes of motor response selection.

Dopaminergic treatment proves to be effective not only in restoring movement initiation mechanisms, but also the mechanisms of EVA, suggesting an involvement of the dopaminergic pathway in the control of the top-down mechanisms of visual attention.

In parallel with the amelioration of the mechanisms of target selection, the observed enhancement of AC under dopaminergic treatment suggests that the dopaminergic pathway may be involved also in the mechanisms that compute salience of visual stimuli, or the bottom-up control of attention.

The STN-DBS shows a similar effect to that obtained by dopaminergic treatment, establishing a direct involvement of the basal ganglia in visual attention control. In particular, our results strengthen the idea of a functional specialization of different sub-territories of the STN, and of the different cortico-basal ganglia loops in which they are integrated in relation to the top-down mechanisms of visual attention. As a matter of fact, two well distinct patterns seem to emerge depending on the stimulated region: SM stimulation produces marked effects on the movement initiation processes and appreciable positive effects on EVA mechanisms, while AS stimulation seems to be especially effective in improving the mechanisms of target selection. On the other hand, no functional specialization of the sub-territories of STN in relation to the exogenous mechanisms of visual attention seems to emerge, suggesting that top-down and bottom-up mechanisms are supplied by different anatomical networks involving the cortico-basal-ganglia loops.

References

1. Quinn N, Critchley P, Marsden CD. Young onset Parkinson's disease. Mov Disord 1987;2(2):73-91.
2. Schapira AH, Agid Y, Barone P, et al. Perspectives on recent advances in the understanding and treatment of Parkinson's disease. Eur J Neurol 2009;16(10):1090-1099.
3. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. Lancet Neurol 2006;5(4):355-363.
4. Caballol N, Marti MJ, Tolosa E. Cognitive dysfunction and dementia in Parkinson disease. Mov Disord 2007;22 Suppl 17:S358-366.
5. Pirozzolo FJ, Hansch EC, Mortimer JA, Webster DD, Kuskowski MA. Dementia in Parkinson disease: a neuropsychological analysis. Brain Cogn 1982;1(1):71-83.
6. Reitan RM, Boll TJ. Intellectual and cognitive functions in Parkinson's disease. J Consult Clin Psychol 1971;37(3):364-369.
7. Ranchet M, Paire-Ficout L, Marin-Lamellet C, Laurent B, Broussolle E. Impaired updating ability in drivers with Parkinson's disease. J Neurol Neurosurg Psychiatry 2011;82(2):218-223.
8. Boller F, Passafiume D, Keefe NC, Rogers K, Morrow L, Kim Y. Visuospatial impairment in Parkinson's disease. Role of perceptual and motor factors. Arch Neurol 1984;41(5):485-490.
9. Bowen FP, Kamienny RS, Burns MM, Yahr M. Parkinsonism: effects of levodopa treatment on concept formation. Neurology 1975;25(8):701-704.
10. Flowers KA, Robertson C. The effect of Parkinson's disease on the ability to maintain a mental set. J Neurol Neurosurg Psychiatry 1985;48(6):517-529.
11. Wilson RS, Kaszniak AW, Klawans HL, Garron DC. High speed memory scanning in parkinsonism. Cortex 1980;16(1):67-72.
12. Matison R, Mayeux R, Rosen J, Fahn S. "Tip-of-the-tongue" phenomenon in Parkinson disease. Neurology 1982;32(5):567-570.
13. Cools AR, van den Bercken JH, Horstink MW, van Spaendonck KP, Berger HJ. Cognitive and motor shifting aptitude disorder in Parkinson's disease. J Neurol

Neurosurg Psychiatry 1984;47(5):443-453.
14. Lees AJ, Smith E. Cognitive deficits in the early stages of Parkinson's disease. Brain 1983;106 (Pt 2):257-270.
15. Bulpitt CJ, Shaw K, Clifton P, Stern G, Davies JB, Reid JL. The symptoms of patients treated for Parkinson's disease. Clin Neuropharmacol 1985;8(2):175-183.
16. Sanes JN. Information processing deficits in Parkinson's disease during movement. Neuropsychologia 1985;23(3):381-392.
17. Sharpe MH. Auditory attention in early Parkinson's disease: an impairment in focused attention. Neuropsychologia 1992;30(1):101-106.
18. Filoteo JV, Delis DC, Roman MJ, et al. Visual attention and perception in patients with Huntington's disease: comparisons with other subcortical and cortical dementias. J Clin Exp Neuropsychol 1995;17(5):654-667.
19. Wright MJ, Burns RJ, Geffen GM, Geffen LB. Covert orientation of visual attention in Parkinson's disease: an impairment in the maintenance of attention. Neuropsychologia 1990;28(2):151-159.
20. Yamada T, Izyuuinn M, Schulzer M, Hirayama K. Covert orienting attention in Parkinson's disease. J Neurol Neurosurg Psychiatry 1990;53(7):593-596.
21. Henik A, Singh J, Beckley DJ, Rafal RD. Disinhibition of automatic word reading in Parkinson's disease. Cortex 1993;29(4):589-599.
22. Pillon B, Dubois B, Bonnet AM, et al. Cognitive slowing in Parkinson's disease fails to respond to levodopa treatment: the 15-objects test. Neurology 1989;39(6):762-768.
23. Deijen JB, Stoffers D, Berendse HW, Wolters E, Theeuwes J. Abnormal susceptibility to distracters hinders perception in early stage Parkinson's disease: a controlled study. BMC Neurol 2006;6:43.
24. Sharpe MH. Distractibility in early Parkinson's disease. Cortex 1990;26(2):239-246.
25. Uc EY, Rizzo M, Anderson SW, Sparks JD, Rodnitzky RL, Dawson JD. Impaired navigation in drivers with Parkinson's disease. Brain 2007;130(Pt 9):2433-2440.
26. Posner MI. Orienting of attention. Q J Exp Psychol 1980;32(1):3-25.
27. Theeuwes J. Exogenous and endogenous control of attention: the effect of visual onsets and offsets. Percept Psychophys 1991;49(1):83-90.

28. Yantis S, Jonides J. Abrupt visual onsets and selective attention: evidence from visual search. J Exp Psychol Hum Percept Perform 1984;10(5):601-621.
29. Talsma D, Coe B, Munoz DP, Theeuwes J. Brain structures involved in visual search in the presence and absence of color singletons. J Cogn Neurosci 2009;22(4):761-774.
30. Desimone R, Duncan J. Neural mechanisms of selective visual attention. Annu Rev Neurosci 1995;18:193-222.
31. Pessoa L, Kastner S, Ungerleider LG. Attentional control of the processing of neural and emotional stimuli. Brain Res Cogn Brain Res 2002;15(1):31-45.
32. Moran J, Desimone R. Selective attention gates visual processing in the extrastriate cortex. Science 1985;229(4715):782-784.
33. Reynolds JH, Chelazzi L, Desimone R. Competitive mechanisms subserve attention in macaque areas V2 and V4. J Neurosci 1999;19(5):1736-1753.
34. Rolls ET, Tovee MJ. The responses of single neurons in the temporal visual cortical areas of the macaque when more than one stimulus is present in the receptive field. Exp Brain Res 1995;103(3):409-420.
35. Sato T. Interactions of visual stimuli in the receptive fields of inferior temporal neurons in awake macaques. Exp Brain Res 1989;77(1):23-30.
36. Kastner S, De Weerd P, Desimone R, Ungerleider LG. Mechanisms of directed attention in the human extrastriate cortex as revealed by functional MRI. Science 1998;282(5386):108-111.
37. Kastner S, De Weerd P, Pinsk MA, Elizondo MI, Desimone R, Ungerleider LG. Modulation of sensory suppression: implications for receptive field sizes in the human visual cortex. J Neurophysiol 2001;86(3):1398-1411.
38. Hahn B, Ross TJ, Stein EA. Neuroanatomical dissociation between bottom-up and top-down processes of visuospatial selective attention. Neuroimage 2006;32(2):842-853.
39. Posner MI, Cohen Y. Components of visual orienting. In Bouma, H., Bouwhuis, D. (Eds.), Attention and Performance, vol. X. Lawrence Erlbaum, London, pp. 531-554., 1984.
40. Kastner S, Ungerleider LG. The neural basis of biased competition in human visual cortex. Neuropsychologia 2001;39(12):1263-1276.

41. Umarova RM, Saur D, Schnell S, et al. Structural connectivity for visuospatial attention: significance of ventral pathways. Cereb Cortex 2010;20(1):121-129.
42. Klein RM. Inhibition of return. Trends Cogn Sci 2000;4(4):138-147.
43. Briand KA, Hening W, Poizner H, Sereno AB. Automatic orienting of visuospatial attention in Parkinson's disease. Neuropsychologia 2001;39(11):1240-1249.
44. Ungerleider LG, Gaffan D, Pelak VS. Projections from inferior temporal cortex to prefrontal cortex via the uncinate fascicle in rhesus monkeys. Exp Brain Res 1989;76(3):473-484.
45. Webster MJ, Bachevalier J, Ungerleider LG. Connections of inferior temporal areas TEO and TE with parietal and frontal cortex in macaque monkeys. Cereb Cortex 1994;4(5):470-483.
46. Luck SJ, Chelazzi L, Hillyard SA, Desimone R. Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. J Neurophysiol 1997;77(1):24-42.
47. Bundesen C. A theory of visual attention. Psychol Rev 1990;97(4):523-547.
48. Duncan J. Converging levels of analysis in the cognitive neuroscience of visual attention. Philos Trans R Soc Lond B Biol Sci 1998;353(1373):1307-1317.
49. Knight RT, Staines WR, Swick D, Chao LL. Prefrontal cortex regulates inhibition and excitation in distributed neural networks. Acta Psychol (Amst) 1999;101(2-3):159-178.
50. Bartus RT, Levere TE. Frontal decortication in rhesus monkeys: a test of the interference hypothesis. Brain Res 1977;119(1):233-248.
51. Yamaguchi S, Knight RT. Gating of somatosensory input by human prefrontal cortex. Brain Res 1990;521(1-2):281-288.
52. Weinberger DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. I. Regional cerebral blood flow evidence. Arch Gen Psychiatry 1986;43(2):114-124.
53. Corbetta M, Miezin FM, Shulman GL, Petersen SE. A PET study of visuospatial attention. J Neurosci 1993;13(3):1202-1226.
54. Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002;3(3):201-215.

55. Gitelman DR, Nobre AC, Parrish TB, et al. A large-scale distributed network for covert spatial attention: further anatomical delineation based on stringent behavioural and cognitive controls. Brain 1999;122 (Pt 6):1093-1106.
56. Nobre AC, Sebestyen GN, Gitelman DR, Mesulam MM, Frackowiak RS, Frith CD. Functional localization of the system for visuospatial attention using positron emission tomography. Brain 1997;120 (Pt 3):515-533.
57. Rosen AC, Rao SM, Caffarra P, et al. Neural basis of endogenous and exogenous spatial orienting. A functional MRI study. J Cogn Neurosci 1999;11(2):135-152.
58. Kastner S, Pinsk MA, De Weerd P, Desimone R, Ungerleider LG. Increased activity in human visual cortex during directed attention in the absence of visual stimulation. Neuron 1999;22(4):751-761.
59. Kastner S, Pinsk MA, Desimone R, Ungerleider LG. Activity in human visual cortex is differentially modulated during expectation of color or face stimuli. Neuroimage 2000;11:S14.
60. Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. Nat Neurosci 2000;3(3):292-297.
61. Mesulam MM. A cortical network for directed attention and unilateral neglect. Ann Neurol 1981;10(4):309-325.
62. Posner MI, Snyder CR, Davidson BJ. Attention and the detection of signals. J Exp Psychol 1980;109(2):160-174.
63. Vallar G, Perani D. The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. Neuropsychologia 1986;24(5):609-622.
64. Damasio AR, Damasio H, Chui HC. Neglect following damage to frontal lobe or basal ganglia. Neuropsychologia 1980;18(2):123-132.
65. Janer KW, Pardo JV. Deficits in selective attention following bilateral anterior cingulotomy. J Cogn Neurosci 1991;3:231-241.
66. Watson RT, Heilman KM. Thalamic neglect. Neurology 1979;29(5):690-694.
67. Koch C, Ullman S. Shifts in selective visual attention: towards the underlying neural circuitry. Hum Neurobiol 1985;4(4):219-227.
68. Itti L, Koch C. Computational modelling of visual attention. Nat Rev Neurosci

2001;2(3):194-203.
69. Thompson KG, Bichot NP. A visual salience map in the primate frontal eye field. Prog Brain Res 2005;147:251-262.
70. Treisman A. Features and objects: the fourteenth Bartlett memorial lecture. Q J Exp Psychol A 1988;40(2):201-237.
71. Niebur E, Koch C. Control of Selective Visual Attention: Modeling the `Where' Pathway. Neural Information Processing Systems 1996;8:802-808.
72. Van der Stigchel S, Belopolsky AV, Peters JC, Wijnen JG, Meeter M, Theeuwes J. The limits of top-down control of visual attention. Acta Psychol (Amst) 2009;132(3):201-212.
73. Wolfe JM. What can 1,000,000 trials tell us about isual search? Psychological Science 1998;9(1):33-39.
74. Egeth HE, Virzi RA, Garbart H. Searching for conjunctively defined targets. J Exp Psychol Hum Percept Perform 1984;10(1):32-39.
75. Bundesen C, Habekost T, Kyllingsbaek S. A neural theory of visual attention: bridging cognition and neurophysiology. Psychol Rev 2005;112(2):291-328.
76. Wolfe JM. Guided Search 2.0: A Revised Model of Visual Search. Psychonomic Bulletin & Review 1994;1(2):202-238.
77. Wolfe JM, Cave KR, Franzel SL. Guided search: an alternative to the feature integration model for visual search. J Exp Psychol Hum Percept Perform 1989;15(3):419-433.
78. Crick F. Function of the thalamic reticular complex: the searchlight hypothesis. Proc Natl Acad Sci U S A 1984;81(14):4586-4590.
79. Robinson DL, Petersen SE. The pulvinar and visual salience. Trends Neurosci 1992;15(4):127-132.
80. Kustov AA, Robinson DL. Shared neural control of attentional shifts and eye movements. Nature 1996;384(6604):74-77.
81. Li Z. A saliency map in primary visual cortex. Trends Cogn Sci 2002;6(1):9-16.
82. Mazer JA, Gallant JL. Goal-related activity in V4 during free viewing visual search. Evidence for a ventral stream visual salience map. Neuron 2003;40(6):1241-1250.
83. Gottlieb J. From thought to action: the parietal cortex as a bridge between

perception, action, and cognition. Neuron 2007;53(1):9-16.

84. Noudoost B, Chang MH, Steinmetz NA, Moore T. Top-down control of visual attention. Curr Opin Neurobiol 2010;20(2):183-190.
85. Schall JD, Morel A, King DJ, Bullier J. Topography of visual cortex connections with frontal eye field in macaque: convergence and segregation of processing streams. J Neurosci 1995;15(6):4464-4487.
86. Bruce CJ, Goldberg ME. Primate frontal eye fields. I. Single neurons discharging before saccades. J Neurophysiol 1985;53(3):603-635.
87. Livingstone M, Hubel D. Segregation of form, color, movement, and depth: anatomy, physiology, and perception. Science 1988;240(4853):740-749.
88. Mohler CW, Goldberg ME, Wurtz RH. Visual receptive fields of frontal eye field neurons. Brain Res 1973;61:385-389.
89. Schall JD, Hanes DP, Thompson KG, King DJ. Saccade target selection in frontal eye field of macaque. I. Visual and premovement activation. J Neurosci 1995;15(10):6905-6918.
90. Treisman AM, Gelade G. A feature-integration theory of attention. Cogn Psychol 1980;12(1):97-136.
91. Itti L. Quantitative modelling of perceptual saliency at human eye position. Visual Cognition 2006;14:959-984.
92. Theeuwes J. Perceptual selectivity for color and form. Percept Psychophys 1992;51(6):599-606.
93. Theeuwes J. Stimulus-driven capture and attentional set: selective search for color and visual abrupt onsets. J Exp Psychol Hum Percept Perform 1994;20(4):799-806.
94. Theeuwes J. Top-down search strategies cannot override attentional capture. Psychon Bull Rev 2004;11(1):65-70.
95. Theeuwes J, Kramer AF, Hahn S, Irwin DE. Our eyes do not always go where we want then go: Capture of eyes by new objects. Psychological Science 1998;9(379-385).
96. Theeuwes J, Kramer AF, Hahn S, Irwin DE, Zelinsky GJ. Influence of attentional capture on oculomotor control. J Exp Psychol Hum Percept Perform 1999;25(6):1595-1608.

97. Belopolsky AV, Theeuwes J. No capture outside the attentional window. Vision Res 2010;50(23):2543-2550.
98. Nakayama K, Silverman GH. Serial and parallel processing of visual feature conjunctions. Nature 1986;320(6059):264-265.
99. Theeuwes J, Godijn R. Attentional and oculomotor capture. In Folk, C. Gibson, B (Eds.) Attraction, distraction and action: Multiple perspectives on attentional capture pp.121-149 New York: Elsevier Science, 2002.
100. Egeth HE, Yantis S. Visual attention: control, representation, and time course. Annu Rev Psychol 1997;48:269-297.
101. Rauschenberger R. Attentional capture by auto- and allo-cues. Psychon Bull Rev 2003;10(4):814-842.
102. Ruz M, Lupianez J. A review of attentional capture: On its automaticity and sensitivity to endogenous control. Psicologica 2002;23:283-309.
103. Theeuwes J. Cross-dimensional perceptual selectivity. Percept Psychophys 1991;50(2):184-193.
104. Theeuwes J. Bottom-up capture and attentional set: Selectiv search for colour and visual abrupt onsets. Journal of Experimental Psychology: Human Perception and Performance 1994;20:799-806.
105. Theeuwes J. Parallel search for conjunction of color and orientation: The effect of spatial proximity. Acta Psychol (Amst) 1996;94:291-397.
106. Hickey C, McDonald JJ, Theeuwes J. Electrophysiological evidence of the capture of visual attention. J Cogn Neurosci 2006;18(4):604-613.
107. Luck SJ, Girelli M, McDermott MT, Ford MA. Bridging the gap between monkey neurophysiology and human perception: an ambiguity resolution theory of visual selective attention. Cogn Psychol 1997;33(1):64-87.
108. Stam CJ, Visser SL, Op de Coul AA, et al. Disturbed frontal regulation of attention in Parkinson's disease. Brain 1993;116 (Pt 5):1139-1158.
109. Theeuwes J, Kramer AF, Kingstone A. Attentional capture modulates perceptual sensitivity. Psychon Bull Rev 2004;11(3):551-554.
110. Jonides J, Yantis S. Uniqueness of abrupt visual onset in capturing attention. Percept Psychophys 1988;43(4):346-354.
111. Yantis S, Egeth HE. On the distinction between visual salience and stimulus-

driven attentional capture. J Exp Psychol Hum Percept Perform 1999;25(3):661-676.

112. Bacon WF, Egeth HE. Overriding stimulus-driven attentional capture. Percept Psychophys 1994;55(5):485-496.
113. Folk CL, Annett S. Do locally defined feature discontinuities capture attention? Percept Psychophys 1994;56(3):277-287.
114. Leber AB, Egeth HE. It's under control: top-down search strategies can override attentional capture. Psychon Bull Rev 2006;13(1):132-138.
115. de Fockert J, Rees G, Frith C, Lavie N. Neural correlates of attentional capture in visual search. J Cogn Neurosci 2004;16(5):751-759.
116. Kinchla RA. Attention. Annu Rev Psychol 1992;43:711-742.
117. Rizzolatti G, Riggio L, Dascola I, Umilta C. Reorienting attention across the horizontal and vertical meridians: evidence in favor of a premotor theory of attention. Neuropsychologia 1987;25(1A):31-40.
118. Beauchamp MS, Petit L, Ellmore TM, Ingeholm J, Haxby JV. A parametric fMRI study of overt and covert shifts of visuospatial attention. Neuroimage 2001;14(2):310-321.
119. Grosbras MH, Paus T. Transcranial magnetic stimulation of the human frontal eye field: effects on visual perception and attention. J Cogn Neurosci 2002;14(7):1109-1120.
120. Muggleton NG, Juan CH, Cowey A, Walsh V. Human frontal eye fields and visual search. J Neurophysiol 2003;89(6):3340-3343.
121. Moore T, Fallah M. Control of eye movements and spatial attention. Proc Natl Acad Sci U S A 2001;98(3):1273-1276.
122. Moore T, Armstrong KM, Fallah M. Visuomotor origins of covert spatial attention. Neuron 2003;40(4):671-683.
123. Godijn R, Theeuwes J. Programming of endogenous and exogenous saccades: evidence for a competitive integration model. J Exp Psychol Hum Percept Perform 2002;28(5):1039-1054.
124. Hietanen M, Teravainen H. Cognitive performance in early Parkinson's disease. Acta Neurol Scand 1986;73(2):151-159.
125. Maddox WT, Filoteo JV, Delis DC, Salmon DP. Visual selective attention

deficits in patients with Parkinson's disease: a quantitative model-based approach. Neuropsychology 1996;10(2):197-218.

126. Filoteo JV, Delis DC, Salmon DP, Demadura T, Roman MJ, Shults CW. An examination of the nature of attentional deficits in patients with Parkinson's disease: evidence from a spatial orienting task. J Int Neuropsychol Soc 1997;3(4):337-347.
127. Yamaguchi S, Kobayashi S. Contributions of the dopaminergic system to voluntary and automatic orienting of visuospatial attention. J Neurosci 1998;18(5):1869-1878.
128. Houghton G, Tipper SP. A model of inhibitory mechanisms in selective attention. In Dagenbach, D., Carr, T.H. (Eds.), Inhibitory processes in attention, memory, and language, Academic Press, San Diego, pp. 53-107., 1994.
129. Tipper SP. The negative priming effect: inhibitory priming by ignored objects. Q J Exp Psychol A 1985;37(4):571-590.
130. Tipper SP, Cranston M. Selective attention and priming: inhibitory and facilitatory effects of ignored primes. Q J Exp Psychol A 1985;37(4):591-611.
131. Downes JJ, Sharp HM, sagar HJ. The time-course of negative priming in Parkinson's disease. Journal of Clinical and Experimental Neuropsychology 1991;13:75.
132. Filoteo JV, Rilling LM, Strayer DL. Negative priming in patients with Parkinson's disease: evidence for a role of the striatum in inhibitory attentional processes. Neuropsychology 2002;16(2):230-241.
133. Grande LJ, Crosson B, Heilman KM, Bauer RM, Kilduff P, McGlinchey RE. Visual selective attention in Parkinson's disease: dissociation of exogenous and endogenous inhibition. Neuropsychology 2006;20(3):370-382.
134. Lang AE, Lozano AM. Parkinson's disease. First of two parts. N Engl J Med 1998;339(15):1044-1053.
135. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357-381.
136. Obeso JA, Rodriguez MC, DeLong MR. Basal ganglia pathophysiology. A critical review. Adv Neurol 1997;74:3-18.

137. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. Brain Res Brain Res Rev 1995;20(1):128-154.
138. Yelnik J. Modeling the organization of the basal ganglia. Rev Neurol (Paris) 2008.
139. Funkiewiez A, Ardouin C, Krack P, et al. Acute psychotropic effects of bilateral subthalamic nucleus stimulation and levodopa in Parkinson's disease. Mov Disord 2003;18(5):524-530.
140. Mallet L, Schupbach M, N'Diaye K, et al. Stimulation of subterritories of the subthalamic nucleus reveals its role in the integration of the emotional and motor aspects of behavior. Proc Natl Acad Sci U S A 2007;104(25):10661-10666.
141. Voon V, Kubu C, Krack P, Houeto JL, Troster AI. Deep brain stimulation: neuropsychological and neuropsychiatric issues. Mov Disord 2006;21 Suppl 14:S305-327.
142. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. Science 1990;249(4975):1436-1438.
143. Limousin P, Pollak P, Benazzouz A, et al. Effect on parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. Lancet 1995;345(8942):91-95.
144. Ballanger B, Jahanshahi M, Broussolle E, Thobois S. PET functional imaging of deep brain stimulation in movement disorders and psychiatry. J Cereb Blood Flow Metab 2009;29(11):1743-1754.
145. Mallet L, Mesnage V, Houeto JL, et al. Compulsions, Parkinson's disease, and stimulation. Lancet 2002;360(9342):1302-1304.
146. Ulla M, Thobois S, Lemaire JJ, et al. Manic behaviour induced by deep-brain stimulation in Parkinson's disease: evidence of substantia nigra implication? J Neurol Neurosurg Psychiatry 2006;77(12):1363-1366.
147. Krack P, Kumar R, Ardouin C, et al. Mirthful laughter induced by subthalamic nucleus stimulation. Mov Disord 2001;16(5):867-875.
148. Tommasi G, Lanotte M, Albert U, et al. Transient acute depressive state induced by subthalamic region stimulation. J Neurol Sci 2008;273(1-2):135-138.
149. Robledo P, Feger J. Excitatory influence of rat subthalamic nucleus to substantia

nigra pars reticulata and the pallidal complex: electrophysiological data. Brain Res 1990;518(1-2):47-54.

150. Dodd ML, Klos KJ, Bower JH, Geda YE, Josephs KA, Ahlskog JE. Pathological gambling caused by drugs used to treat Parkinson disease. Arch Neurol 2005;62(9):1377-1381.
151. Boshes B, Arbit J. A controlled study of the effect of L-dopa upon selected cognitive and behavioral functions. Trans Am Neurol Assoc 1970;95:59-63.
152. Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia 1989;27(11-12):1329-1343.
153. Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology (Berl) 1992;107(2-3):394-404.
154. Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 1988;111 (Pt 2):299-321.
155. Kulisevsky J. Role of dopamine in learning and memory: implications for the treatment of cognitive dysfunction in patients with Parkinson's disease. Drugs Aging 2000;16(5):365-379.
156. Nieoullon A. Dopamine and the regulation of cognition and attention. Prog Neurobiol 2002;67(1):53-83.
157. Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 2001;11(12):1136-1143.
158. Weder BJ, Leenders KL, Vontobel P, et al. Impaired somatosensory discrimination of shape in Parkinson's disease: association with caudate nucleus dopaminergic function. Hum Brain Mapp 1999;8(1):1-12.
159. Breit S, Schulz JB, Benabid AL. Deep brain stimulation. Cell Tissue Res 2004.
160. Moro E, Lang AE. Criteria for deep-brain stimulation in Parkinson's disease: review and analysis. Expert Rev Neurother 2006;6(11):1695-1705.
161. Benabid AL, Chabardes S, Mitrofanis J, Pollak P. Deep brain stimulation of the

subthalamic nucleus for the treatment of Parkinson's disease. Lancet Neurol 2009;8(1):67-81.

162. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med 2003;349(20):1925-1934.
163. Rodriguez-Oroz MC, Obeso JA, Lang AE, et al. Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up. Brain 2005;128(Pt 10):2240-2249.
164. Schupbach WM, Chastan N, Welter ML, et al. Stimulation of the subthalamic nucleus in Parkinson's disease: a 5 year follow up. J Neurol Neurosurg Psychiatry 2005;76(12):1640-1644.
165. Ardouin C, Pillon B, Peiffer E, et al. Bilateral subthalamic or pallidal stimulation for Parkinson's disease affects neither memory nor executive functions: a consecutive series of 62 patients. Ann Neurol 1999;46(2):217-223.
166. Pillon B, Ardouin C, Damier P, et al. Neuropsychological changes between "off" and "on" STN or GPi stimulation in Parkinson's disease. Neurology 2000;55(3):411-418.
167. Alegret M, Junque C, Valldeoriola F, et al. Effects of bilateral subthalamic stimulation on cognitive function in Parkinson disease. Arch Neurol 2001;58(8):1223-1227.
168. Jahanshahi M, Ardouin CM, Brown RG, et al. The impact of deep brain stimulation on executive function in Parkinson's disease. Brain 2000;123(Pt 6):1142-1154.
169. Funkiewiez A, Ardouin C, Cools R, et al. Effects of levodopa and subthalamic nucleus stimulation on cognitive and affective functioning in Parkinson's disease. Mov Disord 2006;21(10):1656-1662.
170. Saint-Cyr JA, Trepanier LL, Kumar R, Lozano AM, Lang AE. Neuropsychological consequences of chronic bilateral stimulation of the subthalamic nucleus in Parkinson's disease [In Process Citation]. Brain 2000;123(Pt 10):2091-2108.
171. Alberts JL, Voelcker-Rehage C, Hallahan K, Vitek M, Bamzai R, Vitek JL. Bilateral subthalamic stimulation impairs cognitive-motor performance in

Parkinson's disease patients. Brain 2008;131(Pt 12):3348-3360.

172. Trepanier LL, Kumar R, Lozano AM, Lang AE, Saint-Cyr JA. Neuropsychological outcome of GPi pallidotomy and GPi or STN deep brain stimulation in Parkinson's disease [In Process Citation]. Brain Cogn 2000;42(3):324-347.
173. Baunez C, Christakou A, Chudasama Y, Forni C, Robbins TW. Bilateral high-frequency stimulation of the subthalamic nucleus on attentional performance: transient deleterious effects and enhanced motivation in both intact and parkinsonian rats. Eur J Neurosci 2007;25(4):1187-1194.
174. Baunez C, Robbins TW. Bilateral lesions of the subthalamic nucleus induce multiple deficits in an attentional task in rats. Eur J Neurosci 1997;9(10):2086-2099.
175. Javoy-Agid F, Agid Y. Is the mesocortical dopaminergic system involved in Parkinson disease? Neurology 1980;30(12):1326-1330.
176. Brozoski TJ, Brown RM, Rosvold HE, Goldman PS. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 1979;205(4409):929-932.
177. Simon H, Scatton B, Moal ML. Dopaminergic A10 neurones are involved in cognitive functions. Nature 1980;286(5769):150-151.
178. Montaron MF, Bouyer JJ, Rougeul A, Buser P. Ventral mesencephalic tegmentum (VMT) controls electrocortical beta rhythms and associated attentive behaviour in the cat. Behav Brain Res 1982;6(2):129-145.
179. Bouyer JJ, Joseph JP, Rougeul A. Effects of two neuroleptic drugs on focal somatoparietal rhythms in free awake cats. Psychopharmacology (Berl) 1979;65(1):55-58.
180. Schultz W. Behavior-related activity of primate dopamine neurons. Rev Neurol (Paris) 1994;150(8-9):634-639.
181. Chudasama Y, Baunez C, Robbins TW. Functional disconnection of the medial prefrontal cortex and subthalamic nucleus in attentional performance: evidence for corticosubthalamic interaction. J Neurosci 2003;23(13):5477-5485.
182. Goldberg ME, Eggers HM, Gouras P. The oculor motor system, In: Kandel E.R., Schwartz J.H., Jessel T.M. (Eds.), Principles of Neural Science. 3rd ed. New

York: Elsevier, pp. 660-678, 1991.

183. Muller JR, Philiastides MG, Newsome WT. Microstimulation of the superior colliculus focuses attention without moving the eyes. Proc Natl Acad Sci U S A 2005;102(3):524-529.
184. Corbetta M, Miezin FM, Dobmeyer S, Shulman GL, Petersen SE. Selective and divided attention during visual discriminations of shape, color, and speed: functional anatomy by positron emission tomography. J Neurosci 1991;11(8):2383-2402.
185. Volkow ND, Gur RC, Wang GJ, et al. Association between decline in brain dopamine activity with age and cognitive and motor impairment in healthy individuals. Am J Psychiatry 1998;155(3):344-349.
186. Heo JH, Lee KM, Paek SH, et al. The effects of bilateral subthalamic nucleus deep brain stimulation (STN DBS) on cognition in Parkinson disease. J Neurol Sci 2008;273(1-2):19-24.
187. Witt K, Pulkowski U, Herzog J, et al. Deep brain stimulation of the subthalamic nucleus improves cognitive flexibility but impairs response inhibition in Parkinson disease. Arch Neurol 2004;61(5):697-700.
188. Benabid AL, Koudsie A, Benazzouz A, Le Bas JF, Pollak P. Imaging of subthalamic nucleus and ventralis intermedius of the thalamus. Mov Disord 2002;17 Suppl 3:S123-129.
189. Defer GL, Widner H, Marie RM, Remy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). Mov Disord 1999;14(4):572-584.
190. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In Bellak, L. & Karasu, T.B. (Eds.), Geriatric psychiatry. New York: Grune & Stratton; pp. 77-121, 1976.
191. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198.
192. Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology 2000;55(11):1621-1626.
193. Beck A, Steer R, Brown G. Manual for Beck Depression Inventory II (BDI-II).

San Antonio, Tex: Psychology Corporation. . 1996.

194. Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992;4(2):134-139.
195. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971;9(1):97-113.
196. Lanthony P. The desaturated panel D-15. Doc Ophthalmol 1978;46(185-9).
197. Buttner T, Kuhn W, Patzold T, Przuntek H. L-Dopa improves colour vision in Parkinson's disease. J Neural Transm Park Dis Dement Sect 1994;7(1):13-19.
198. Buttner T, Muller T, Kuhn W. Effects of apomorphine on visual functions in Parkinson's disease. J Neural Transm 2000;107(1):87-94.
199. Diederich NJ, Raman R, Leurgans S, Goetz CG. Progressive worsening of spatial and chromatic processing deficits in Parkinson disease. Arch Neurol 2002;59(8):1249-1252.
200. Lanthony P. [Evaluation of the desaturated Panel D-15. I. Method of quantification and normal scores]. J Fr Ophtalmol 1986;9(12):843-847.
201. Pieri V, Diederich NJ, Raman R, Goetz CG. Decreased color discrimination and contrast sensitivity in Parkinson's disease. J Neurol Sci 2000;172(1):7-11.
202. Lanthony P. [Quantification and automation of Panel D-15]. Bull Soc Ophtalmol Fr 1985;85(12):1287-1290.
203. Yelnik J, Bardinet E, Dormont D, et al. A three-dimensional, histological and deformable atlas of the human basal ganglia. I. Atlas construction based on immunohistochemical and MRI data. Neuroimage 2007;34(2):618-638.
204. Yelnik J, Damier P, Demeret S, et al. Localization of stimulating electrodes in patients with Parkinson disease by using a three-dimensional atlas-magnetic resonance imaging coregistration method. J Neurosurg 2003;99(1):89-99.
205. Deep Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001;345(13):956-963.
206. Geyer T, Muller HJ, Krummenacher J. Expectancies modulate attentional capture by salient color singletons. Vision Res 2008;48(11):1315-1326.
207. Montagnini A, Chelazzi L. The urgency to look: prompt saccades to the benefit

of perception. Vision Res 2005;45(27):3391-3401.
208. Laming DR. Information Theory of Choice -Reaction Times: Academic Press (London) 1968.
209. Luce RD. Response Times: Their Role in Inferring Elementary Mental Organization: Oxford University Press (New York), 1986.
210. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B. Motivation, reward, and Parkinson's disease: influence of dopatherapy. Neuropsychologia 2002;40(13):2257-2267.
211. Frank MJ, Samanta J, Moustafa AA, Sherman SJ. Hold your horses: impulsivity, deep brain stimulation, and medication in parkinsonism. Science 2007;318(5854):1309-1312.
212. Pagonabarraga J, Garcia-Sanchez C, Llebaria G, Pascual-Sedano B, Gironell A, Kulisevsky J. Controlled study of decision-making and cognitive impairment in Parkinson's disease. Mov Disord 2007;22(10):1430-1435.
213. Witt K. Decision-making in Parkinson's disease. Mov Disord 2007;22:1371-1372.
214. Busigny T, Rossion B. Acquired prosopagnosia abolishes the face inversion effect. Cortex;46(8):965-981.
215. Shore DI, Barnes ME, Spence C. Temporal aspects of the visuotactile congruency effect. Neurosci Lett 2006;392(1-2):96-100.
216. Townsend JT, Ashby FG. Stochastic Modelling of Elementary Psychological Processes. Landon: Cambridge University Press, 1983.
217. Donders FC. On the speed of mental processes. Acta Psychol (Amst) 1969;30:412-431.
218. Welford AT. Choice reaction time: Basic concepts. In A. T. Welford, Reaction times New York: Academic Press, 1980.
219. Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 1996;50(4):381-425.
220. Cools R, Ivry RB, D'Esposito M. The human striatum is necessary for responding to changes in stimulus relevance. J Cogn Neurosci 2006;18(12):1973-1983.
221. De Weerd P, Peralta MR, 3rd, Desimone R, Ungerleider LG. Loss of attentional stimulus selection after extrastriate cortical lesions in macaques. Nat Neurosci 1999;2(8):753-758.

222. Lee EY, Cowan N, Vogel EK, Rolan T, Valle-Inclan F, Hackley SA. Visual working memory deficits in patients with Parkinson's disease are due to both reduced storage capacity and impaired ability to filter out irrelevant information. Brain 2010;133(9):2677-2689.
223. Chan F, Armstrong IT, Pari G, Riopelle RJ, Munoz DP. Deficits in saccadic eye-movement control in Parkinson's disease. Neuropsychologia 2005;43(5):784-796.
224. Posner MI, Rafal RD, Choate LS, Vaughan J. Inhibition of return: Neural basis and function. Cognitive Neuropsychology 1985;2(3):211-228.
225. Kingstone A, Klein R, Morein-Zamir S, Hunt A, Fisk J, Maxner C. Orienting attention in aging and Parkinson's disease: distinguishing modes of control. J Clin Exp Neuropsychol 2002;24(7):951-967.
226. Brown RG, Marsden CD. Internal versus external cues and the control of attention in Parkinson's disease. Brain 1988;111 (Pt 2):323-345.
227. Cools R, Rogers R, Barker RA, Robbins TW. Top-down attentional control in Parkinson's disease: salient considerations. J Cogn Neurosci 2009;22(5):848-859.
228. Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 1995;118 (Pt 4):913-933.
229. Mennemeier M, Fennell E, Valenstein E, Heilman KM. Contributions of the left intralaminar and medial thalamic nuclei to memory. Comparisons and report of a case. Arch Neurol 1992;49(10):1050-1058.
230. Van Der Werf YD, Weerts JG, Jolles J, Witter MP, Lindeboom J, Scheltens P. Neuropsychological correlates of a right unilateral lacunar thalamic infarction. J Neurol Neurosurg Psychiatry 1999;66(1):36-42.
231. Watson RT, Valenstein E, Heilman KM. Thalamic neglect. Possible role of the medial thalamus and nucleus reticularis in behavior. Arch Neurol 1981;38(8):501-506.
232. McNab F, Klingberg T. Prefrontal cortex and basal ganglia control access to working memory. Nat Neurosci 2008;11(1):103-107.
233. Einhauser W, Rutishauser U, Koch C. Task-demands can immediately reverse the

effects of sensory-driven saliency in complex visual stimuli. J Vis 2008;8:2 1-19.
234. Shomstein S, Lee J, Behrmann M. Top-down and bottom-up attentional guidance: investigating the role of the dorsal and ventral parietal cortices. Exp Brain Res 2010;206(2):197-208.
235. Bisley JW, Goldberg ME. Neuronal activity in the lateral intraparietal area and spatial attention. Science 2003;299(5603):81-86.
236. Serences JT, Shomstein S, Leber AB, Golay X, Egeth HE, Yantis S. Coordination of voluntary and stimulus-driven attentional control in human cortex. Psychol Sci 2005;16(2):114-122.
237. Bush G, Whalen PJ, Rosen BR, Jenike MA, McInerney SC, Rauch SL. The counting Stroop: an interference task specialized for functional neuroimaging--validation study with functional MRI. Hum Brain Mapp 1998;6(4):270-282.
238. Hazeltine E, Bunge SA, Scanlon MD, Gabrieli JD. Material-dependent and material-independent selection processes in the frontal and parietal lobes: an event-related fMRI investigation of response competition. Neuropsychologia 2003;41(9):1208-1217.
239. Paus T. Location and function of the human frontal eye-field: a selective review. Neuropsychologia 1996;34(6):475-483.
240. Zysset S, Muller K, Lohmann G, von Cramon DY. Color-word matching stroop task: separating interference and response conflict. Neuroimage 2001;13:29-36.
241. Gleichgerrcht E, Ibanez A, Roca M, Torralva T, Manes F. Decision-making cognition in neurodegenerative diseases. Nat Rev Neurol 2010;6(11):611-623.
242. Cools R, Barker RA, Sahakian BJ, Robbins TW. L-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 2003;41(11):1431-1441.
243. Moskovitz C, Moses H, 3rd, Klawans HL. Levodopa-induced psychosis: a kindling phenomenon. Am J Psychiatry 1978;135(6):669-675.
244. Kischka U, Kammer TH, Maier S, Weisbrod M, Thimm M, Spitzer M. Dopaminergic modulation of semantic network activation. Neuropsychologia 1996;34:1107-1113.
245. Rafal RD, Posner MI, Friedman JH, Inhoff AW, Bernstein E. Orienting of visual attention in progressive supranuclear palsy. Brain 1988;111 (Pt 2):267-280.

246. Cools R, Clark L, Robbins TW. Differential responses in human striatum and prefrontal cortex to changes in object and rule relevance. J Neurosci 2004;24(5):1129-1135.
247. van Schouwenburg MR, den Ouden HE, Cools R. The human basal ganglia modulate frontal-posterior connectivity during attention shifting. J Neurosci 2010;30(29):9910-9918.
248. Schultz W. Behavioral dopamine signals. Trends Neurosci 2007;30(5):203-210.
249. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science 1997;275(5306):1593-1599.
250. Redgrave P, Prescott TJ, Gurney K. The basal ganglia: a vertebrate solution to the selection problem? Neuroscience 1999;89(4):1009-1023.
251. Redgrave P, Prescott TJ, Gurney K. Is the short-latency dopamine response too short to signal reward error? Trends Neurosci 1999;22(4):146-151.
252. Cohen JD, Servan-Schreiber D. A theory of dopamine function and its role in cognitive deficits in schizophrenia. Schizophr Bull 1993;19(1):85-104.
253. Sarter M. Neuronal mechanisms of the attentional dysfunctions in senile dementia and schizophrenia: two sides of the same coin? Psychopharmacology (Berl) 1994;114(4):539-550.
254. Temel Y, Blokland A, Ackermans L, et al. Differential effects of subthalamic nucleus stimulation in advanced Parkinson disease on reaction time performance. Exp Brain Res 2006;169(3):389-399.
255. Goldman PS. Functional development of the prefrontal cortex in early life and the problem of neuronal plasticity. Exp Neurol 1971;32(3):366-387.
256. Dimitrov M, Grafman J, Soares AH, Clark K. Concept formation and concept shifting in frontal lesion and Parkinson's disease patients assessed with the California Card Sorting Test. Neuropsychology 1999;13(1):135-143.
257. Owen AM, Roberts AC, Hodges JR, Summers BA, Polkey CE, Robbins TW. Contrasting mechanisms of impaired attentional set-shifting in patients with frontal lobe damage or Parkinson's disease. Brain 1993;116 (Pt 5):1159-1175.
258. Hershey T, Mink JW. Using functional neuroimaging to study the brain's response to deep brain stimulation. Neurology 2006;66(8):1142-1143.
259. Temel Y, Blokland A, Steinbusch HW, Visser-Vandewalle V. The functional role

of the subthalamic nucleus in cognitive and limbic circuits. Prog Neurobiol 2005;76(6):393-413.

260. Butson CR, Cooper SE, Henderson JM, McIntyre CC. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. Neuroimage 2007;34(2):661-670.
261. Brusa L, Pierantozzi M, Peppe A, et al. Deep brain stimulation (DBS) attentional effects parallel those of l-dopa treatment. J Neural Transm 2001;108(8-9):1021-1027.
262. Aziz TZ, Peggs D, Sambrook MA, Crossman AR. Lesion of the subthalamic nucleus for the alleviation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced parkinsonism in the primate. Mov Disord 1991;6(4):288-292.
263. Jahanshahi M, Ardouin CM, Brown RG, et al. The impact of deep brain stimulation on executive function in Parkinson's disease. Brain 2000;123 (Pt 6):1142-1154.
264. Page D, Jahanshahi M. Deep brain stimulation of the subthalamic nucleus improves set shifting but does not affect dual task performance in Parkinson's disease. IEEE Trans Neural Syst Rehabil Eng 2007;15(2):198-206.
265. Monchi O, Petrides M, Doyon J, Postuma RB, Worsley K, Dagher A. Neural bases of set-shifting deficits in Parkinson's disease. J Neurosci 2004;24:702-710.
266. Limousin P, Greene J, Pollak P, Rothwell J, Benabid AL, Frackowiak R. Changes in cerebral activity pattern due to subthalamic nucleus or internal pallidum stimulation in Parkinson's disease. Ann Neurol 1997;42(3):283-291.
267. Schroeder U, Kuehler A, Haslinger B, et al. Subthalamic nucleus stimulation affects striato-anterior cingulate cortex circuit in a response conflict task: a PET study. Brain 2002;125(Pt 9):1995-2004.
268. Thobois S, Hotton GR, Pinto S, et al. STN stimulation alters pallidal-frontal coupling during response selection under competition. J Cereb Blood Flow Metab 2007;27(6):1173-1184.
269. Ballanger B, van Eimeren T, Moro E, et al. Stimulation of the subthalamic nucleus and impulsivity: release your horses. Ann Neurol 2009;66(6):817-824.