**UNIVERSIDADE FEDERAL DO PARANÁ**

**SETOR DE CIÊNCIAS BIOLÓGICAS**

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# USO DA TÉCNICA DA VOLTAMETRIA CÍCLICA DE VARREDURA RÁPIDA PARA O ESTUDO DE DROGAS QUE AFETAM A LIBERAÇÃO SINÁPTICA DE DOPAMINA: UM ESTUDO DO EFEITO DE BENZODIAZEPINAS

**Gonzalo Alexander Gómez Acosta**

**CURITIBA**
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GONZALO ALEXANDER GOMEZ ACOSTA

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Tese apresentada ao Programa de Pós-Graduação em Farmacologia: Setor de Ciências Biológicas da Universidade Federal do Paraná, como requisito parcial à obtenção do título de Doutor em Farmacologia.
Orientador: Prof. Dr. Cláudio Da Cunha
Co-orientador: Profa. Dra. Patricia Dowmbrosky

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## TERMO DE APROVAÇÃO

Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em FARMACOLOGIA da Universidade Federal do Paraná foram convocados para realizar a arguição da Dissertação de Doutorado de **GONZALO ALEXANDER GOMEZ ACOSTA**, intitulada: "**Voltametria Cíclica de Varredura Rápida no registro ?in vivo? de dopamina em animais anestesiados e acordados: padronização da técnica.**", após terem inquirido o aluno e realizado a avaliação do trabalho, são de parecer pela sua aprovação, completando-se assim todos os requisitos previstos nas normas desta Instituição para a obtenção do Grau de **Doutor em FARMACOLOGIA**.

Curitiba, 22 de Fevereiro de 2016.

Prof CLAUDIO DA CUNHA (UFPR)
(Presidente da Banca Examinadora)

Prof PAULO ROBERTO DALSENTER (UFPR)

Prof ROBERTO ANDREATINI (UFPR)

Prof ROMULO ANTONIO FUENTES FLORES ( UCH)

Prof SUELEN LUCIO BOSCHEN (UFRJ)

## Dedicatória

***Dedico este trabajo a mis hijos!***

***Por ellos llegue aquí e iría a donde fuese necesario.***

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## Resumo

O presentre trabalho mostra uma revisão ampla das diferentes teorias sobre os processos do aprendizado e motivação assim como a relação que estes pocessos tem com diferentes estruturas corticais e sucorticais no sistema nervoso central. Adicionalmente, é feita uma revisão do conhecimento atual sobre o papel dos gânglios da base nesses processos assim como o seu envolvimento em processos emocionais, afetivos e motores. O conhecimento atual dessa ralação tem aberto a possibilidade de melhorar as estratégias de tratamento psicosociais, farmacológicas e cirúrgicas em doenças relacionadas com o funcionamento inadequado de algumas estruturas cerebrais, entre elas os gânglios da base. Uma dessas estratégias, com múltiplos usos na atualidade, é a estimulação cerebral prufunda, da qual é feita uma exaustiva revisão neste documento. Finalmente, são mostrados o resultados de um experimento onde a aplicacao de um fármaco benzodiazepinico modifica a liberação evocada de dopamina no núcleo accumbens. O farmaco usado, diazepam, é um agonista benzodiazepínico com propriedades ansiolíticas e aditivas. Diferentes estudos usando microdiálise têm mostrado que, enquanto outras drogas de abuso aumentam direta ou indiretamente a concentração de dopamina no núcleo accumbens, os fármacos benzodiazepínicos fazem o contrário: diminuem a concentração de dopamina no núcleo accumbens. No presente estudo usamos a técnica de voltametria cíclica de varredura rápida visando estudar o efeito do tratamento agudo com diazepam (1, 2 e 3 mg/kg, i.p.) na liberação de dopamina no núcleo accumbens quando evocada pela estimulação elétrica da área tegmentar ventral de camundongos anestesiados. Os resultados mostraram uma redução dose-dependente na liberação de dopamina no núcleo accumbens que foi significante para as doses de 2 e 3 mg/kg. Esse efeito foi prevenido pela administração do antagonista de receptor benzodiazepínico flumazenil (2.5 mg/kg, i.p.). Após a administração de diazepam não foram observados efeitos significantes sobre a recaptação de dopamina. Uma redução significante na recaptação de dopamina foi observada com um controle positivo para esse efeito: após a administração do inibidor do transportador de dopamina, nomifensina (20 mg/kg, i.p.). Esses resultados sugerem que o efeito ansiolítico dos fármacos benzodiazepínicos poderia ter um componente dopaminérgico. Adicionalmente, este estudo provê um possível mecanismo pelo qual as benzodiazepinas são efetivas no tratamento de outras drogas de abuso tais como a cocaína, as anfetaminas e opiódes

## Abstract

This work shows a comprehensive review about learning and motivation theories and their relation with several cortical and subcortical structures in the Central Nervous System. In addition, we review current knowledge about the role of the Basal Ganglia over emotional, affective and motor processes. This knowledge has improved psychosocial, pharmacological and surgical treatments for diseases related to inadequate functioning of several brain structures included the basal ganglia. One of the most important advances regarding basal ganglia disease treatment is Deep Brain Stimulation and we provide an exhaustive review of this treatment. Finally, we show the results of an experiment where the application of a benzodiazepine drug (diazepam) modifies electrically evoked dopamine release in the nucleus accumbens. Diazepam is a benzodiazepine receptor agonist with anxiolytic and addictive properties. Microdialysis studies have shown that while most addictive drugs increase dopamine concentration in the nucleus accumbens, benzodiazepines cause the opposite effect. In the present study we used sub-second fast-scan cyclic voltammetry measures to show that diazepam (2 and 3 mg/kg, i.p.) caused a dose-dependent decrease in the dopamine release in the nucleus accumbens evoked by electrical stimulation of the ventral tegmental area of mice. This effect was prevented by the administration of the benzodiazepine receptor antagonist flumazenil (2.5 mg/kg, i.p.). No significant effects on measures of dopamine re-uptake were observed. This finding suggests that the anxiolytic effect of benzodiazepines might have a dopaminergic component. In addition, this study provides a likely mechanism by which benzodiazepines are effective in the treatment of other drugs of abuse such as cocaine, amphetamines and opioids.

## Lista de abreviações

AMPc- monofosfato de adenosina cíclica
ATP- trifosfato de adenosina
BZ- benzodiazepina
COMT- catecol orto-metiltransferase
CPF- córtex pré-frontal
CREB- proteína responsiva ao elemento de ligação AMPc (do inglês *cAMP response element-binding protein*)
DA- dopamina
DAT – transportador de dopamina
FSCV- voltametria cíclica de varredura rápida (do inglês *fast-scan cyclic voltammetry*)
GABA- ácido gama-amino butírico
$GABA_AR$- Receptor $GABA_A$
HVA- ácido homovanílico (do inglês *homovanilic acid*)
ISRS- inibidores seletivos da recaptação de serotonina
ISRSN- inibidores não-seletivos da recaptação de serotonina e noradrenalina
MAO- monoamina oxidase
NAc- núcleo Accumbens
NEMs- neurônios espinhosos médios
PKA- proteína cinase A
SCP- substância cincenta periacueductal
SNc- substância negra pars compacta
TA- transtornos de ansiedade
TAG- Transtorno de ansiedade Generalizada
TH- tirosina hidroxilase
VMAT- transportador vesicular de monoaminas (do inglês *vesicular monoamine transporter*)
VTA- área tegmentar ventral (do inglês *ventral tegmental area*)

## Lista de tabelas e figuras

**Sumário**

## Apresentação

Essa tese consiste em dois artigos de revisão e um artigo de resultados experimentais. O primeiro artigo de revisão aborda o desenvolvimento de técnicas eletroquímicas de registro da concentração de dopamina no cérebro de animais acordados em tempo real e suas aplicações em sistemas fechados de estimulação cerebral profunda. O segundo artigo revisa o estado da arte sobre o papel dos núcleos da base em comportamentos motivados. O artigo de resultados mostra a aplicação da mais moderna técnica eletroquímica usada para registro intra-cerebral *in vivo* da concentração de neurotransmissores a um estudo farmacológico – o papel da dopamina no mecanismo de ação dos ansiolíticos benzodiazepínicos. A revisão de literatura mais detalhada sobre as técnicas eletroquímicas, estimulação cerebral profunda e neurobiologia dos núcleos da base está contida nos artigos de revisão. A introdução da tese contêm uma revisão sobre os aspectos teóricos do tratamento farmacológico dos transtornos de ansiedade e da neurotransmissão dopaminérgica. Os resultados, métodos e discussão desse trabalho experimental estão apresentados no paper que está sendo submetido à revista ACS Chemical Neuroscience encartado na tese. Essa tese é finalizada com a um tópico de conclusões gerais e as referências usadas no texto em português.

## 1. Introdução

Os Transtornos de Ansiedade (TA) incluem uma série de entidades clínicas caracterizadas por manifestações excessivas de medo além de outras expressões comportamentais. Embora o medo e a ansiedade façam parte do repertório de comportamento normal dos animais, nos TA há uma super-estimação das situações de perigo resultando em uma resposta emocional desproporcional (AMERICAN PSYCHIATRIC ASSOCIATION, 2013). Os TA não podem ser resumidos simplesmente ao ser "muito ansioso", mas sim a uma permanente preocupação e evitação irracional de situações que constituem o foco de tal preocupação. Dessa forma, pessoas com transtorno de pânico ficam preocupadas com a possibilidade de sofrer um colapso, pessoas com transtorno de ansiedade social se preocupam que seu comportamento resulte em vergonha e aquelas com fobias específicas se preocupam com a possibilidade de sofrer algum tipo de dano. A preocupação é uma característica central nos TA, embora seja mais evidente em alguns deles quando comparado com outros. Tal como acontece no caso do transtorno de ansiedade generalizada (TAG) onde a persistente e excessiva preocupação abarca vários domínios tais como o desempenho no trabalho e na escola, a família, a economia, entre outras preocupações (TYRER e BALDWIN, 2006; ANDREWS et al, 2003). Além da preocupação, os indivíduos com TAG apresentam sintomas físicos como tensão muscular e fadiga e comportamentos como agitação e irritação. Esses sintomas vêm acompanhados de manifestações cognitivas como falta de concentração, dificuldades no aprendizado e déficits de memória e atenção constantemente relacionada com os focos da preocupação (a lista completa dos critérios diagnósticos para TAG pode ser conferida na Tabela 1). Adicionalmente, boa parte dos indivíduos diagnosticados apresentam dificuldades no sono (AMERICAN PSYCHIATRIC ASSOCIATION, 2013) e são mais suscetíveis ao estresse – que rapidamente se transforma em ansiedade. Além disso, podem desenvolver outros transtornos de ansiedade e depressão por conta da sua vulnerabilidade.

## Transtorno de Ansiedade Generalizada

### Critérios Diagnósticos **300.02** (F41.1)

A. Ansiedade e preocupação excessivas (expectativa apreensiva), ocorrendo na maioria dos dias por pelo menos seis meses, com diversos eventos ou atividades (tais como desempenho escolar ou profissional).

B. O indivíduo considera difícil controlar a preocupação.

C. A ansiedade e a preocupação estão associadas com três (ou mais) dos seguintes seis sintomas (com pelo menos alguns deles presentes na maioria dos dias nos últimos seis meses).

**Nota:** Apenas um item é exigido para crianças.

1. Inquietação ou sensação de estar com os nervos à flor da pele.
2. Fatigabilidade.
3. Dificuldade em concentrar-se ou sensações de "branco" na mente.
4. Irritabilidade.
5. Tensão muscular.
6. Perturbação do sono (dificuldade em conciliar ou manter o sono, ou sono insatisfatório e inquieto).

D. A ansiedade, a preocupação ou os sintomas físicos causam sofrimento clinicamente significativo ou prejuízo no funcionamento social, profissional ou em outras áreas importantes da vida do indivíduo.

E. A perturbação não se deve aos efeitos fisiológicos de uma substância (p. ex., droga de abuso, medicamento) ou a outra condição médica (p. ex., hipertireoidismo).

F. A perturbação não é mais bem explicada por outro transtorno mental (p. ex., ansiedade ou preocupação quanto a ter ataques de pânico no transtorno de pânico, avaliação negativa no transtorno de ansiedade social [fobia social], contaminação ou outras obsessões no transtorno obsessivo-compulsivo, separação das figuras de apego no transtorno de ansiedade de separação, lembranças de eventos traumáticos no transtorno de estresse pós-traumático, ganho de peso na anorexia nervosa, queixas físicas no transtorno de sintomas somáticos, percepção de problemas na aparência no transtorno dismórfico corporal, ter uma doença séria no transtorno de ansiedade de doença ou o conteúdo de crenças delirantes na esquizofrenia ou transtorno delirante).

**Tabela 1**. Critérios diagnósticos para o Transtorno de Ansiedade Generalizada (TAG). Manual Diagnostico e Estatístico de Transtornos Mentais (DSM-V, American Psychiatric Association, 2014)

Em geral, os TA representam boa parte das estatísticas em saúde mental do mundo. Segundo o último estudo em saúde mental da Organização Panamericana da Saúde para América Latina e o Caribe feito em 2009, os TA avaliados (TAG, transtorno de pânico, agorafobia, transtorno de estrese pós-traumático e transtorno obsessivo-compulsivo) se apresentaram em 66,5 milhões de pessoas maiores de 15 anos, durante algum momento da vida. Levando em conta que a população da América Latina em 2010 era de 575,867,000 de pessoas (CEPAL, 2009), perto de 10% da população (tabela 2) apresentou algum tipo de TA ao longo da sua vida. De fato, observando só os dados do TAG, 20.7 milhões de pessoas foram diagnosticadas em 2009. Isso explica os elevados valores investidos em medicamentos para se tratar transtornos de ansiedade na região. Segundo o último informe mundial de saúde mental feito pela Organização Mundial da Saúde em 2011, nesse ano foram investidos em torno de U$ 2,680.oo por cada 100.000 habitantes em medicamentos para o tratamento dos transtornos de ansiedade (ORGANIZAÇÃO MUNDIAL DA SAÚDE, 2011) o que daria um total aproximado de US$1,.433,235.oo uma quantidade assombrosa levando em conta que esse valor diz somente aos fármacos ansiolíticos.

### 1.1. Tratamento dos TA

Existe uma grande quantidade de abordagens psicossociais e farmacológicas para o tratamento dos transtornos de ansiedade, cada uma delas com vantagens e desvantagens dependendo do tipo de transtorno e as características de intervenção. Por meio da intervenção, procura-se a redução da piora dos sintomas cognitivos e somáticos da ansiedade. Apesar da importância de complementar estratégias psicossociais e farmacológicas no tratamento dos TA, a ênfase para o presente trabalho será farmacológica.

Em relação aos tratamentos farmacológicos, a natureza dos medicamentos usados varia em função das suas características farmacodinâmicas e farmacocinéticas. Estão disponíveis no mercado fármacos benzodiazepínicos (BZ), inibidores seletivos da

| | Prevalência | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | A vida toda | | | Ultimo Ano | | | Atual | | |
| Transtorno | Total | Hom | Mul | Total | Hom | Mul | Total | Hom | Mul |
| Psicose não afetiva. | 5,5 | 2,3 | 3 | 3,9 | 1,7 | 2,2 | 5,9 | 2,3 | 3,4 |
| Depressão Maior | 38,4 | 12,8 | 25,3 | 19,6 | 6,1 | 13,3 | 17,2 | 5,7 | 11,2 |
| Distimia | 12,5 | 3,1 | 9,2 | 6,7 | 1,7 | 5,2 | 3,9 | 1,3 | 2,6 |
| Transtorno Bipolar | 5,1 | 2,7 | 2,8 | 2,7 | 1,3 | 1,4 | 2 | 0,8 | 1 |
| Ansiedade Generalizada | 20,7 | 7,1 | 13,7 | 12,9 | 4,8 | 8,4 | 5,1 | 1,5 | 3,4 |
| Transtorno de pânico | 5,9 | 1,7 | 4,2 | 3,5 | 1,1 | 2,4 | 2,3 | 0,6 | 1,6 |
| Agorafobia | 14,5 | 7 | 20,7 | 8,6 | 3,1 | 13,3 | 5,9 | 2 | 9,4 |
| Transtorno de estrese pós-traumático | 18 | 14,1 | 21,5 | 7 | 7,4 | 6,3 | 2,3 | 1,2 | 3,5 |
| Transtorno obsessivo-compulsivo | 7,4 | 3,1 | 4,2 | 5,5 | 2,3 | 3 | 5,9 | 1,9 | 3,8 |
| Abuso ou dependência de Álcool | 44,2 | 38,9 | 6,2 | 22,3 | 18,7 | 3,8 | 13,3 | 11,4 | 2,6 |
| Abuso o dependência de drogas | 8,2 | 6,1 | 2,4 | 2,7 | 1,7 | 1 | - | - | - |

**Tabela 2**. Adultos maiores de 15 anos e mais afetados por algum tipo de transtorno mental em América Latina e o Caribe. (Organização Panamericana da Saúde, 2009). Traduzida do original para língua portuguesa pelo autor da tese.

recaptação de serotonina (ISRS), inibidores seletivos da recaptação de serotonina e noradrenalina (ISRSN), valproato de sódio, gabapentina, pregabalina; antipsicóticos sedativos; anti-histamínicos e vários outros agentes estão sob pesquisa (JANICAK et al, 2011). Contudo, os fármacos de maior uso no tratamento dos transtornos de ansiedade, particularmente do TAG, continuam sendo as BZs. Diferentes estudos têm mostrado a eficácia das BZs no tratamento agudo do TAG com um tamanho do efeito de 0.70 (GOULD et al., 1997). Porém, existe uma grande quantidade de efeitos indesejados que incluem déficits cognitivos, sonolência e letargia e dependência física e psicológica posterior a uso prolongado.

Adicionalmente, a descontinuação do tratamento resulta na volta ou intensificação da ansiedade com suas manifestações físicas e psicológicas em 25% a 75% dos pacientes, síndrome de abstinência em 40% a 100% e tolerância em 63% a 81% dos indivíduos (DUBOVSKY, 1990). Esses resultados levaram a recomendação do uso das BZs na sua menor dose eficaz pelo menor tempo possível (RICKELS, 1987; GORMAN e PAPP, 1990).

## 1.2. Mecanismo de ação das BZs

As BZs agem incrementando a afinidade do ácido γ-aminobutírico (GABA) por alguns subtipos de receptores $GABA_A$ resultando na inibição do neurônio pós-sináptico pelo incremento na condutância da sua membrana para íons de $Cl^-$ (RUDOLPH E KNOFLACH, 2011). O GABA é o neurotransmissor inibitório mais abundante do sistema nervoso e está associado com o controle da excitabilidade neuronal, redução da ansiedade, controle dos ritmos circadianos, cognição, vigilância, memória e aprendizado (SIEGHART e SPERK, 2002). São conhecidas duas classes principais de receptores GABA: os receptores $GABA_A$ (ionotrópicos) e os receptores $GABA_B$ (metabotrópicos). A maioria das ações fisiológicas do GABA são geradas pela sua ligação a receptores $GABA_{A,}$ e a sua atividade pode ser modulada por uma grande variedade de drogas tais como as BZs, barbitúricos, esteróides anestésicos e anticonvulsivantes (SIEGHART, 1995).

Essas drogas produzem os seus efeitos ao se ligar em um sítio específico localizado nos receptores $GABA_A$ modulando a atividade dos canais através dos quais os íons $Cl^-$ entram na célula. Essa modulação resulta no aumento da afinidade do GABA pelo receptores $GABA_A$ (ANDREWS et al, 2003). Consistente com o incremento da afinidade do GABA pelo receptor, as BZ prolongam a queda das correntes inibitórias pós-sinápticas espontâneas e aumentam a sua amplitude em diferentes populações neuronais (PERRAIS e ROPERT, 1999; HAJOS et al., 2000) sugerindo que tal incremento na afinidade resulta num maior recrutamento de receptores para serem ativados pelo GABA. Contudo, em outras populações de neurônios, as correntes inibitórias pós-sinápticas espontâneas permanecem inalteradas pelas BZs (MODY et al., 1994; PONCER et al., 1995; HAJOS et al., 2000).

Os receptores GABAérgicos apresentam uma grande heterogeneidade estrutural (MOHLER et al, 2001). Eles são compostos por 5 subunidades, cada uma com diferentes subtipos (6α, 4β, 3γ, 1δ, 1ε, 1π, 3ρ, 1θ) (SIEGHART e SPERK, 2002). A maioria dos receptores $GABA_A$ se compõem de subunidades α, β, γ e a diversidade na configuração dessas subunidades determina diferenças na cinética dos receptores, a afinidade pelo

GABA, a taxa de dessensibilização e a sua distribuição em neurônios pré- e pós-sinápticos (Fig. 1) (SIEGHART E SPERK, 2002). Receptores contendo subunidades α1, α2, α3, ou α5, combinadas com qualquer das unidades β e a subunidade γ2 são os mais prevalentes no cérebro e apresentam um sítio com alta afinidade por BZs.

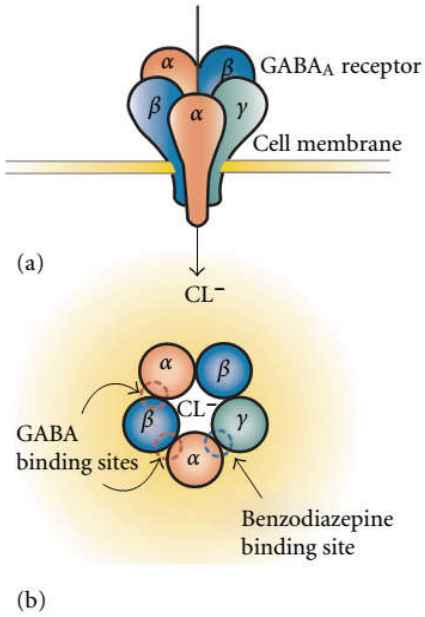


**Figura 1**. Estrutura receptor GABA$_A$ (Vinkers e Olivier, 2011).

O subtipo de receptor mais comum é composto pelas subunidades α1β2γ2 (FRITSCHY e MOHLER, 1995; PIRKER et al., 2000) embora receptores formados por subunidades α2 e α3 também existam em menor quantidade no cérebro. Acredita-se que o sítio de ligação das BZs no receptor esteja localizado na interface da subunidade α com a subunidade γ (Fig. 1). As subunidades α2, α3 e α5 estão frequentemente expressas com subunidades β3 e γ2 (para ver as diferentes possibilidades de expressão e localização dos

receptores $GABA_A$ ver Tabela 3). Receptores que expressam subunidades α4 e α6 são menos abundantes no cérebro e não apresentam resposta frente ao uso de BZs.

GABA$_A$ Receptor Subtypes

| Composition | Pharmacological Characteristics[a] | | Neuronal Localization[b] |
|---|---|---|---|
| $\alpha_1\beta_2\gamma_2$ | Major subtype (60% of all GABA$_A$ receptors). Mediates the sedative, amnestic, and—to a large extent—the anticonvulsant action of benzodiazepine site agonists. High affinity for classical benzodiazepines, zolpidem, and the antagonist flumazenil. | Synaptic and extrasynaptic | Cerebral cortex (Somogyi, 1989; J.M. Fritschy, unpublished data)<br>Hippocampus, dentate gyrus (interneurons and principal cells) (Nusser et al., 1995)<br>Pallidum (Somogyi et al., 1996)<br>Striatum (interneurons) (J.M. Fritschy, unpublished data)<br>Thalamic relay nuclei (Somogyi, 1989; J.M. Fritschy, unpublished data)<br>Olfactory bulb (mitral cells and interneurons) (Giustetto et al., 1998)<br>Cerebellum (Purkinje cells, stellate, basket cells, and granule cells) (Somogyi et al., 1996; Nusser et al., 1997, 1998, 1999; Sassoè-Pognetto et al., 2000)<br>Deep cerebellar nuclei (Sassoè-Pognetto et al., 2000) |
| $\alpha_2\beta_3\gamma_2$ | Minor subtype (15–20%). Mediates anxiolytic action of benzodiazepine site agonists. High affinity for classical benzodiazepine agonists and the antagonist flumazenil. Intermediate affinity for zolpidem. | Synaptic | Cerebral cortex (Fritschy et al., 1998a)<br>Hippocampus, dentate gyrus (principal cells mainly on the axon initial segment) (Sassoè-Pognetto et al., 2000; Fritschy et al., 1998a; Nusser et al., 1996a)<br>Olfactory bulb (granule cells) (Sassoè-Pognetto et al., 2000)<br>Striatum (spiny stellate cells) (Fritschy et al., 1998a)<br>Inferior olivary neurons (mainly on dendrites) (Devor et al., 2001) |
| $\alpha_3\beta_n\gamma_2$ | Minor subtype (10–15%). High affinity for classical benzodiazepine agonists, and the antagonist flumazenil. Intermediate affinity for zolpidem | Synaptic | Cerebral cortex (principal cells in particular in layers V and VI; some axon initial segments) (Fritschy et al., 1998a)<br>Hippocampus (some hilar cells) (J.M. Fritschy, unpublished data)<br>Olfactory bulb (tufted cells) (Giustetto et al., 1998)<br>Thalamic reticular nucleus (Fritschy et al., 1998a)<br>Cerebellum (Golgi cells) (Sassoè-Pognetto et al., 2000)<br>Medullary reticular formation (Fritschy et al., 1998a) |
| | | Extrasynaptic | Inferior olivary neurons (Devor et al., 2001) |
| $\alpha_4\beta_n\gamma$/$\alpha_4\beta_n\delta$ | Less than 5% of all receptors. Insensitive to classical benzodiazepine agonists and zolpidem. | Extrasynaptic | Dentate gyrus (granule cells) (Mody and Nusser, 2000) |
| $\alpha_5\beta_{1/3}\gamma_2$ | Less than 5% of all receptors; high affinity for classical benzodiazepine agonists and the antagonist flumazenil. Very low affinity for zolpidem. | Synaptic<br>Extrasynaptic | Spinal trigeminal nucleus, superior olivary neurons (J.M. Fritschy, unpublished data)<br>Cerebral cortex (J.M. Fritschy, unpublished data)<br>Hippocampus (pyramidal cells) (Fritschy et al., 1998b)<br>Olfactory bulb (granule cells) (Fritschy et al., 1998b) |
| $\alpha_6\beta_{2,3}\gamma_2$ | Less than 5% of all receptors. Insensitive to classical benzodiazepine agonists and zolpidem. | Synaptic<br>Extrasynaptic | Cerebellum (granule cells) (Nusser et al., 1996b, 1998, 1999)<br>Cerebellum (granule cells) (Nusser et al., 1996b, 1998, 1999; Sassoè-Pognetto et al., 2000) |
| $\alpha_6\beta_n\delta$ | Minor population. Lacks benzodiazepine site. | | |
| $\rho$ | Homomeric receptors: insensitive to bicuculline, barbiturates, baclofen, and all benzodiazepine site ligands. Also termed GABA$_C$ receptor; for nomenclature see Barnard et al., 1998. | Synaptic | Retina (Kaulen et al., 1998) |

[a] Reviewed in Macdonald and Olsen, 1994; Barnard et al., 1998; Rudolph et al., 1999; Löw et al., 2000; Möhler et al., 2000; Whiting et al., 2000; Möhler, 2001. The term classical benzodiazepines refers to diazepam and structurally related agonists in clinical use.

[b] Synaptic localization is based mainly on ultrastructural evidence or on the colocalization with gephyrin and refers to the respective type of α-subunit.

**Tabela 3**. Subtipos de receptor GABA$_A$, características farmacológicas e expressão neuronal (Molher et al, 2002

### 1.3. Efeitos das BZs associados às subunidades do receptor $GABA_A$

Os principais efeitos das BZs estão associados à configuração dos receptores $GABA_A$ com os quais se ligam. A sedação, amnésia anterógrada, a proteção frente a convulsão e os efeitos ansiolíticos guardam relação com a subunidade α expressa no receptor. Assim, os efeitos sedativos, amnésicos e protetivos parciais frente a convulsões são mediados por receptores contendo a subunidade α1 (Fig. 2) (MCKERNAN et al., 2000; CRESTANI et al., 2000; RUDOLPH et al., 1999). Os efeitos ansiolíticos das BZs parecem estar ligados à atividade de receptores contendo subunidades α2 (LOW et al, 2002) e em menor proporção, receptores α3 e α5 (com fármacos em desenvolvimento como L-838,417 ou SL65.1498) (MCKERNAN et al., 2000; SCATTON et al., 2000).

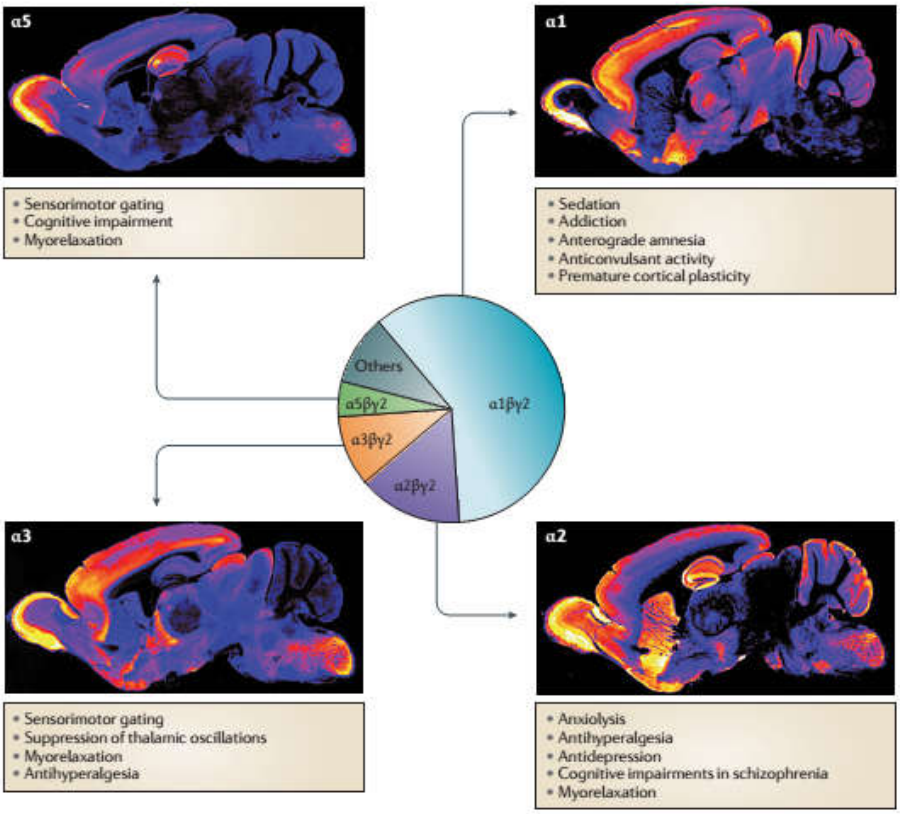


**Figura 2**. Efeitos farmacológicos dos receptores $GABA_A$ de acordo a com a distribuição da subunidade α. Essa figura ilustra a distribuição desses receptores no cérebro de camundongos (Rudolph et al., 1999)

## 1.4. Dopamina

O neurotransmissor dopamina (DA) tem um papel importante na modulação de funções motoras, mas também tem sido associado com motivação, recompensa e reforço (DA CUNHA, 2012).

A dopamina (DA), assim como a adrenalina e noradrenalina pertence à família de neurotransmissores da classe química das catecolaminas (TRITSCH e SABATINI, 2012). Esses neurotransmissores não causam despolarização de outros neurônios; eles modulam a neurotransmissão glutamatérgica e GABAérgica. Por essa razão podem ser mais propriamente chamados de neuromoduladores que neurotransmissores.

A síntese da DA tem como precursor o aminoácido tirosina. A tirosina é convertida em L-3,4-diidroxifenilalanina (levodopa, L-DOPA) por ação da enzima tirosina-hidroxilase . Subsequentemente, a L-DOPA é convertida em DA por ação da enzima DOPA-descarboxilase. Uma vez sintetizada, a DA é transportada para vesículas sinápticas pela proteína transportadora de catecolaminas (VMAT) (KOLB e WHISHAW, 2007). Quando os terminais sinápticos dos neurônios dopaminérgicos são despolarizados a DA é liberada por exocitose e se liga a receptores específicos, tanto pré- quanto pós-sinápticos (TRITSCH e SABATINI, 2012). A DA liberada pode ser degradada pela enzima catecol-O-metil-transferase (COMT) assim como pela enzima monoamina-oxidase (MAO) extracelular ou ser transportada de volta para o terminal sináptico pela ação do transportador de DA (DAT) onde é armazenada em vesículas sináptica ou degradada pela ação da MAO intracelular. Além disso, uma parte da DA liberada se difunde, podendo atuar em receptores que estão fora da sinapse. (STANDAERT e GALANTER, 2012; BJORKLUND e DUNNETT, 2007)

Os receptores dopaminérgicos são do tipo metabotrópicos (acoplado à proteína G) e fazem parte de duas famílias: D1 e D2. A ligação da DA a receptores da família D1 (formada por receptores D1 e D5), leva ao aumento do AMP cíclico (AMPc), o que resulta na ativação da proteína cinase A (PKA). O contrário ocorre quando a DA se liga com receptores da família D2 (formada por receptores D2, D3 e D4). Estes receptores estão

acoplados a proteína $G_i$ e $G_0$ e a sua ativação resulta na diminuição da concentração de AMPc. A PKA fosforila canais iônicos de $K^+$ e $Ca^{+2}$ voltagem-dependentes. Isso altera o potencial de membrana resultando em uma maior ou menor probabilidade de que a liberação de glutamato despolarize o neurônio pós-sináptico. Na maioria das situações, a ativação de receptores da família D1 resulta em uma maior probabilidade de despolarização, enquanto a ativação de receptores da família D2 resulta em uma menor probabilidade de despolarização. Porém, a depender do potencial de repouso da membrana pós-sinática e da frequência de potenciais de ação das fibras glutamatérgicas, a ativação dos receptores D1 pode resultar em uma menor probabilidade de despolarização (FLORES-BARRER a et al., 2011, BEAULIEU e GAINETDINOV, 2011; NEVE et al., 2004). A ativação de receptores D2 pré-sinápticos inibe a síntese e a liberação de DA (STANDAERT e GALANTER, 2012).

Os corpos dos neurônios que produzem DA formam pequenos núcleos localizados no mesencéfalo chamados de substância negra *pars compacta* (SNc) e área tegmentar ventral (ATV) (GERFEN e SURMEIER, 2011). Os neurônios da SNc formam projeções para o estriado dorsal e os neurônios da ATV formam projeções para o estriado ventral (incluindo o núcleo accumbens, NAc), córtex pré-frontal, amígdala e hipocampo.

Existem três principais vias dopaminérgicas: a via nigroestriatal que vai da SNc aos núcleos caudado e putâmen, dois núcleos que em conjunto são chamados estriado dorsal; a via mesolímbica que forma projeções da ATV direcionadas ao córtex pré-frontal, ao NAc e outras estruturas do sistema límbico relacionadas com os transtornos de ansiedade, tais como a amígdala e hipocampo e a via túbero-infundibular, em que os neurônios que contêm DA nos núcleos arqueado e periventricular do hipotálamo projetam axônios para a eminência mediana do hipotálamo. Entre as áreas do córtex pre-frontal que recebem aferências dos neurônios dopaminérgicos meso-límbicos estão também estruturas relacionadas aos transtornos de ansiedade, tais como o córtex órbito-frontal e o córtex cingulado anterior (KOLB e WHISHAW, 2007).

## 1.5. Técnicas de monitoramento da DA

Existem técnicas de monitoramento da concentração extracelular da DA como a microdiálise e a voltametria cíclica de varredura rápida, ambas usadas no nosso estudo. A microdiálise tem uma boa seletividade química, porém, tem uma resolução temporal pobre, da ordem de minutos a horas, sendo mais adequada para observar as liberações tônicas de DA (CHEFER Et al., 2009; ROBINSON et al., 2009). Já a voltametria cíclica de varredura rápida ou FSCV (fast scan cyclic voltammetry) realiza uma amostragem com alta resolução temporal (décimos de segundos), embora não apresente uma alta seletividade química. A FSCV é a técnica mais adequada para registrar a liberação fásica de DA.

Os registros de FSCV são feitos com eletrodos de fibra de carbono, onde é aplicado repetidamente um ciclo de variação de potencial elétrico. Essa variação ou varredura tem a forma de uma onda triangular que vai de valores de potencial elétrico onde nenhum dos analitos se oxida até valores superiores aos necessários para oxidar todos os analitos. Após a inflexão do potencial, este faz uma varredura decrescente, diminuindo gradativamente até os valores iniciais (ver Fig. 3). Na fase ascendente dessa rampa de potencial elétrico, os grupos químicos dos analitos que podem se oxidar, doam os seus elétrons para a superfície da fibra de carbono. Na rampa descendente de potencial, os analitos que podem se reduzir, recuperam os elétrons anteriormente perdidos para o eletrodo, regenerando, assim, o analito que serviu de substrato às reações de oxi-redução. Após os registros de FSCV *in vivo*, os eletrodos de carbono são calibrados com concentrações conhecidas de DA para que os valores de corrente possam ser extrapolados para as concentrações de DA reais (ROBINSON et al., 2003; WIGHTMAN, 2006; ROBERTS et al., 2013).

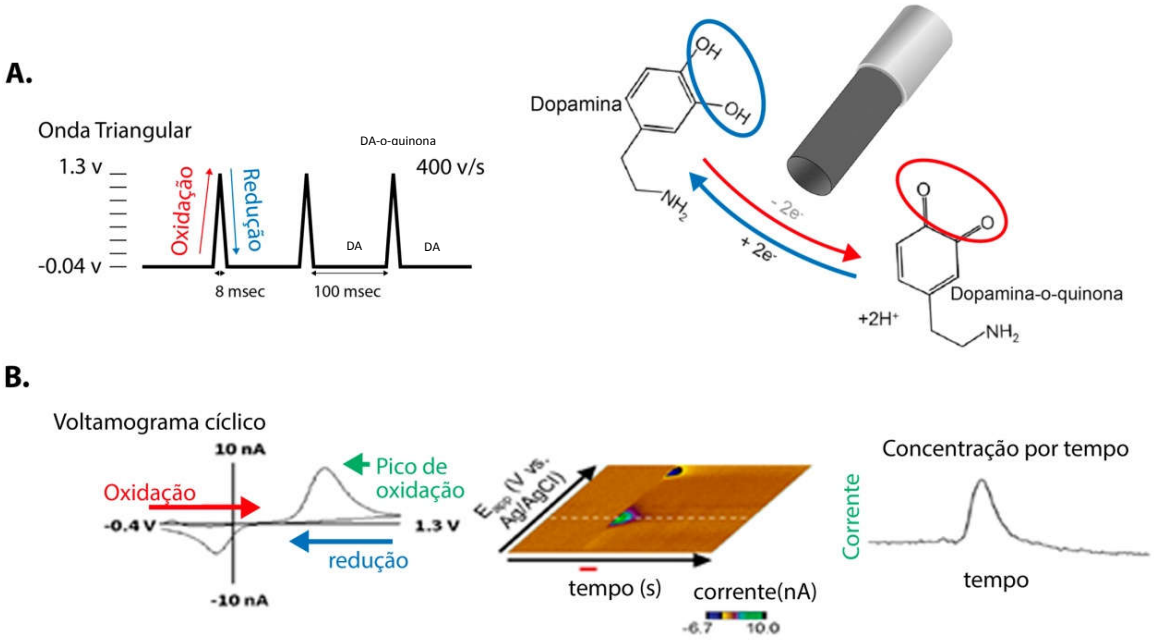


**Figura 3**. Voltametria cíclica de varredura rápida. A) Ondas triangulares cíclicas de varredura do potencial elétrico são aplicadas ao eletrodo de registro. Isso faz com que a dopamina se oxide na fase ascendente da varredura e que o seu produto de oxidação, a dopamina orto-quinona, se reduza a dopamina na fase descendente da varredura. Os elétrons gerados pela dopamina durante a oxidação são doados para o eletrodo e os elétrons necessários para a oxidação da quinona são doados de volta pelo eletrodo. B) As correntes de oxi-redução da dopamina e sua quinona estão representadas em 3 tipos de gráfico. Aqui estão representados apenas os dados após a subtração da linha de base (veja texto). O voltamograma cíclico da oxi-redução dopamina/dopamina orto-quinona mostra seus potencias ótimos de oxidação (valores positivos) e de redução (valores negativos). Os dados de todos os voltamogramas (10 voltamogramas a cada segundo) são representados em um color plot onde o tempo é representado no eixo do x , a variação de potencial elétrico a cada ciclo é representada no eixo y e as correntes de oxidação/redução são representadas por cores. Os pontos verde e preto desse color plot mostram a oxidação e redução da dopamina respectivamente. A variação de corrente no potencial ótimo de oxidação da dopamina ao longo do tempo (linha pontilhada do gráfico central em B) é mostrada no gráfico de linha à direita. Esses valores podem ser transformados em valores de variação na concentração de dopamina usando uma curva de calibração do eletrodo obtida com concentrações conhecidas de dopamina (Robinson e Wightman, 2007).

## 1.6. Substrato neural da ansiedade, o medo e o panico

Um dos assuntos mais estudados nos TA, são os seus substratos neurobiológicos. Assim, tem sido estabelecida a participação de diferentes estruturas corticais e subcorticais modulando reações emocionais como a ansiedade, o medo e o panico (GRAEFF, 2010). Na ansiedade humana, o Sistema septo-hipocampal parece estar relacionado com as manifestações cognitivas na ansiedade, como a típica preocupação sobre eventos futuros e o rumo desses pensamentos. A ativação que acompanha esses processamentos cognitivos parece ser mediada pela amígdala. Esta última, parece estar envolvida adicionalmente nos processo de medo aprendido, assim como, na recuperação e evocação das memórias emocionais (FANSELOW, 2010; DAVIS, 2004).

Por outro lado, a emoção que é experimentada naqueles casos em que a tendência é evitar a fonte de perigo, a emoção presente é medo e não ansiedade. As estruturas envolvidas nesse sistema, chamado "sistema cerebral de defesa" são a amígdala, o hipotálamo medial e a substância cinzenta periaquedutal (SCP) (GRAEFF, 2010). A amígdala avaliaria o tipo e magnitude do perigo enviando essa informação ao hipotálamo e SCP que e organizariam os comportamentos adaptativos de defesa (FANSELOW, 2010). Paralelamente, outro grupo de estruturas, incluindo o complexo septo-hipocampal foi chamado de "Sistema cerebral de aproximação". O principal subtrato desse Sistema de defesa (defesa proximal) é a coluna dorsolateral da SCP (BANDLER E KEAY, 1996).

O Córtex Prefrontal Medial (CPFm) esta envolvido na coordenação das reações de defesa dadas as conexões diretas com estruturas subcorticais (amígdala), diencefálicas (hipotálamo) e no tronco encefálico (PAG e núcleo dorsal da raphe que contém células serotoninérgicas). Como foi comentado previamente, estas estruturas participam na modulação de comportamentos de defesa (GRAEFF, 2010). A CPFm pode também modular a atividade do feixe Hipotálamo-Pituitária-Adrenal (HPA) através de conexões diretas com o Núcleo Vermelho da Estria Terminalis (NVET) ou o Núcleo Paraventricular

do Hipotálamo (NPV) e indiretamente através da suas conexões com a amígdala a qual projeta para o NPV através do NVET (GRAEFF, 2010). Finalmente, o CPFm modula a atividade cognitiva característica dos humanos é de particular interesse nos TA. Tal atividade permite, emtre outras coisas, prever eventos futuros e anticipar as consequências do próprio comportamento, ambos os dois possiveis fontes de preocupação (BERKOWITZ et al, 2007), o sintoma pricipal do TAG. Essa modulação tem um efeito direto na resposta emocional exacerbada tambem característica deste trastorno.

Finalmente, o CPF tem uma importante tarefa na regulação das expressões emocionais (o que tem sido observado através de estudos de neuroimagem) atenuando a resposta emocional nas estruturas subcorticais involvidas o que poderia ser a base da modulação da experiência emocional (GRAEFF, 2010).

### 1.7. Núcleo Accumbens, DA e Ansiedade

Embora o NAc não tenha sido centro da pesquisa em Ansiedade, as conexões que mantém com estruturas diretamente envolvidas no processamento emocional tem dado bases para estudar a sua possível participação no processamento da experiência emocional (LE MAITRE et al, 2006). O NAc está localizado na parte ventral do estriado e tem sido relacionado com diferentes funções que podem ser relevantes para os transtornos de ansiedade, tais como o medo, estresse, motivação, recompensa, comportamento de defesa, cognição, atividade motora, comportamento sexual, estresse (ZARRINDAST, 2015). O NAc contém duas sub-regiões conhecidas como *“core*” e “*Shell*”, as quais têm algumas diferenças na sua conectividade e nas suas funções (PISTILLO et al, 2015). A principal população de células no NAc se compõe de neurônios espinhosos médios (NEM) que representam 95% das células nervosas localizadas nesta região. O outro 5% consiste de inter-neurônios colinérgicos e GABAérgicos (TEPPER E BOLAM, 2004). Embora tenha sido identificada uma organização similar às chamadas vias diretas e indiretas do estriado dorsal (NICOLA, 2007), a organização dos NEM no NAc é menos clara

(SESACK E GRACE, 2010). O NAc core projeta para a porção dorsolateral do pálido ventral e do núcleo subtâlamico que, por sua vez, projeta para o núcleo médio dorsal do tálamo. Os NEMs do NAc shell que recebem projeções da ATV projetam de volta para os NEMs do NAc core (PISTILLO et al, 2015). Os NEM recebem também projeções glutamatérgicas do córtex pré-frontal, do hipocampo ventral, da amígdala basolateral e do tálamo medial. Eles levam diferentes tipos de informações, particularmente aquelas relacionadas com o aprendizado por reforço positivo (BRITT E BONCI, 2013).

O NAc participa do circuito neuronal da ansiedade. Ele forma uma estação que recebe da amígdala e de outras estruturas límbicas informação sobre a relevância motivacional de estímulos e pode deflagrar respostas motoras relacionadas à ansiedade (LE MAITRE et al., 2006). Alguns neurotransmissores liberados no NAc podem estar envolvidos na ansiedade como acontece no caso da DA (ZARRINDAST et al, 2008). O NAc pode mudar a atividade dos neurônios dopaminérgicos da ATV direta ou indiretamente, através dos NEM que projetam do NAc para a ATV ou envolvendo o pálido ventral respectivamente (NICOLA, 2007). Assim, tem sido observado que em ambientes estressantes ocorre o aumento da DA no NAc (ZARRINDAST et al, 2008; LECOURTIER ET AL, 2008; XIA et al, 2011) levando a uma reorganização funcional dos NEM, um efeito que poderia ser relevante na explicação dos estados motivacionais alterados observados nos transtornos de ansiedade (CHRISTOFFEL ET AL, 2011). Dar mas detalles

O presente estudo visa elucidar, por meio de uma abordagem neuroquímica, o efeito do agonista benzodiazepínico diazepam (DZP) na liberação de DA evocada eletricamente no NAc, assim como o efeito do antagonista benzodiazepínico flumazenil (FLU) sobre esse mesmo parâmetro. Os resultados deste estudo são importantes para compreender melhor o mecanismo de ação das BZs, dada a sua importância terapêutica no tratamento dos transtornos de ansiedade e outros usos na clinica, assim como os possíveis mecanismos envolvidos nas suas propriedades aditivas.

## 2. Objetivo Geral

Determinar o efeito de um agonista benzodiazepinico (DZP) e de um antagonista benzodiazepínico (FLU) na liberação de DA evocada eletricamente no NAc de camundongos anestesiados.

### 2.1. Objetivos específicos

1. Padronizar o uso da técnica de voltametria cíclica de varredura rápida (FSCV) para uso em animais anestesiados.
2. Monitorar os níveis extra-celulares de DA evocada eletricamente no NAc de camundongos anestesiados durante aplicação de um agonista e um antagonista BZs
3. Observar a capacidade da voltametria cíclica de varredura rápida (FSCV) para identificar variações na cinética de liberação e recaptação da DA após a aplicação de um agonista e um antagonista benzodizepínico assim como do inibidor do transportador de DA nomifensina.
4. Interpretar os dados à luz do conhecimento atual sobre o mecanismo de ação dos BZs e os resultados obtidos neste trabalho.

## 3. Artigos Científicos

### 3.1. Toward sophisticated basal ganglia neuromodulation: review on basal ganglia deep brain stimulation

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Review

# Toward sophisticated basal ganglia neuromodulation: Review on basal ganglia deep brain stimulation

Claudio Da Cunha [a], Suelen L. Boschen [a], Alexander Gómez-A [a], Erika K. Ross [b], William S.J. Gibson [b], Hoon-Ki Min [b,c], Kendall H. Lee [b,c], Charles D. Blaha [d,*]

[a] Departamento de Farmacologia, Universidade Federal do Paraná, Curitiba, PR, Brazil
[b] Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, USA
[c] Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA
[d] Department of Psychology, The University of Memphis, Memphis, TN, USA

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ABSTRACT

This review presents state-of-the-art knowledge about the roles of the basal ganglia (BG) in action-selection, cognition, and motivation, and how this knowledge has been used to improve deep brain stimulation (DBS) treatment of neurological and psychiatric disorders. Such pathological conditions include Parkinson's disease, Huntington's disease, Tourette syndrome, depression, and obsessive-compulsive disorder. The first section presents evidence supporting current hypotheses of how the cortico-BG circuitry works to select motor and emotional actions, and how defects in this circuitry can cause symptoms of the BG diseases. Emphasis is given to the role of striatal dopamine on motor performance, motivated behaviors and learning of procedural memories. Next, the use of cutting-edge electrochemical techniques in animal and human studies of BG functioning under normal and disease conditions is discussed. Finally, functional neuroimaging studies are reviewed; these works have shown the relationship between cortico-BG structures activated during DBS and improvement of disease symptoms.



**Contents**

## 1. Introduction

Deep brain stimulation (DBS) of the basal ganglia (BG) is a well-established FDA-approved therapy for a variety of movement disorders such as Parkinson's disease (PD), essential tremor, and dystonia (Benabid et al., 1989, 1994, 2006; Benabid, 2003; Lang and Lozano, 1998). Additionally, it is an emerging therapy for several psychiatric and neurological conditions, including epilepsy, Tourette syndrome (TS), major depression, and obsessive-compulsive disorder (OCD) (Mayberg et al., 2005; Fisher et al., 2010). Despite its clinical success on these and other neurologic and psychiatric disorders, there is a limited understanding of the therapeutic mechanism behind DBS. In this review we discuss the current theories of DBS behind modulating BG dysfunction. Here, we explore current theories regarding BG dysfunction and the mechanisms underlying the associated motor deficit and neuropsychiatric symptoms in order to explore BG dysfunction improvement in response to DBS of cortico-BG targets.

A complete implanted DBS system consists of a pulse generator in the abdominal or infraclavicular region, which delivers the stimulation pulses via an intracerebrally implanted electrode. The stimulus is delivered via a clinical multi-contact electrode in which each contact is typically 1.5 mm in length and 1.27 mm in diameter (Godinho et al., 2006). The generator is connected to the electrode and battery powered. Stimulation parameters (pulse width, amplitude, frequency etc.) can be changed transdermally in order to optimize the therapeutic effects (Lyons, 2011).

There are several DBS targets within the basal ganglia (BG) that have been optimized to treat the aforementioned disorders. The subthalamic nucleus (STN) (Rodriguez-Oroz et al., 2004), internal part of the globus pallidum (GPi), or pedunculopontine tegmental nucleus (PPT) (Stefani et al., 2007) are shown to be effective in treating PD. To treat Huntington's disease (HD) and primary dystonia, GPi has been effectively targeted (Moreno et al., 2014; Vidailhet et al., 2013). The nucleus accumbens (NAc), cingulate cortex, and anterior limb of the internal capsule are targets to treat major depression (Kuhn et al., 2014; Schlaepfer et al., 2008; Lozano et al., 2008; Baker et al., 2007; Bewernick et al., 2010; Pandya et al., 2012). The anterior limb of the internal capsule is targeted to treat OCD (Greenberg et al., 2006). Finally, the internal capsule/NAc, centromedian/parafascicularis (CMPf) and the GPi are used to treat TS (Hariz and Robertson, 2010; Neuner et al., 2009; Saleh et al., 2012; Welter et al., 2008; Williams and Okun, 2013). Here, we will discuss the rationale and potential mechanism behind the effective treatment of the disorders associated with these BG DBS targets.

In this review, we explain how BG dysfunction is thought to give rise to an array of motor-related and neuropsychiatric disease states, and present the current theories surrounding how DBS of cortico-BG targets may lead to symptom relief. The BG has been proposed as a system to make selections: action-selection, reasoning/cognition related selections, and motivational state selections (Da Cunha et al., 2009, 2012; Redgrave et al., 2011). Understanding how the cortico-BG circuitry is suited for such computations is critical to understand how electrical stimulation of parts of this system can improve motor and psychiatric functions. Here, we present new emerging theories pertaining to the diverse roles of the BG in action-selection, cognition, and motivation that support the notion that BG function is highly complex, and may therefore be sub-optimally controlled by simple continuous large area electrical stimulation. We go on to discuss potential avenues for increasing the sophistication of future BG neuromodulation techniques. Finally, we review new research approaches that may be critical to the development of such advances, including electrochemical monitoring of neurochemicals, functional neuroimaging, and new large animal models of neuropsychiatric disorders. In summary, we emphasize that future research aimed at elucidating normal and pathological BG function, in combination with improved understanding of DBS mechanisms on a cellular and systems level, will open the door to more sophisticated and individualized DBS technologies.

## 2. BG cortico-thalamic loop

### 2.1. Circuits and connections

A growing body of evidence has shown that the BG forms a neural network dedicated to selection (Nicola, 2007; Redgrave et al., 2008, 2010; Da Cunha et al., 2009, 2012; Grillner et al., 2013). The strongest evidence is related to action-selection by the cortico-BG motor loop (Frank and Claus, 2006; Frank, 2011; Isoda and Hikosaka, 2011; Mink, 1996; Mogenson et al., 1980). In this loop, information from nearly all cortical and limbic subcortical areas flow into the BG input stations, including the dorsal striatum (Alexander et al., 1986) and STN (Nambu et al., 2002). The dorsal striatum also receives input from the thalamus (Parent and Hazrati, 1995a). More than 90% of the striatal neurons are GABAergic projection neurons named medium spiny neurons (MSNs) (Sesack and Grace, 2010). They compose two populations that make direct and indirect projections to the main output stations of the BG: the substantia nigra pars reticulata (SNr) and the GPi (Alexander et al., 1986). The external part of the globus pallidum (GPe) sends inhibitory projections to the SNr/GPi. Next, the STN sends excitatory projections to the SNr/GPi (Alexander et al., 1986). The BG output stations (SNr/GPi) project mostly to motor areas of the thalamus (e.g., the ventrolateral thalamus), which in turn, project to motor areas of the neocortex (Alexander et al., 1986; Albin et al., 1989; Parent and Hazrati, 1995a,b). The inhibitory control of the BG over the thalamocortical neurons can be increased by the hyperdirect pathway formed by cortical projections that bypass the striatum by sending "hyperdirect" excitatory projections to the STN that stimulate the SNr/GPi (Nambu et al., 2002) (Fig. 1). All

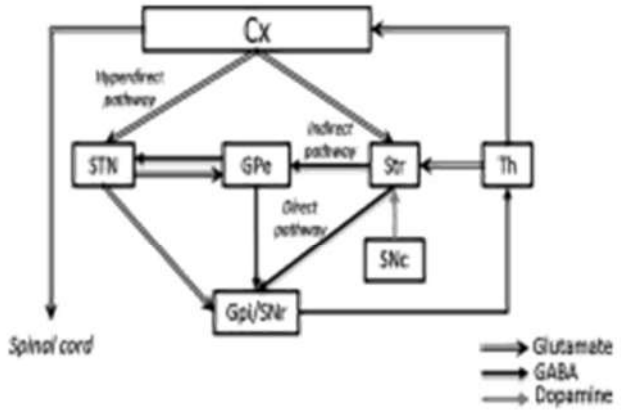


**Fig. 1.** Normal functioning of cortico-BG motor loop as proposed by Alexander et al. (1986), Albin et al. (1989) and Nambu et al. (2002). Cx, cerebral cortex; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, substantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; Th, thalamus.
Illustration adapted with permission from Nambu (2011).

BG nuclei are modulated by dopaminergic and GABAergic projections from the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) , and by cholinergic, glutamatergic and, to a lesser extent, by GABAergic projections from the PPT (Parent and Hazrati, 1995b; Inglis and Winn, 1995).

### 2.2. Dopamine as the main modulator of the BG

In the dorsal striatum, both direct and indirect pathways are modulated by dopaminergic neurons. Dopamine (DA) is released in the dorsal and ventral striatum (which includes the NAc) by SNc and VTA neurons, respectively (Bjorklund and Dunnett, 2007). Population release of DA produces a slow time course of changes in extra-synaptic DA concentrations (Grace, 1991). Under this tonic release of DA, the extra-synaptic DA concentration in the striatum may be as low as 40 to 50 nanomolar (Sharp et al., 1986; Church et al., 1987). Short duration bursts of high-frequency firing of DA neurons cause transient increases in the extracellular DA concentration to micromolar levels, which have been labeled as phasic DA release. While changes in tonic DA do not seem to impact behavior, phasic DA is proposed to cause robust changes in behavior and to be involved in prediction-error encoding and reinforcement learning (Kuczenski and Segal, 1989; Kalivas and Duffy, 1990; Shultz, 1997).

DA receptors have been classified into two subtypes designated D1- and D2-like DA receptors (Richfield et al., 1989). Tonic levels of extracellular DA concentrations can activate high affinity D2 receptors. In contrast, phasic activity of DA neurons is needed to increase the extracellular DA to a concentration necessary to activate D1 receptors (Richfield et al., 1989; Grace, 1995; Floresco et al., 2003). D1-like receptors (D1 and D5) stimulate Gs proteins; D2-like receptors (D2, D3 and D4) stimulate Go or Gi proteins (Neve et al., 2004). The result is stimulation or inhibition of the cyclic adenosine monophosphate (cAMP) dependent protein kinase A (PKA) (Stoof and Kebabian, 1984). PKA, in turn, phosphorylates voltage-dependent $K^+$ and $Ca^{2+}$ channels, leading to changes in the resting potentials of pre- and post-synaptic membranes (Svenningsson et al., 2004). Although all five DA receptors are expressed in the striatum, D1 and D2 receptors are by far the most abundant (Surmeier et al., 1996). MSNs of the direct and indirect pathways (see Fig. 1) express predominantly D1 and D2 DA receptors, respectively (Gerfen et al., 1990; Valjent et al., 2009; Gertler et al., 2008; Hersch et al., 1995; Surmeier et al., 2007). D2-like receptors are also expressed in the presynaptic terminals of nigral and VTA dopaminergic neurons (Benoit-Marand et al., 2001) and in the terminals of corticostriatal neurons (Wang and Pickel, 2002). As mentioned above, in the dorsal and ventral striatum, D1- and D2-like receptors are mostly segregated into two populations of MSNs which send direct and indirect projections to the BG output stations (Robertson and Jian, 1995; Nicola, 2007). Although this has not been completely established, it has been proposed that MSNs in the NAc expressing predominantly D1- and D2-like receptors are also segregated into two subpopulations of MSNs; both project to the ventral pallidum (the main output station of the ventral striatum) in a manner that might be equivalent to the direct and indirect pathways of the dorsal striatum (Nicola, 2007).

Striatal MSNs oscillate between the so-called down state (hyperpolarized) and up state (membrane potential closer to the depolarization threshold). MSNs fire in response to excitatory glutamatergic cortical and thalamic inputs only when they are in the up state and DA is released in a concentration enough to activate D1-like receptors. Under these conditions activation of D1-like receptors increase the likelihood of an MSN of the direct pathway to fire. In contrast, in the hyperpolarized down state activation of D1 receptors cause inhibition of MSNs (Flores-Barrera et al., 2011; for a review see Surmeier et al., 2011). This dual-condition mechanism probably works as a filter to increase the signal-to-noise ratio of corticostriatal neurotransmission. MSNs switch between down and up states depending on the activity of corticostriatal neurons. Stronger corticostriatal signals are supposed to encode relevant information for action-selection while weak signals are more likely to be irrelevant noise. This might increase the likelihood of the most proper action to be chosen by activation of specific MSNs. Activation of D2 receptors prevents the transition of MSNs from the down state to the up state (Surmeier et al., 2011).

## 3. Current theory of DBS on modulating BG dysfunction

### 3.1. DBS in Parkinson's disease (PD)

PD is one of the most common neurological movement disorders. It is characterized by a progressive loss of dopaminergic neurons in the SNc, leading to a massive reduction of extracellular DA levels in the striatum (Lim and Lang, 2010; Wichmann and Delong, 2011). This reduction prevents activation of both D1 and D2 dopaminergic post-synaptic receptors in the striatum that stimulate the direct and inhibit the indirect cortico-BG pathways. Thus, activity in the direct pathway is diminished and activity in the indirect pathway is increased (Alexander et al., 1986). High frequency neuronal discharges in GPi/SNr and STN and low frequency firing in the GPe are observed and this causes inhibition of motor nuclei in the thalamus (Bergman et al., 1994; Miller and DeLong, 1987; Soares et al., 2004; Wichmann et al., 1999) (Fig. 2). The final result is the inhibition of movement initiation (akinesia) and increased inhibition of ongoing movements (muscular rigidity) (Okun, 2012).

DBS has grown considerably in the past decade as a therapeutic alternative for advanced PD and is considered an effective intervention to treat PD motor deficits (Wichmann and Delong, 2011). The most common targets for this intervention include the motor portions of GPi or STN. In 2009, NIH COMPARE trial revealed no significant differences in STN or GPi DBS regarding motor deficit improvement (Williams and Okun, 2013). In addition, recent trials found comparable results for medication reduction, notably L-DOPA, in patients with STN or GPi DBS (Deuschl et al., 2006; Okun et al., 2012; Schuepbach et al., 2013; Odekerken et al., 2013; Follett, 2010). However, long-term cognitive problems have been reported in some STN DBS patients (Weaver et al., 2012). Hence, STN DBS is considered to be more suitable for patients with high dose medications and no significant cognitive deficits (Rodriguez-Oroz

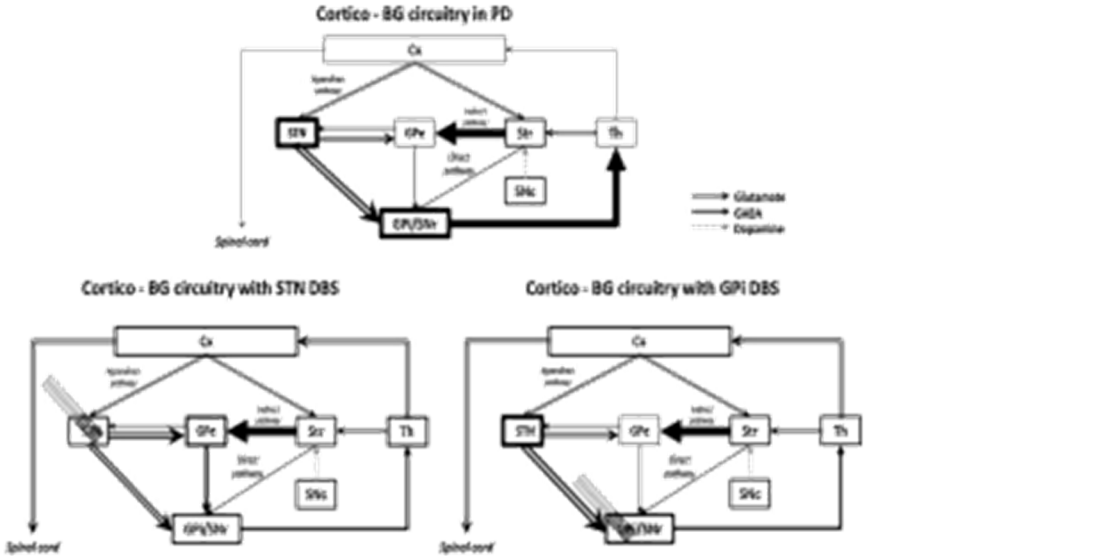


**Fig. 2.** Proposed cortico-BG circuitry functioning in Parkinson's disease (PD) before and after STN or GPi DBS. Cx, cerebral cortex; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, substantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; Th, thalamus. Illustration adapted from Nambu (2011).

et al., 2004). GPi is a good target for patients with dyskinesia and/or preexisting cognitive issues (Williams and Okun, 2013). Thus, DBS in both STN and GPi significantly improves the quality of life for advanced PD patients and is more effective than medication management (Weaver et al., 2009).

The mechanisms of action of DBS for motor improvement in PD patients are still unclear. In agreement with the hypothesis that DBS modulates neural activity, GPe and SNr neuronal firing records show that pathological low-frequency (~9 Hz) network oscillations are regularized by high-frequency STN DBS; and that neurons are entrained to fire at the stimulation frequency pattern (McConnell et al., 2012). In addition, STN DBS may inhibit STN neurons through activation of GABAergic neurons projecting from the GPe to directly activate axons of nearby neurons (McIntyre et al., 2004). Recent studies in rodents suggest that STN DBS influences cortical activity via antidromic activation of the hyperdirect pathway (Li et al., 2007; Gradinaru et al., 2009). In general terms, there are multiple putative mechanisms by which STN/GPi DBS may affect BG neural activity in a manner that improves PD motor deficits. DBS inhibits local neural firing while activating antidromic and orthodromic axonal conduction (Li et al., 2007; Dejean et al., 2009; Gradinaru et al., 2009). It alters concentrations of excitatory and inhibitory neurotransmitters, neural firing patterns, and may increase neurogenesis (Lee et al., 2009; Tye et al., 2009; Bourne et al., 2012). Thus, it appears that the multiple mechanisms of action of DBS in cortico-BG function culminate in the reinstatement of balance within BG connections (Wichmann and Delong, 2011). One potential explanation for effective STN or GPi DBS is the idea that DBS normalizes inhibition from GPi to thalamus (Rubin et al., 2012).

A recent study investigated functional magnetic resonance imaging (fMRI) analysis of the effects of unilateral (single electrode) DBS of the STN and entopeduncular nucleus (EN), the non-primate analog of the primate GPi, in a normal large animal (swine). This study showed that STN and EN/GPi DBS significantly increased blood-oxygen-level dependent (BOLD) activation in the sensorimotor network (Min et al., 2012). Concomitant fMRI with DBS has also been described in rodents, revealing non-specific motor cortex BOLD increase (Lai et al., 2013; Younce et al., 2014). Finally, the network effects of DBS in nonhuman primates have been investigated, showing that STN DBS similarly increased BOLD activation in the sensorimotor cortex, supplementary motor area, caudate nucleus, PPT, cingulate cortex, insular cortex and contralateral cerebellum. These results demonstrate that STN DBS evokes neural network grouping within the motor network and the BG (Min et al., 2014).

There is increasing evidence that DBS exerts both its therapeutic and adverse effects by modulating neural activity through anatomical and functional connections related to the target stimulation area and its surrounding structures (Chopra et al., 2011; Frankemolle et al., 2010; Kringelbach et al., 2007; Mallet et al., 2007; McIntyre and Hahn, 2010). The brain's dense wiring makes it challenging to characterize the effect of electrical stimulation on neuronal communication beyond a few synapses. Functional brain imaging has the advantage of providing global assessment of simultaneous neural activity. Much as we have found in swine and non-human primates, studies in PD patients during STN DBS show modulation of motor and non-motor areas including the primary sensorimotor cortex, premotor cortex, sensory motor area (SMA), dorsolateral prefrontal cortex, thalamus, BG, insular cortex and contralateral cerebellum (Asanuma et al., 2006; Grafton et al., 2006; Haslinger et al., 2003; Kahan et al., 2012; Phillips et al., 2006; Stefurak et al., 2003). Positron emission tomography (PET) studies have implicated parietal and temporal cortices classically defined as associative and limbic structures (Hershey et al., 2003; Le Jeune et al., 2010).

There are several clinical observations pointing toward an additional mechanism of action of STN DBS in PD involving the indirect activation of surviving nigrostriatal dopaminergic neurons. For example, STN DBS typically decreases or eliminates the need for L-DOPA (Moro et al., 1999; Molinuevo et al., 2000). It is most effective in PD patients who respond well to L-DOPA (Breit et al., 2004) and is contraindicated for those who do not respond to L-DOPA (Kern and Kumar, 2007). This suggests that therapeutic DBS requires endogenous DA production in the BG. DBS may even elicit dyskinesias that resemble those observed with increased L-DOPA dosage (Limousin et al., 1998) and impulsivity, a DA-related behavior (Frank et al., 2007). These clinical observations point toward the hypothesis that STN DBS may evoke DA release from surviving nigrostriatal dopaminergic neurons projecting to the BG to contribute to the therapeutic effects of STN DBS. They also elicit unwanted side effects when combined with inappropriately high doses of L-DOPA.

Using in vivo electrochemical recording techniques, it has been shown that high-frequency stimulation of the STN is capable of evoking striatal DA release in the intact and 6-OHDA DA lesioned rat (Lee et al., 2006; Covey et al., 2008; Blaha et al., 2008). An important question for future investigation is whether STN DBS improves PD symptoms via the release of DA in the BG.

Another STN DBS mechanism may be stimulation-induced adenosine (ADO) release. This important, but understudied, endogenous neuromodulator is present in all cells and plays a role in the regulation of physiological activity in various tissues (Latini and Pedata, 2001). ADO has been shown to be released near the DBS electrode in the thalamus, and appears to be critical for tremor relief (Bekar et al., 2008). In the central nervous system, ADO regulates cerebral blood flow by signaling at A2A receptors, and to a lesser extent at A2B receptors (Cechova and Venton, 2008). As it is a product of ATP degradation, its release from cells is a sign of a high metabolic rate (Masino and Dulla, 2005). Thus, increases in extracellular ADO appear to match elevations in cerebral blood flow that result from increases in neural activity, directly amenable to measurement with fMRI (Phillips, 2004; Brundege and Dunwiddie, 1997). ADO A2A and DA D2 receptors are found on striatal GABAergic MSNs that comprise the indirect striatal output pathway, whereas ADO A1 and DA D1 receptors are found on GABAergic MSNs that form the direct striatal output pathway (Fredholm et al., 2005). In the striatum, cholinergic interneurons are one of the main sources of ADO (James and Richardson, 1993). Dopaminergic input from the SNc into the striatum inhibits the release of acetylcholine through D2 receptors and also stimulates its release through DA D1 receptors (Damsma et al., 1990; Bertorelli and Consolo, 1990). In this regard, it is of interest to note that at the circuit level, using fast scan cyclic voltammetry (FSCV) to measure ADO release several groups have demonstrated that high-frequency stimulation of the SNc elicits ADO release in the striatum of the rat and pig (Cechova and Venton, 2008; Shon et al., 2010a,b).

Current DBS practice is based on the idea that high-frequency stimulation acts as a functional lesion by inhibiting or exciting specific brain regions. However, as our understanding of the mechanism behind DBS expands, we understand that there is substantial variability in its therapeutic effect. A recent study comparing pre- and postoperative diffusion tensor imaging in a PD patient undergoing bilateral STN DBS showed changes in structural connectivity before and after DBS. Using a computational model of spontaneous brain activity in this patient, van Hartevelt et al. found significant localized structural changes after long-term DBS in sensory-motor, prefrontal/limbic, and olfactory brain regions. This suggests that long-term DBS affects global structural and functional connectivity and changes in neural plasticity (van Hartevelt et al., 2014). Although our general understanding is improving, there are still large gaps of knowledge regarding neural plasticity changes from DBS in neurologic and neuropsychiatric disease.

### 3.2. DBS in Huntington's disease (HD)

HD is an autosomal dominant neurodegenerative disorder of striatal MSNs caused by the extensive repetition of the CAG sequence in the *huntingtin* gene (Sapp et al., 1997). The mutant form of the protein is responsible for dysfunctional cellular processes, such as gene transcription, protein trafficking, mitochondrial respiration, autophagy and calcium homeostasis (Eidelberg and Surmeier, 2011).

A predominant death of striatal MSNs in the indirect cortico-BG pathway is observed in HD (Reiner et al., 1988; Albin et al., 1989; Menalled et al., 2000; Raymond et al., 2011). Loss of this circuit leads to a condition where the 'break' provided by the indirect pathway is absent; therefore, improper movements are no longer inhibited. This is proposed to be the cause of chorea, the main observed

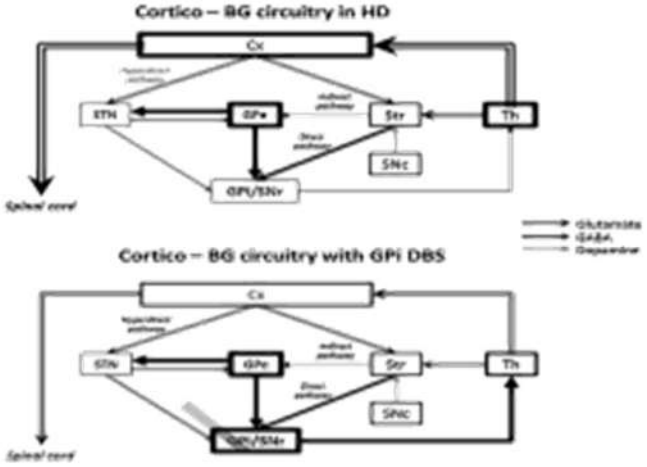


**Fig. 3.** Hypothetical cortico-BG functioning in Huntington's disease (HD) before and after GPi DBS. Cx, cerebral cortex; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, substantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; Th, thalamus.

Illustration adapted from Nambu (2011).

motor disability, characterized by spasmodic irregular movements in arms, legs, or in face muscles (Albin et al., 1990). Motor incoordination and cognitive deficits are also observed. In addition, other hyperkinetic (dystonia, myoclonia, tics) and hypokinetic dysfunctions (akinesia and muscular rigidity) are present. These motoric deficits are claimed to result from increased DA function in the early phase and decreased DA function in the late phase of HD (Raymond et al., 2011).

The preferential loss of indirect pathway MSNs reduces inhibitory GABAergic input to the GPe leading to an increase in GABAergic inhibition of the STN from the GPe. This inhibition is thought to lead to a decrease in STN glutamatergic excitatory drive on the GPi/SNr. In turn, GPi/SNr GABAergic inhibition of the thalamus is reduced, inducing an overflow of glutamate in motor areas of the cortex, and resultant hyperkinetic movements (Chevalier and Deniau, 1990; Raymond et al., 2011). Although much more is understood into the mechanism of DBS and PD, the documented increased firing rates in GPe and decreased firing rates in GPi observed in a HD patient strongly point toward a mechanism behind effective GPi DBS for motor deficits in HD patients (Fig. 3) (Starr et al., 2008; Edwards et al., 2012).

### 3.3. DBS in obsessive-compulsive disorder (OCD)

OCD is a type of anxiety disorder that happens when habits become compulsions. Obsessions are failures to inhibit invasive thoughts or images and compulsions are failures in inhibiting certain behaviors (Bourne et al., 2012). Disturbances in the cortico-BG limbic loop, especially the orbitofrontal cortex, anterior cingulate cortex, NAc, and mediodorsal thalamus have been reported (Bourne et al., 2012; Kopell and Greenberg, 2008).

Functional imaging studies report a significant dysfunction in the orbitofrontal cortex (Chamberlain et al., 2008) in OCD patients, whereby the orbitofrontal cortex and the basal ganglia are hyperconnected (Beucke et al., 2013). Distinct dysconnectivity has also been shown in the default mode network between the prefrontal cortex and BG (Anticevic et al., 2014). Additional studies investigating OCD in adolescent-patient populations has helped in disease prediction revealing that the caudate nucleus volume correlates significantly with the OCD symptoms in early adulthood (Bloch et al., 2005).

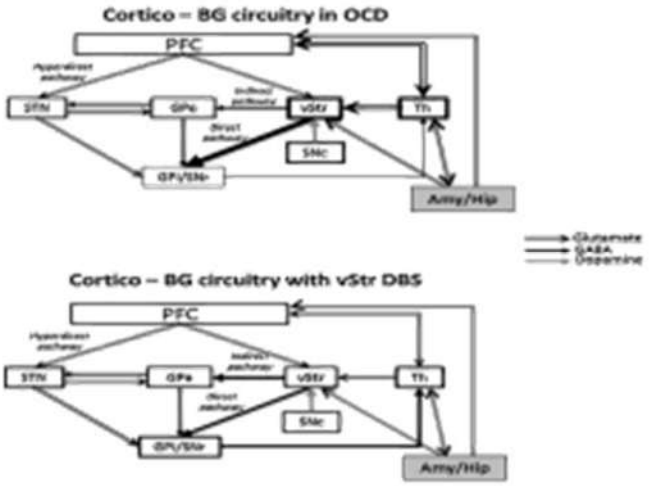


**Fig. 4.** Hypothetical cortico-BG circuitry functioning in obsessive compulsive disorder (OCD) before and after ventral striatum DBS. According to this model, obsessions would permanently reverberate in the loop formed by the stimulating activity of the amygdala/hypocampus to the thalamus and then to the ventral striatum. The original emotional information would be transmitted through the overactive direct pathway back to thalamus where it could become a compulsion through thalamo-cortical activation or return to ventral striatum or amygdala/hypocampus, closing the circuit. Amy, amygdala; GPe, external globus pallidum; GPi, internal globus pallidum; Hip, hippocampus; PFC, prefrontal cortex; SNc, substantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; vStr, ventral striatum (also as the nucleus accumbens); Th, thalamus.
Illustration adapted from Nambu (2011).

There is also a deficit of behavioral inhibition due to a misbalance between the direct and indirect BG pathways. Increase in the activity of the direct pathway, without the control of the indirect pathway, results in positive feedback where obsessive thoughts would permanently reverberate (Goodman et al., 2010) (Fig. 4). Abnormal activity in the amygdala and the hippocampus are linked to the anxiety generated by certain stimuli that often accompany the patient's urge to perform compulsive behaviors (Bourne et al., 2012; Kopell and Greenberg, 2008).

A number of DBS targets including the anterior limb of the internal capsule (Greenberg et al., 2006), ventral capsule/NAc (Do-Monte et al., 2013; Rodriguez-Romaguera et al., 2012), STN (Welter et al., 2011), and NAc (Denys et al., 2010) have been investigated for the treatment of OCD. DBS of the anterior limb of the internal capsule in OCD patients is proposed to influence activity of the nearby NAc which, in turn, alters activity in other brain areas, predominantly in limbic areas of the cortex, BG and its projections to the thalamus (Nuttin et al., 2003; Rauch et al., 2006; Wichmann and Delong, 2011; Okun et al., 2013). A double-blind cross-over study carried out by Denys et al. (2010) in which the NAc was targeted found a 25% improvement in OCD deficits and significant reductions in depression and anxiety. Interestingly, depression improved within seconds of stimulation, anxiety in minutes, obsessions in days and compulsions in months.

Some reports suggest that excessive connectivity between the striatum and prefrontal cortex is normalized with NAc DBS (Figee et al., 2013, 2014). A relatively small number of clinical studies have investigated the efficacy of DBS for OCD. These do not permit a sufficiently detailed hypothesis of how DBS may work to improve OCD deficits. However, it has been proposed that the mechanisms of action behind the therapeutic effects of DBS in OCD result from a complex combination of effects on the cortico-BG circuit as proposed for the mechanisms of DBS in PD discussed above.

### 3.4. DBS in major depression

Major depression disorder is one of the most severe and prevalent neuropsychiatric disorders and the most common cause of disability. It is as debilitating as coronary heart disease and more debilitating as diabetes mellitus or arthritis (Prince et al., 2007). DBS might be of some help to treat the nearly 30% of major depression disorder patients who are unresponsive to traditional antidepressants, behavioral therapy, vagus nerve stimulation and electroconvulsive therapy (Rush et al., 2006). To date, there is no consensus on which brain regions are responsible for the major depression disorder deficits. However, ablation and imaging studies have indicated some structures that might be involved in the pathophysiology of the disease: the cingulate cortical area 25 (Dougherty et al., 2003; Mottaghy et al., 2002); the anterior limb of the internal capsule and the NAc (Malone et al., 2009; Hauptman et al., 2008); the inferior thalamic peduncle (Jimenez et al., 2005); and the lateral habenula (Sartorius et al., 2010). Improvement of depression deficits has been reported in patients receiving DBS in some of these brain areas. Decreased blood flow in the medial and frontal orbital areas and in the hypothalamus has been observed in major depression patients with DBS in cortical area 25 (Lozano et al., 2008). Stimulation of the anterior limb of the internal capsule has been shown to result in activational changes in the ipsilateral striatum, medial thalamus, anterior cingulate and contralateral cerebellum (Baker et al., 2007), while stimulation of the NAc decreased metabolism in orbitofrontal and dorsolateral prefrontal cortex and amygdala (Bewernick et al., 2010). Although the number of available up-to-date clinical studies is relatively small, it has been speculated that DBS of the targeted nuclei may lead to activation or deactivation of adjacent white matter projections in other cortical and subcortical areas involved in mood regulation, which includes the limbic loop of the BG (Pandya et al., 2012). Data from a recent fMRI study of NAc DBS in a large animal (swine) has shown alterations in the ipsilateral prefrontal cortex, insula, cingulate and bilateral parahippocampal gyrus along with a decreased BOLD signal in the ipsilateral dorsal region of the thalamus (Knight et al., 2013). This large animal model may offer a new and effective approach for identifying the cerebral nuclei and brain structures involved in DBS treatment of intractable drug-resistant depression.

### 3.5. DBS in Tourette syndrome (TS)

TS is a neuropsychiatric disorder with childhood onset that manifests itself in repetitive, stereotyped, involuntary movements and vocalizations called tics (Kuhn et al., 2011; Tye et al., 2009). These tics reach a peak in adolescence but tend to alleviate in adulthood (Wichmann and Delong, 2011; Williams and Okun, 2013). Comorbidities can also be observed such as OCD, attention-deficit hyperactivity disorder, depression and psychosocial difficulties (Ludolph et al., 2012).

It has been postulated that an overactive thalamocortical system is responsible for TS deficits. However, the exact location within these pathways remains unclear (Singer and Minzer, 2003; Singer et al., 1993). Research has indicated that stimulation of various neural targets promotes amelioration of some of the deficits of TS, such as diminishing frequency of tics and improving comorbid psychiatric disorders. The main target areas proposed for DBS in TS are the thalamic centromedial/parafascicular nucleus (Savica et al., 2013), the motor and limbic portions of the GPi (Diederich et al., 2005; Ackermans et al., 2008), and the NAc (Kuhn et al., 2007).

A clinical study involving 18 refractory TS patients who underwent bilateral DBS in the thalamic centromedial/parafascicular nucleus reported decreased tics, self-injurious behaviors and anxiety (Servello et al., 2008). In this regard, a recent study investigating centromedial/parafascicular DBS in a large animal model supports

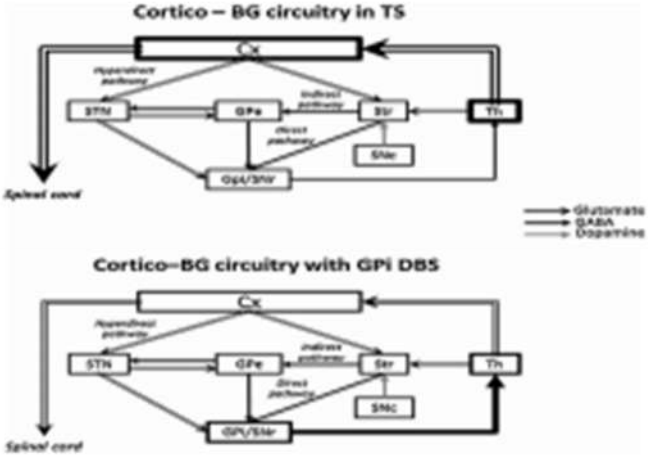


**Fig. 5.** Hypothetical cortico-BG circuitry functioning in Tourette syndrome (TS) before and after GPi DBS. Cx, cerebral cortex; GPe, external globus pallidum; GPi, internal globus pallidum; SNc, substantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; STN, subthalamic nucleus; Str, striatum; Th, thalamus.
Illustration adapted from Nambu (2011).

that thalamic DBS has an inhibitory effect in regions that contribute to impaired sensory-motor and emotional processing (Kim et al., 2013). Only more recently the GPi has also been considered as a DBS target to treat TS. Some studies have shown great efficacy of GPi DBS in reducing motor tics and comorbid psychiatric deficits (Welter et al., 2008; Williams and Okun, 2013). Saleh et al. (2012) observed amelioration of hyperkinetic states in TS patients under GPi DBS. They proposed that this was a result of inhibition of thalamic neurons that project to motor areas of the cortex, as described in Fig. 5.

## 4. Negative effects in DBS of the BG

DBS is an emerging treatment option to improve both motor disabilities and psychiatric symptoms observed in neuropsychological diseases, such as PD, OCD, and depression. However, negative effects have been described following electrode implantation and/or after long-term stimulation which may directly worsen DBS outcome. Relative to pharmacological treatment, DBS is substantially more intrusive as is any surgical procedure where technical devices are implanted into the brain. Moreover, these devices are constantly active and may differentially affect brains regions as the disease progresses and the overall structure of the brain changes (Woopen et al., 2013). Hence, DBS negative side effects may result from procedure-related complications, hardware implant and/or stimulation-related issues (Martinez-Ramirez et al., 2014).

### 4.1. STN DBS and GPi DBS side effects in PD patients

Stimulation of the motor portions of the STN and GPi has near equivalent benefits in improving parkinsonian symptoms of PD patients. The site for DBS is therefore chosen based on clinical aspects, such as the intention to reduce medication intake (STN DBS) or preexistence of dyskinesia or cognitive symptoms (GPi DBS), and the incidence of negative side effects associated to the stimulation of each of these targets (Williams and Okun, 2013). The most common procedure-related complications found for STN and GPi DBS are psychiatric side effects such as confusion and delirium. Moreover, these symptoms appear more prevalent in patients with STN DBS than GPi DBS (Videnovic and Metman, 2008). Also, surgical-site pain, low-risk intracerebral hemorrhaging (1–2%), and 10% risk of infection associated with the surgery or with the device have been reported for DBS regardless of the targeted nucleus (Weaver et al., 2009).

In a randomized controlled trial conducted by Weaver and coworkers (2009), patients undergoing DBS surgical intervention had a 3.8 times higher risk of experiencing serious side effects than patients on medical therapy. However, these serious side effects were resolved in 99% of cases by 6 months follow-up. They also reported other serious side effects that were device-related, such as lead migration and defective lead wire, and stimulation-related such as delusions and hallucinations (Weaver et al., 2009).

Stimulation of the STN may produce weight-gain (Deuschl et al., 2006; Videnovic and Metman, 2008), cognitive side effects (e.g., reduced verbal fluency and deficits in executive functions) (Stefurak et al., 2003; Funkiewiez et al., 2004; Parsons et al., 2006), and psychiatric symptoms such as depression (with suicide attempts or completed suicide), mania, anxiety, and apathy (Bejjani et al., 1999; Stefurak et al., 2003; Funkiewiez et al., 2004; Anderson et al., 2005; Borgohain et al., 2012). Adverse motor symptoms are also observed during STN stimulation adjustment or after long-term STN stimulation and include induction of paresthesias, severe dysarthria (Rodriguez-Oroz et al., 2004; Okun et al., 2013), and other parkinsonian-like effects such as bradykinesia, rigidity, swallowing difficulties, and worsening of gait or speech (Anderson et al., 2005).

GPi DBS presents relatively insignificant neuropsychiatric impairments compared to STN DBS (Borgohain et al., 2012). This is likely due to the more extensive separation of motor and non-motor functions in the GPi relative to the STN (Wichmann and Delong, 2011). However, weight gain, gait ignition failure, dysarthria (Videnovic and Metman, 2008), and mild visual field defects have been reported (Anderson et al., 2005). The apparent better "risk-benefit" of GPi DBS may lead this structure to be the preferred target to treat PD in the future.

### 4.2. GPi DBS side effects in HD patients

Stimulation of the GPi has been used to treat motoric symptoms in HD patients based on improvement of choreic dyskinesias of PD patients under GPi DBS (Anderson et al., 2005; Weaver et al., 2009). Although this improvement has been substantially observed, bradykinesia can be aggravated by GPi DBS depending on the stimulation frequency (Spielberger et al., 2012; Cislaghi et al., 2013; Gruber et al., 2014; Moro et al., 2004). Other motoric symptoms occasionally exacerbated in HD patients under GPi DBS are gait disturbance and dystonia of the feet (Gruber et al., 2014). Impairments in cognition (decline in executive functions and working memory) have been described, but they are likely related to disease progression, rather than from GPi stimulation solely (Fasano et al., 2008; Kang et al., 2011; Gruber et al., 2014). There are relatively few clinical data about the effects of GPi DBS in HD and critical parameters such as patient selection criteria and stimulation settings need to be carefully considered (Chen et al., 2013).

### 4.3. Limbic targets – DBS side effects in OCD, depression, and TS patients

Stimulation of limbic targets such as the anterior limb of the internal capsule/ventral striatum, the NAc, the ventral STN and limbic portions of the GPi, has improved psychiatric symptoms of compulsion, obsession, depression, anxiety, and motor and vocal tics (Wichmann and Delong, 2011). Nevertheless, DBS of the anterior limb of the internal capsule and the NAc have been shown to produce forgetfulness and word-finding difficulties (Mallet et al., 2008; Denys et al., 2010; Greenberg et al., 2013). In addition, several other psychiatric symptoms such as mania, fear, irritability, and anger may result from this DBS therapy (Shapira et al., 2006;

Denys et al., 2010; Haq et al., 2010). Furthermore, the occurrence of suicidal feelings has been reported in some patients with anxiety and depression under DBS treatment (Greenberg et al., 2013; Williams and Okun, 2013).

## 5. Emerging theories in BG mechanism

### 5.1. Role of the BG motor loop in action-selection

MSNs of the direct pathway are proposed to be in position to select actions encoded in the motor cortex, while MSNs of the indirect pathway can inhibit improper and/or concurrent actions. A clear means of understanding this process is by the cortico-BG circuitry backwards:

(i) Actions are encoded in motor areas of the cortex that include the area M1, the premotor cortex, and the supplementary motor cortex.
(ii) Cortical neurons encoding an action are selectively activated by neurons of the motor thalamus.
(iii) Thalamic neurons are under tonic inhibition of GABAergic neurons of the BG output stations, providing a distinct selective threshold prior to activation (e.g., the SNr/GPi).
(iv) In order to trigger the onset of an action, selective striatal MSNs of the direct pathway disinhibit a few selective thalamocortical neurons. At the same time, firing rates of a large number of MSNs of the indirect pathway and neurons of the hyperdirect pathway increase inhibition of the SNr/GPi on the other thalamocortical neurons, thus preventing initiation of the not selected actions.

Fundamentally, BG connectivity literature supports the model where activation of the direct pathway facilitates movements and activation of the hyperdirect and indirect pathways prevents movement (Nambu, 2011; Obeso et al., 2013). However, although there is extensive evidence that action-selection depends on the cortico-BG loop such evidence is still insufficient to clearly support that action selection occurs as proposed above. Some critical, though insufficient, pieces of evidence for each of the i–iv points of the the BG action-selection hypothesis are summarized below:

(i) It is largely unknown how motor actions are encoded in motor areas of the cortex. Recent evidence suggests that it is not as simple as the selective control of all muscles or joint movements as represented in Penfield's functional maps. Instead, it has been proposed that broader areas of the motor cortex encode stereotyped behaviors such as defensive movements of the arms or purposeful actions such as pointing to and reaching for a specific place (Schieber, 2001; Capaday et al., 2013).
(ii) Tracing (Asanuma et al., 1983; Holsapple et al., 1991; Flaherty and Graybiel, 1993) and probabilistic tractography (Hyam et al., 2012) evidence have consistently shown that neurons of the motor thalamus (e.g., central anterior/ventrolateral thalamus) receive hyperdepolarizing inputs from GPi neurons (Hoover and Strick, 1993) and send projections that can activate motor areas of the cortex (primary motor cortex, premotor cortex, and supplementary motor area). Single-unit recording studies in awake behaving monkeys show thalamocortical neurons presenting direction-related sustained change in activity during cue-guided motor action (Kurata, 2005), and before the onset of self-generated movements (Van Donkelaar et al., 1999). This suggests that these neurons play a role in initiation and execution preparation of instructed and spontaneous motor actions. Studies have also revealed that the nucleus ventralis lateralis, pars oralis (VLo) which is a part of the motor thalamus that receives projections from the BG, is the thalamic region presenting the highest percentage of neurons responding to active movements and that these neurons are organized in a somatotopic manner (Vitek et al., 1994, 1996). In addition, it has been shown that electrical microstimulation of the motor thalamus evokes movements in the contralateral limbs, trunk or face. Nearly 20% of the VLo neurons evoked movements when stimulated (Vitek et al., 1996). These findings are coherent with the hypothesis that activation of a subset of thalamocortical neurons can selectively trigger motor actions carried out by specific body parts.
(iii) The general model of the direct and indirect pathways controlling movement vs. non-movement predicts that when an animal is at rest the GPi/SNr neurons fire tonically at a high rate and that they decrease their activity just before a movement starts. It has been shown that most monkey GPi neurons present firing rates which vary from 20–140 spikes/s (Filion and Tremblay, 1991; Miller and DeLong, 1987); most of the time they present firing rates of approximately 60–80 spikes/s (DeLong, 1971; DeLong et al., 1985). A study by Oviedo et al. (2008) showed that electrical stimulation or infusion of glutamate into the dorsal striatum of rats produced a significant spike rate reduction in pallidal neurons. However, some studies did not confirm the prediction that GPi neurons present a pause before the onset of a motor action. Instead, these studies have shown that most pallidal neurons alter their firing rate after the action was selected, i.e., after the firing rates of neurons in the primary motor cortex and supplementary motor area (SMA) are increased (Crutcher and Alexander, 1990). In addition, most GPi neurons increased firing rate at movement onset (for a review see Goldberg and Bergman, 2011). This might happen because only a subset of GPi neurons pause to select a specific action while the majority increases firing to prevent concurrent actions. Indeed, most of the studies have shown movement related to decreased activity in a subpopulation of GPi neurons (Georgopoulos et al., 1983; Mitchell et al., 1987; Anderson and Horak, 1985; Turner and Anderson, 1997). Although less frequent a few GPi neurons fired before the movement onset. However, more problematic to the action-selection hypothesis is the fact that after inactivation of the GPi, as in pallidotomy or GPi DBS treatment of patients with PD, HD, or TS, patients maintain the ability to avoid improper actions (Turner and Desmurget, 2010).
(iv) The Alexander et al. (1986) and Albin et al. (1989) general model of the BG circuitry predicts that activation of the direct (D1+) or indirect (D2+) pathway facilitates or inhibits movement, respectively. Such predictions have been confirmed by several approaches. In a study by Kravitz et al. (2010) optogenetic control of MSNs of the direct and indirect pathways of mice expressing Cre recombinase under control of regulatory elements for the DA D1 and D2 receptors was achieved through Cre-dependent viral expression of channelrhodopsin-2 (ChR2) in the striatum. Bilateral activation of the indirect pathway resulted in increased freezing, bradykinesia and decreased initiation of locomotor episodes. This picture is also seen in PD patients and in animal models of PD (DeLong, 1990). These motor deficits result from decreased striatal DA and, consequently, reduced activation of the direct pathway and reduced inhibition of the indirect pathway by D1 and D2 DA receptors, respectively. Conversely, optogenetic activation of direct pathway MSNs increased locomotion and rescued deficits in freezing, bradykinesia and akinesia in D2-Cre mice pre-treated with 6-OHDA (Kravitz et al., 2010). Coherently, unilateral activation of D2 receptors in hemiparkinsonian rats caused misbalanced locomotor activation in the contralateral side of

the body causing turning behavior (Da Cunha et al., 2008; Dombrowski et al., 2010; Kravitz et al., 2010).

It is currently recognized that other important connections exist making the BG connectivity more complex than initially proposed by Alexander et al. (1986) and Albin et al. (1989). First, it is now understood that cortical neurons synapse not only onto the MSNs but also onto GABAergic interneurons in the striatum. Second, MSNs of the direct pathway are known to have branching collateral fibers that terminate in the GPe. Third, in addition to the striatum, cortical and subcortical inputs target the STN, which is now recognized as another important input station of the BG (see above hyperdirect pathway). Fourth, it is now recognized that the GPe projects not only to the STN but also sends branched collaterals to the GPi, SNr and SNc. Finally, instead of parallel cortico-BG loops, the striatum is now acknowledged to integrate functionally diverse information derived from cortical and subcortical areas (Bolam et al., 2000; Nambu et al., 2000; Miwa et al., 2001; Jaeger and Kita, 2011; Obeso et al., 2013; Surmeier, 2013; Ullsperger et al., 2014; Woolley et al., 2014). In addition, there is emerging evidence that challenges the view that activation of the direct pathway promotes movement and activation of the indirect pathway inhibits movement in a non-selective manner as one might deduce from the Alexander et al. (1986) and Albin et al. (1989) model of the BG circuitry. Contrary to this model, bilateral ablations of the main output station, the GPi, are not detrimental but rather therapeutic to motor deficits in BG diseases such as PD and dystonia.

Alexander et al. (1986) and Albin et al. (1989) model of movement/non-movement mediated by the direct/indirect pathways has also been challenged by recent optogenetic studies and by studies based on optical fiber recordings. These studies have shown that while specific motor actions are carried out, both the direct and the indirect pathways are activated concomitantly (e.g., Cui et al., 2013).

Based on evidence that some MSNs of the primate putamen and rodent dorsolateral striatum are activated by sensory and motor stimulation of the same body part and that they increase their firing when an object projects to that body part (see below), it has been proposed in the mosaic of broken mirrors model (MBMM) that some MSNs can trigger movement of specific body parts toward specific objects and other MSNs can initiate locomotion to specific places (Fig. 6)(Da Cunha et al., 2009, 2012). This means that all neurons of the direct or indirect pathways do not simply act as a switch between movement and non-movement. Rather, the MBMM considers that these neurons form an action-selection mechanism with a great number of channels, each being able to start or prevent specific actions. While interpreting the above-mentioned data under the logic of the MBMM, it is important to note that the MBMM does not predict activation of most MSNs of the direct pathway at the onset of a motor action as the general model of the BG does (Alexander et al., 1986). Instead, the MBMM predicts that selection of a motor action depends on activation of a few specific MSNs of the direct pathway and inhibition of the few MSNs of the indirect pathway that inhibits that specific action. It also requires activation of a large number of MSNs of the indirect pathway that inhibit initiation of the concurrent actions. Such predictions are difficult to be tested because they require recording the activation of only a few neurons of the direct pathway among a huge population of the remaining neurons that remain silent.

Though collecting this type of evidence is difficult, there is some evidence that supports the MBMM. Optogenetic studies investigating D1-Cre and D2-Cre mice expressing ChR2 in the dorsolateral striatum showed that unilateral activation of D1+ MSNs at a decision-making point in a nose-poke reinforcement-learning task shifted the response toward the contralateral side while activation of D2+ MSNs shifted the response toward the ipsilateral side (Tai et al., 2012). Without activation the same mice presented right/left responses according to their previous reward history. These findings are in agreement with the MBMM in that selective MSNs of the direct pathway can trigger motor actions directed to specific places. An additional study revealed that stimulation of D1+ MSNs in the dorsomedial striatum promoted place preference, while stimulation of D2+ MSNs did not promote place preference or place aversion (Kravitz et al., 2012).

A more recent study by Cui et al. (2013) challenged the general prediction based on the Alexander et al. (1986) and Albin et al. (1989) model according to which the MSNs of the direct pathway are expected to be active just before movement initiation and the MSNs of the indirect pathway are expected to be active when movement stops. They used Cre-dependent viral expression of a calcium indicator in the dorsal striatum of D1-Cre and A2A-Cre to monitor neural activity in MSNs of the direct and indirect pathways, respectively. Time-correlated single-photon counting registered transient increases in activity of both direct and indirect pathways just before initiation of a motor action. These results can be explained by the MBMM as reflecting the activation of a few MSNs of the direct pathway to choose and initiate motor action and activation of the MSNs of the indirect pathway to prevent the initiation of concurrent actions.

The MBMM is also supported by evidence correlating activation of MSNs in response to the approach and/or object touch in nonhuman primates (Graziano and Gross, 1993) and rats (West et al., 1990; Carelli and West, 1991). The same studies showed correlation between the firing of specific MSNs of the nonhuman primate putamen or the rat dorsolateral striatum and passive or self-generated movements of specific body parts.

Causal correlations between activation of MSNs in the dorsal striatum and motor action onset have been provided by old studies showing that electrical microstimulation in different regions of the nonhuman primate putamen evokes movement of specific body parts (Alexander and Delong, 1985a,b). These studies also suggest redundancy in the representation of body parts in the striatum as proposed by the MBMM, because they showed that stimulation at different depths of the putamen evoked movement of the same body part, as if MSNs encoding the same body part were organized in columns. The main problem with this evidence is that it does not discard the alternative explanation that such movements resulted from antidromic stimulation of the motor cortex neurons that project to the striatum. The same cannot be said about the evidence provided by Pisa (1988) showing that neurotoxic lesions of the rat lateral striatum caused severe and chronic impairment of tongue and forelimb reach movements.

### 5.2. *Roles of the BG associative and limbic loops in cognition and affect*

In addition to motor control regulation through the motor loop, the BG is also involved in some non-motor aspects of behavior (Leisman et al., 2014). There are other loops connecting cortical areas to function-related regions in the BG. More specifically, these loops involve the prefrontal and limbic cortices through which the BG is thought to play a role in cognitive and emotional functions, respectively (Yin and Knowlton, 2006). The cortico-BG associative loop originates in the dorsolateral prefrontal cortex and projects to the head of the caudate nucleus and to the rostral part of the putamen anterior to the anterior commissure. This prefrontal territory in the striatum projects to the rostral GPe, to the dorsal parts of the caudal GPe and GPi, and to the rostromedial SNr. Projections from these structures have their terminals in the ventral anterior and medial dorsal thalamic nuclei, which in turn project back to the dorsolateral prefrontal cortex (Alexander et al., 1986; Voorn et al., 2004; Nambu, 2011; Leisman et al., 2014). This associative loop is

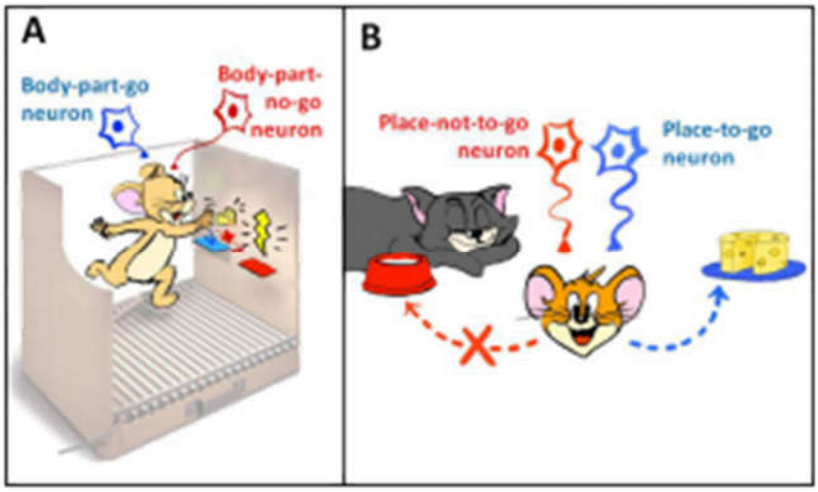


**Fig. 6.** Cartoon illustrating two postulates of the mosaic of broken mirrors model (MBMM). (A) Activation of a few striatal "body-part-go cell" selects and initiates a motor action of a body part toward an object. (B) Activation of a few striatal "place-to-go cell" selects and initiates the approach to a specific place; activation of a "place-not-to-go cells" prevents approaching to a place.

implicated in "executive functions" which include attention, spatial orientation and in cognitive "working memory" tasks (Cagliori et al., 2013).

The selection of an action, among many possibilities stored along the frontal cortex, would be driven by the goal and/or by an intentional signal represented in the prefrontal cortex projections to the striatum (Cagliori et al., 2013; Thill et al., 2013). Within the BG circuitry, information originating from various sources is topographically filtered and supported by prefrontal cortex signals in a manner that properly selects the correct action. Damage to areas forming this associative loop is associated with a variety of behavioral abnormalities related to these cognitive functions such as attention-deficit and hyperactivity disorder, OCD, schizophrenia and autism (Leisman et al., 2014).

The limbic loop has its origin in the pre-limbic, infra-limbic and lateral orbitofrontal cortices, along with the hippocampus and amygdala. Projections from these structures reach the ventromedial caudate nucleus, including the NAc, and the ventromedial part of the pre-commissural putamen. The ventral pallidum, the rostral part of GPe and the medial GPi/SNr receive those striatal projections and, in turn, projects to the paramedian portion of the medial dorsal nucleus of the thalamus and then back to the limbic regions in the cortex (Haber et al., 1990; Ono et al., 2000; Nakano et al., 2000; Nambu, 2011).

Connectivity between the hippocampus and the NAc also provides some support for the MBMM hypothesis that "place-to-go" cells might exist in the NAc. The NAc receives afferents from the hippocampal formation, a region implicated in mapping the animal's location and in spatial memory (Groenewegen et al., 1987; Van Groen and Wyss, 1990; Witter et al., 1990). In addition, the NAc receives a dopaminergic projection from the VTA which is known to carry information about motivational value and salience (Bromberg-Martin et al., 2010). Furthermore, the NAc projects to mesencephalic areas related to locomotor functions (Voorn et al., 2004). These connections put the NAc in a strategic position to select places to go based on expected outcomes (Redish and Touretzky, 1997).

The NAc is modulated by DA and is known as the main brain area that integrates emotional and cognitive information into actions known as motivated behaviors (Berridge and Robinson, 1998; Ono et al., 2000). In general, the limbic loop is involved in the selection of final reward-guided goals based on motivational aspects of the stimuli. Apathy, irritability, social and emotional inability, and lack of empathy are some of the symptoms present in neuropsychiatric disorders associated with damage to areas in the limbic loop such as OCD and depression (Leisman et al., 2014).

The functionality of each of the three cortico-BG loops is given by a hierarchically-based flow of information according to their respective roles in the action-selection process (Yin and Knowlton, 2006). The sensorimotor loop is proposed to control motor actions oriented by decisions made in the current context of the animal. Associative loop-driven decisions are proposed to be guided by motivational aspects of reward processed by the limbic loop. At the highest level, the NAc, enriched with motivational value information provided by other subcortical structures (e.g., amygdala, hippocampus), is proposed to help the limbic and the associative cortex to select the more biologically relevant goals. At the lowest level, the dorsolateral striatum is proposed to selects the more adequate motor action encoded in the pre-motor and primary motor cortices (Haber et al., 2010; Cagliori et al., 2013). Such selection depends critically on DA alterations in the striatum as reviewed below.

### 5.3. *Role of NAc DA in motivation*

DA release in the NAc is related to motivation and drive states. It has been shown that high-arousal states are induced by DA release in the NAc shell/olfactory tubercle (Ikemoto and Panksepp, 1999; Hebb, 1955; Ikemoto, 2002, 2007). This state is particularly important to an organism's survival because it promotes approach behavior to unconditioned stimuli (USs) and conditioned stimuli (CSs) (Parkinson et al., 1999). Such affective and drive states modulated by the NAc DA are referred to as "action-arousal." The limbic system supplies midbrain DA neurons with information about environmental stimuli that are important for self-preservation and procreation; this affects DA release in the NAc in a manner that motivates or "energizes" actions related to self-preservation (e.g., eating, drinking, mating, hiding from predators) (MacLean, 1990; Ikemoto, 2007). This DA system is sensitized by regulatory imbalances (such as hunger) and is activated when animals detect incentive stimuli (Ikemoto, 2007). Another important function of DA release in the NAc shell/olfactory tubercle is acquisition and consolidation of stimulus-outcome associations (CS-US) (Da Cunha et al., 2012). Later on, when DA is released in the NAc core and lateral parts of the NAc shell/olfactory tubercle, the organism selects

previously learned behaviors through CS-US associations (Ikemoto, 2007).

### 5.4. Role of striatal DA in associative learning

Subjects' motor behaviors are driven by changes in unconditioned responses (URs) to biologically relevant stimuli (i.e., USs such as food, sex, and painful or dangerous situations). Motor behavior is also driven by expectations about appetitive and aversive outcomes (USs) based on predictive cues (i.e., CSs). The predictive value of different CSs is learned through classic (Pavlovian) conditioning (Pavlov, 1927; Rescorla, 1988; Li and McNally, 2014). In addition, behavior is also driven by habitual (automatic) responses to neutral stimuli and by goal-directed actions, both learned through instrumental (operant) conditioning (Yin and Knowlton, 2006; Domjan, 2010). During instrumental conditioning learned under appetitive motivation, early responding appears to be goal-directed and slowly progresses to habitual responding (Mishkin et al., 1982; Knowlton et al., 1996; Packard and Knowlton, 2002). Conversely, during extinction (when a response is no longer rewarded), goal-directed responding of appetitive motivated actions rapidly fade while habitual responses persist for a relatively longer time (Devan and White, 1999; Yin et al., 2006; Balleine and O'Doherty, 2009).

An action is considered to be goal-directed if it is sensitive to outcome devaluation; for example, by pre-feeding the animal (Dickinson and Balleine, 1994). In contrast, stimulus-response (S-R) habits are considered to be insensitive to outcome devaluation, being performed not with an intended goal but as an automatic response to the stimulus that precedes the response's outcome (Yin et al., 2008). Therefore, the memory traces of habits are the S-R associations, meaning that, after a habit is acquired, the motor response is automatically triggered by the neutral stimulus, independent of the outcome. In contrast, the memory traces of goal-directed actions are the action-outcome (A-O) associations, meaning that goal-directed actions are selected based on expectation of a rewarding (e.g., appetitive) outcome (Dickinson and Balleine, 1994). Another relevant element in selection of motor responses is related to interaction between classical and instrumental conditioning. This association activates an emotional state that motivates the instrumental behavior where the emotional state is assumed to be either positive or negative in valence, depending on the hedonic property of the US. Conditioned cues that predict relevant stimuli can greatly enhance instrumental responding. This process is known as Pavlovian-to-instrumental transfer (PIT) (Lovibond, 1983). PIT is highly influenced by DA activity (Dickinson et al., 2000; Wyvell and Berridge, 2000; Niv et al., 2006; Belin et al., 2009).

There is compelling evidence that the striatum and other regions of the BG play a role in reward-motivated action selection learning (Schultz et al., 1997; Alderson et al., 2004; Yin et al., 2004, 2006; Da Cunha et al., 2009; Wilson et al., 2009; Haber and Knutson, 2010; Redgrave et al., 2010; Flagel et al., 2011; Da Cunha et al., 2012; Dezfouli and Balleine, 2012; Kravitz et al., 2012; Liljeholm and O'Doherty, 2012). In addition, the striatum and other regions of the BG play a role in learning how to select responses instrumental to avoid aversive stimuli (Wadenberg, 2010; La Lumiere et al., 2005; Manago et al., 2009; Darvas et al., 2011; Dombrowski et al., 2013; Wendler et al., 2014). Striatal DA also plays a key role in aversively driven associative learning (Schultz, 1997; Da Cunha et al., 2009; Niv et al., 2006; Bromberg-Martin et al., 2010; Da Cunha et al., 2012; Fiorillo et al., 2013; Schultz, 2013; Lak et al., 2014).

Strong evidence exists that acquisition of S-R and action-outcome (A-O) memory traces depend on strengthening synapses between cortical or limbic neurons with MSNs. These cortical neurons encode the stimulus or the outcome and the striatal MSNs trigger the proper motor response/motor action. Furthermore, many studies suggest that selection of USs occurs in the medial NAc shell, CRs in the NAc core, S-R habits in the dorsolateral striatum (putamen in primates), and goal-directed actions in the dorsomedial striatum (head of caudate nucleus in primates) (Wendler et al., 2014; for a review see Ikemoto, 2007; Da Cunha et al., 2012). Subregions of the dorsal striatum and NAc are also known to play different roles in learning appetitive-motivated actions (Yin et al., 2004; Yin and Knowlton, 2006; Yin et al., 2006; Redgrave et al., 2010; Dezfouli and Balleine, 2012).

The dorsomedial striatum and the dorsolateral striatum of rodents are thought to be necessary for selection of goal-directed and S-R habits learned under appetitive reinforcement (Yin et al., 2006; Ikemoto, 2007). Although this is well established for appetitive motivated learning, it is not clear whether the same striatal regions play equivalent roles in aversively-motivated learning. There is also evidence that the NAc core plays a role in Pavlovian conditioning (Riedel et al., 1997; Ikemoto and Panksepp, 1999; Berridge, 2012; Bossert et al., 2012; Klucken et al., 2012), but there is some uncertainty about the specific roles that the NAc core and other limbic structures have in Pavlovian conditioning (for a review see Da Cunha et al., 2012).

Potentiation of corticostriatal synapses depends on three events happening concomitantly: depolarization of the pre- and post-synaptic membranes of the involved neurons and phasic release of DA (for review see Da Cunha et al., 2009). Phasic release of DA is evoked by appetitive USs that are better than expected (positive prediction error), CSs that are predictive of appetitive USs and salient stimuli (independent of their rewarding or aversive nature) (Ramnani et al., 2004; Schultz, 2007; Bromberg-Martin et al., 2010; Berridge, 2012). Phasic DA drops in extracellular DA concentrations happen when something rewarding does not occur as expected and when something less rewarding than expected happens (negative prediction errors) (Schultz et al., 1998; Tobler et al., 2003). Different subpopulations of midbrain DA neurons respond to aversive stimuli with phasic increases or phasic decreases in DA release, respectively (Ljungberg et al., 1992; Mirenowicz and Schultz, 1996; Matsumoto and Hikosaka, 2009; Brischoux et al., 2009; Budygin et al., 2012; Ilango et al., 2014). This supports the view that actions or responses to neutral stimuli that result in better than expected outcomes promote phasic release of DA that, in turn, strengthens the S-R and response outcome (R-O) memory traces. This increases the likelihood that a response will be selected as a result of coming in contact with the same stimulus or that an action will be selected. In contrast, phasic decrease of DA release is known to weaken the synapses between the cortical and striatal neurons encoding S-R and A-O associations. This drives avoidance behaviors in situations in which the same stimulus is presented or the subject wants to avoid an aversive outcome (for review see Da Cunha et al., 2009; Da Cunha et al., 2012).

Strong evidence supports the view that activation of DA neurons in the VTA is critical for associative appetitive learning (Cheng et al., 2003; Nicola et al., 2005; Day and Carelli, 2007; Ikemoto, 2007; Berridge and Kringelbach, 2013; Ouachikh et al., 2013; Steinberg et al., 2013; Steinberg and Janak, 2013). Moreover, it has been shown that not only VTA, but also SNc DA neurons are implicated in unconditioned and conditioned responses to appetitive stimuli. Mice bar-press to stimulate either SNc DA neurons (Rossi et al., 2013) or dorsal striatum neurons expressing D1 receptors (Kravitz et al., 2012). This suggests that DA release in the dorsal striatum has reinforcing properties. A recent study presented strong evidence that activation of DA neurons in the SNc are as critical to appetitive and aversive associative learning as the DA neurons of the VTA (Ilango et al., 2014). The latter study showed that optogenetic activation of DA neurons of the SNc sustains conditioned-place preference.

Aversive-driven learning has also been shown to depend on striatal DA. Optogenetic inactivation of DA neurons in the SNc or VTA induces conditioned-place aversion (Ilango et al., 2014). Studies have demonstrated impaired conditioned-avoidance learning in rats with SNc lesions induced by MPTP (Da Cunha et al., 2001; Gevaerd et al., 2001a,b; Perry et al., 2004; Bortolanza et al., 2010) or 6-OHDA (Cooper, 1973) and in rats with dorsal striatum lesions (Wendler et al., 2014), dorsal striatum DA depletion (Rane and King, 2011), and intra-dorsolateral striatum infusion of D1 (Wietzikoski et al., 2012) or D2 DA receptor antagonists (Boschen et al., 2011). A recent microdialysis study by Dombrowski et al. (2013) found that during conditioned-avoidance learning, DA release in the striatum increased only in the first trials in which rats avoided footshocks but not after they had learned the task. However, no alteration in DA release was observed when the footshocks were presented in an unpredictable, unavoidable and inescapable manner. In contrast, SNc-lesioned rats did not learn the task. Another recent study showed that inactivation of the tyrosine hydroxylase gene in the dorsal striatum, and consequent lack of DA synthesis, impaired the ability of mice to learn conditioned-avoidance responses (Darvas et al., 2011). Impairment in rats with SNc lesions has also been observed in the cued- and working-memory version of the Morris Water maze (Bellissimo et al., 2004; Da Cunha et al., 2001; Ferro et al., 2005; Miyoshi et al., 2002).

The understanding that striatal DA is involved not only in motor control, but also in action-selection, learning and memory, and affective states is critical to explain and treat the non-motor symptoms of BG diseases such as PD (Conte et al., 2010), drug addiction (Wanat et al., 2009), bipolar disorder (Cousins et al., 2009), schizophrenia (Carlsson et al., 2004), attention deficit/hyperactive disorder (Del Campo et al., 2011), OCD, and TS. Deficits in aversive-driven learning related to the inability of striatal DA to encode negative-prediction errors may also explain why depression and gambling is much more prevalent in PD (Rosa et al., 2013).

## 6. New approaches for BG-DBS research

### 6.1. Electrophysiological signal as a feedback for DBS

The DBS field has advanced at a rapid pace and supporting technology to improve current use has evolved with it. Advanced DBS systems such as those that rely on real-time feedback from electrophysiological signals, provide the first generation of implantable devices that identify symptomatic and healthy brain states (Gunduz et al., 2014). These devices include the Medtronic Activa PC + S (Ryapolova-Webb et al., 2014) and Neuroscan RNS (Sun et al., 2008). With the understanding that changes in neuronal firing frequency occur in a pathogenic state, this approach shows potential in many disorders that are currently treated with DBS (Gunduz et al., 2014). Exaggerated beta band (8–35 Hz) synchrony in STN local field potentials occurs in PD patients, which is attenuated during therapeutic DBS, and returns when stimulation stops (Kuhn et al., 2008; Barberini et al., 2009). Other studies have shown beta activity in the motor cortex (Whitmer et al., 2012), and phase-amplitude coupling (PAC) between beta and high gamma (>70 Hz) (López-Azcárate et al., 2010), observed in PD, are also potential targets for closed-loop DBS (de Hemptinne et al., 2013). Electrophysiological measurements may also hold promise in DBS for the treatment of psychiatric disorders. For example, symptom provocation in the setting of OCD has been correlated with increased low frequency (2–5 Hz) activity over the frontal cortex (Pogarell et al., 2006), and DBS of the ventral striatum has been shown to attenuate these low frequency oscillations (Figee et al., 2013).

Although electrophysiological feedback is a promising modality for a closed-loop DBS device, these potential feedback signals could also change during rest and/or voluntary movements, therefore limiting their use as a sole biomarker (Miller et al., 2012; de Hemptinne et al., 2013). Additionally, frontal low frequency oscillations, while implicated in OCD, are correlated with normal goal-directed behavior (Knyazev, 2007). Preliminary trials will demonstrate the efficacy of these first generation neural stimulation feedback devices, which may provide direction in development of future generations of closed-loop DBS systems (Gunduz et al., 2014).

### 6.2. Electrochemical methods to determine neural circuitry underlying DBS

The use of in vivo electrochemical methods to investigate the neural circuitry underlying DBS makes it possible to circumvent the assumptions that are necessary with the use of alternative methods. The electrochemical procedures FSCV and fixed potential amperometry (FPA) offer the best temporal resolution of all in vivo electrochemical methods to date (5–10 samples/s for FSCV; 10k samples/s for FPA) (Kimble et al., 2009; Venton et al., 2002).

In Fig. 7, FPA in combination with carbon-fiber microelectrodes (CFM) permitted quantitative detection of striatal DA overflow (efflux) evoked by electrical stimulation of excitatory inputs to DA cells in the SNc such as those originating in the hindbrain PPT (Forster and Blaha, 2003). Overflow of a synaptic transmitter is referred to as "release" throughout this section. Dommett et al. (2005) have shown that FPA can be used to monitor striatal DA release in response to natural stimuli such as light pulses. Visual stimuli evoked increases in striatal DA release via a direct input to the superior colliculus from the retina that, in turn, activated midbrain dopaminergic cells at a short latency. Collectively, these studies have confirmed the utility of fast electrochemical recording procedures to measure DA transmission driven by polysynaptic pathways such as those we have proposed to mediate DBS-evoked DA neurotransmission (Lee et al., 2006, 2009; Shah et al., 2010).

With respect to quantifying glutamate release using FPA, recent development of enzyme-coated platinum microelectrodes based on work by Hu et al. (1994) have shown a high degree of reliability as a selective, sensitive and rapidly responding glutamate sensor in vivo (Wilson and Gifford, 2005). This glutamate sensor system provides an additional quantitative measure of potential glutamatergic transmission in the dorsal striatal complex circuitry interfacing with SNc DA cells. Our preliminary studies have shown that electrical stimulation can evoke frequency- and intensity-dependent increases in glutamate release recorded locally at the site of stimulation (STN) using these procedures (Fig. 7B–E).

In agreement with the hypothesis that STN DBS improves motor symptoms of PD by striatal DA release, several animal studies have shown that STN DBS increases striatal DA levels. For example, in vivo microdialysis studies have shown that STN DBS increases the striatal DA metabolites (DOPAC and HVA) and tyrosine hydroxylase activity in normal and 6-OHDA lesioned rats (Meissner et al., 2001, 2002, 2003; Paul et al., 2000). With one exception (Bruet et al., 2001), STN DBS-evoked increases in striatal DA dialysate could not be detected without first inhibiting DA reuptake with nomifensine and stimulating for prolonged durations (20 min) (Meissner et al., 2003). In vivo monitoring of slow (minutes-hours) changes in DA release is easily accomplished using these conventional microdialysis techniques. However, analysis of more rapid changes in DA release in the absence of DA reuptake inhibition that may result from STN DBS requires an equally rapid 'real-time' detection and monitoring system such as FSCV and FPA. For detection, sensitive CFM and enzymatic sensors used with these methods permit submicromolar monitoring of central DA and glutamate release. As

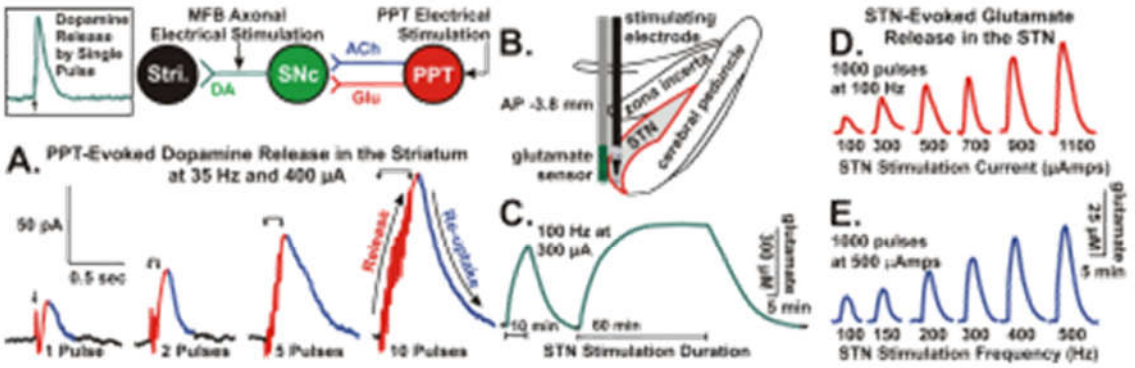


**Fig. 7.** (A) DA release in the striatum (Stri.) of urethane anesthetized rats evoked by 1 to 10 pulses of electrical stimulation of pedunculopontine tegmental nucleus (PPT) glutamatergic and cholinergic projections to substantia nigra pars compacta (SNc) DA cells. Note that the increase in DA release is time locked to the stimulation (pulse artifacts are superimposed on the rising portion of the signal) and the recovery to baseline is a reflection of clearance of DA mainly via presynaptic re-uptake. INSET: rapid response of DA to stimulation of DA axons in the medial forebrain bundle (MFB) illustrating that the relatively slower PPT evoked response is trans-synaptically mediated. Glutamate release in the STN evoked by electrical stimulation of the STN at various durations (C), intensities (D), and frequencies (E). (B) Positioning of a glutamate sensor adjacent to a bipolar stimulating electrode in the STN (see Lee et al., 2007).

such, to establish the functional characteristics of the dorsal striatal complex circuitry, we and others have utilized electrochemical recording procedures established for reliable monitoring of DA and glutamate release and reuptake in dopaminergic and glutamatergic terminal sites in the brain in vivo (Blaha and Phillips, 1996; Michael and Wightman, 1999; Suaud-Chagny, 2004; Wilson and Gifford, 2005).

Our neurochemical studies have focused on determining the functional consequences of STN DBS in terms of rapid changes in striatal DA release elicited by relatively brief and prolonged electrical stimulation of the STN in the urethane anesthetized rat. Brief STN stimulation (15 pulses at 300 µA and 50 Hz) resulted in a stimulus time-locked increase in striatal DA release as measured by FPA in combination with CFMs (Fig. 8). The selectivity of the recording microelectrode to STN stimulation-evoked DA release

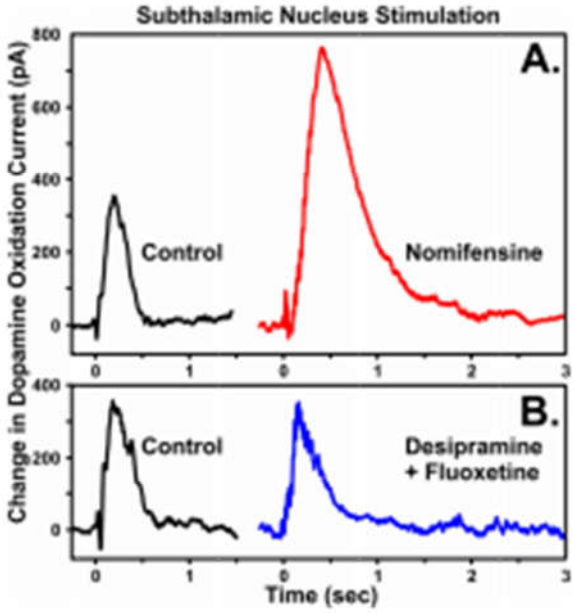


**Fig. 8.** Striatal DA is increased with brief STN stimulation. The selectivity of the response was confirmed by (A) systemic injection of the DA reuptake inhibitor nomifensine (red line), which resulted in a significant increase in DA oxidation current, compared to (B) serotonin (fluoxetine) and norepinephrine (desipramine) reuptake inhibitors (blue line) which did not significantly increase the STN stimulation-evoked response. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was confirmed by systemic injection of the DA reuptake inhibitor nomifensine, which resulted in a significant increase in DA oxidation current, compared to serotonin (fluoxetine) and noradrenaline (desipramine) reuptake inhibitors, which did not alter the STN stimulation-evoked striatal response (Lee et al., 2006). These results support the hypothesis that STN DBS results in quantifiable striatal DA release. However, as these studies were performed in rats with intact SNc dopaminergic neurons, it is crucial to perform systematic measurements in an animal model of PD such as 6-OHDA lesions, where the SNc neurons are selectively and partially destroyed.

In relation to an animal model of PD, our preliminary results have shown that, in combination with L-DOPA, repetitive stimulations in 6-OHDA lesioned rats are capable of facilitating DA release to levels comparable to that seen with stimulation in intact rats and are consistent with recent findings that high-frequency stimulations modulate the action of L-DOPA (Oueslati et al., 2007). Microinfusion of the neurotoxin 6-OHDA onto DA cell bodies in the SNc resulted in the selective degeneration of dopaminergic cells in that region (Ferro et al., 2005). As shown in Fig. 9, compared to intact rats, 6-OHDA lesions resulted in rats exhibiting a marked, but clearly detectable, attenuation in medial forebrain bundle stimulation-evoked DA release in the striatum (16.4 ± 8.3% of 100% intact responses) as monitored using FPA in combination with CFMs. Most significantly, compared to intact animals receiving a systemic injection of saline, systemic administration of a relatively low dose of L-DOPA to lesioned rats resulted in a near complete recovery in the magnitude of the evoked DA responses (84.87 ± 16.22% of 100% intact responses at 30 min post-injection). Since L-DOPA increased the DA response in the lesioned animals to the statistical equivalent of the non-lesioned (saline-treated) animals, it can be inferred that on-line FPA or FSCV would be capable of (1) detecting depleted extracellular levels of DA in the striatum and (2) enhancing these levels in response to L-DOPA treatment across various dose ranges in PD patients (Blaha et al., 2008). These data highlight the relevance of monitoring dopaminergic transmission during STN DBS; these data also provide a framework for the development of a closed-loop neuroprosthesis with chemical sensing feedback and neuromodulation to maintain neurotransmitter levels consistent with optimal therapeutic efficacy.

Stimulation frequencies in the range of 37 to 75 Hz and current intensities in the range of 200–600 µA evoked maximal DA responses in the striatum (Fig. 10A and B) (see Lee et al., 2006). More prolonged STN stimulation evoked a DA response that peaked within 15–20 applied pulses and fell off to ~30% of pre-stimulus baseline levels despite continuous stimulation.

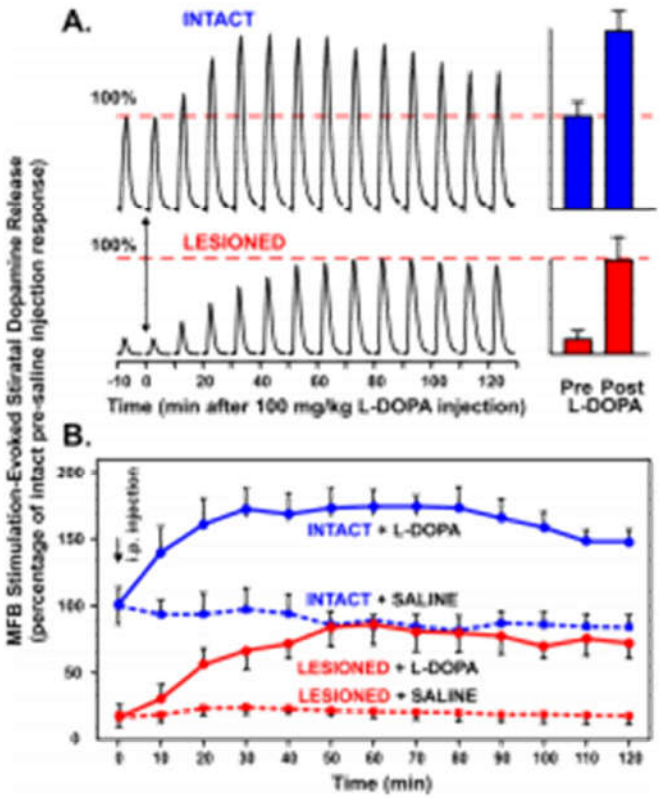


**Fig. 9.** (A) Representative example of medial forebrain bundle stimulation-evoked (20 pulses at 100 Hz applied every 10 min) striatal DA release in a urethane anesthetized intact rat and a rat sustaining neurotoxic 6-OHDA lesioning of the nigrostriatal dopaminergic pathway before and following systemic injection of L-DOPA (100 mg/kg i.p.). Note the recovery of stimulated DA release to 100% baseline levels of evoked striatal DA release following administration of L-DOPA in lesioned animals. (B) Mean ± SEM time courses of effects of L-DOPA injections, compared to saline administration, on striatal DA release in intact and lesioned rats before and following systemic injection of L-DOPA. Solid and dashed blue lines: intact mice that received L-DOPA and saline, respectively. Percentage changes refer to intact pre-saline treated mice.

Stimulation dorsomedial to STN, corresponding to a portion of the medial forebrain bundle containing ascending nigrostriatal dopaminergic axons, resulted in an increase in striatal DA release that plateaued 5 s into stimulation (Fig. 10C). These results suggest that DBS in PD patients typically applied to the STN and adjacent regions increases brain extracellular DA levels, but also indicate that the pattern and magnitude of DA release varies significantly depending on the site and nature of stimulation. This latter finding has therapeutic implications for the site and pattern of stimulation in PD patients, which so far have not been fully explored.

In addition to DA, we have also demonstrated our ability to measure in vivo real-time oxygen, ADO, histamine, and serotonin release with CFMs and glutamate release with an enzyme-linked biosensor during DBS (Lee et al., 2007; Agnesi et al., 2009; Bledsoe et al., 2009; Chang et al., 2012a; Shon et al., 2010a,b). We have also shown that we can use the Mayo Clinic Engineering Department developed Wireless Instantaneous Neurotransmitter Concentration Sensing (WINCS) system to electrochemically codetect in vivo changes in ADO and DA concentrations in small and large animal models of DBS (Shon et al., 2010a). More importantly, our results (Shon et al., 2010b) have shown that STN DBS elicits DA and ADO release in the caudate nucleus of isoflurane anesthetized pigs. Additionally, we examined striatal DA release evoked by STN DBS in awake monkeys. We identified a site-dependency of DA release by stimulating at multiple points along a trajectory passing through the thalamus and STN. Greater DA release was observed when the stimulating electrode was within the dorsal region of the STN. Our results showed that the amount of DA release depends critically on the location of the stimulating electrode (Gale et al., 2013).

Our pig experiments have demonstrated that STN DBS elicits DA and ADO release distally in the caudate nucleus, shown in Fig. 11 (see Shon et al., 2010b). For these experiments we implanted a single CFM into the caudate nucleus of isoflurane (1%) anesthetized pigs; FSCV recordings were taken during brief (2 s) electrical stimulations of the human Medtronic 3389 DBS electrode implanted in the ipsilateral STN. With high-frequency stimulation (140 Hz), ADO and DA were clearly released (Fig. 11A). The temporal patterns and magnitude of DA (black line) and ADO release (1st peak blue line and oxidation product 2nd peak red line) evoked by STN DBS are shown in Fig. 11B. The voltammograms obtained with WINCS in the pig revealed one peak at +0.6 V for DA oxidation and two oxidation peaks for ADO (1st peak near +1.5 V and 2nd peak near +1.0 V), as shown in Fig. 11C and D, respectively. Our now established pig model has permitted testing of our human neurochemical recording electrodes, as well as study of distal neurotransmitter release by STN DBS.

From knowledge and experience gained from tests conducted in our large animal (pig) experiments, we have successfully used WINCS to monitor DA and ADO release in the hippocampus of human patients undergoing resective surgery for medically intractable epilepsy (Van Gompel et al., 2014). A CFM was implanted 5 μm into the temporal lobe cortical surface of each patient for 15 min during intraoperative electrocorticography (ECoG) and 10 min of FSCV recordings prior to resection. One, out of ten patients tested, expressed a lateral neocortical seizure in which ADO release was observed and this was time-locked with the onset and termination of the seizure. These findings support a

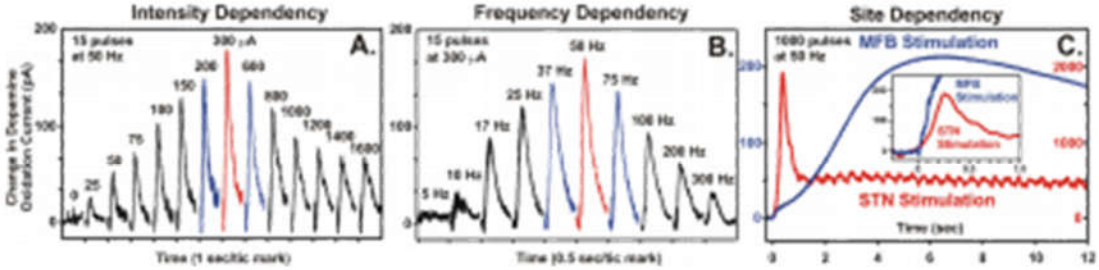


**Fig. 10.** Intensity, frequency, and site dependency of STN stimulation evoked striatal DA release of the urethane anesthetized rat. (A) The optimal current intensity for STN stimulation was 300 μA, with the stimulation evoked DA response falling off at 600 μA and greater. (B) The optimal frequency for STN stimulation was 50 Hz, with the stimulation evoked DA response falling off at 75 Hz and greater. (C) Prolonged STN stimulation evoked a transient response that peaked within 20 applied pulses (red line), as compared to a 10-fold greater and more sustained DA response to stimulation of the medial forebrain bundle (MFB) (blue line). INSET: DA release evoked by stimulation of the MFB (blue line) was significantly faster at onset compared to STN stimulation when viewed on the same scale as the STN response (red line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

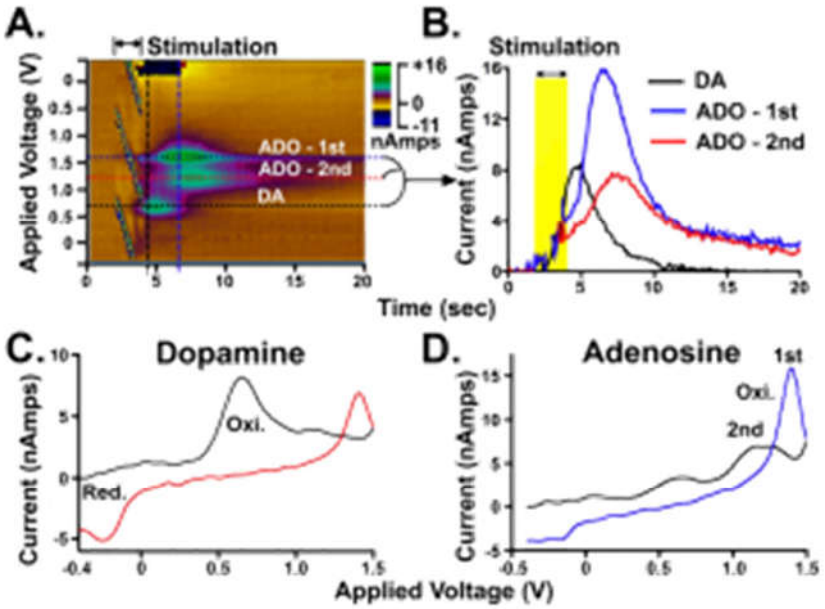


**Fig. 11.** In vivo dopamine (DA) and adenosine (ADO) release measured with WINCS-based FSCV at CFMs in the CN of the isoflurane anesthetized pig. (A) Electrical stimulation (140 Hz, 0.5 ms-pulse width, for 2 s) of the STN evoked both DA and adenosine release in the CN. The color plot shows the appearance of DA release immediately during and after stimulation, while the peak corresponding to adenosine release was delayed. (B) Current versus time plot at +1.5 V (blue), +1.0 V (red), and +0.6 V (black line) shows adenosine first and second oxidation (ADO – 1st, blue and ADO – 2nd, red) and DA (DA, black line) release following electrical stimulation (yellow box). (C and D) Background subtracted voltammograms for DA and adenosine, respectively, demonstrate simultaneous measurements of DA and adenosine releases (black and blue vertical dashed lines in A). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

potential role of ADO in seizure termination during temporal lobe seizures.

In addition, WINCS-based FSCV measurements were taken in the thalamus of essential tremor patients during DBS neurosurgery (Fig. 12); all the patients were awake during surgery. Arm and hand tremor were measured using a triaxial accelerometer which patients held in the hands opposite to the implanted hemisphere. Upon implantation of the DBS electrode, but prior to activation of the pulse generator, tremor amplitude was significantly reduced ($n = 7$; Fig. 12A). Referred to as the microthalamotomy effect, symptom relief prior to neurostimulation has been observed in as many as 53% of patients undergoing DBS surgery for essential tremor (Tasker, 1998). Our results showed that, as expected (Lakie et al., 1992), there was no change in tremor frequency, but average tremor amplitude was reduced by 61.2 ± 13.7% upon DBS electrode insertion ($n = 7$ patients).

Coincident with tremor reduction, DBS electrode implantation evoked a large increase in the FSCV oxidation current peak at +1.45 ± 0.03 V ($n = 7$; Fig. 12B). In four patients, this peak was followed by a second significantly smaller oxidation current peak at +1.19 ± 0.06 V (white arrow in Fig. 12B). Post-calibration analyses showed that the two oxidation current peaks recorded by FSCV matched those for authentic ADO and its oxidation byproduct (second peak). In accordance with post-calibration of the human CFM (see Chang et al., 2012b), the maximal increase in ADO at the first oxidation peak potential corresponded to an increase of 1.76 ± 0.12 μM. These results demonstrate the first application of WINCS during DBS neurosurgery in patients (see Chang et al., 2012b; Kasasbeh et al., 2013).

To monitor real-time neurochemical changes associated with DBS, we performed similar FSCV measurements (-0.4 to +1.5 V every 100 ms) in the ventral intermediate nucleus (VIM) of the thalamus of essential tremor patients during DBS neurosurgery using WINCS (Fig. 13A–C). A FSCV color plot (Fig. 13D) revealed that, during DBS, an oxidation peak current was detected at +1.4 V, corresponding to ADO oxidation (Swamy and Venton, 2007; Cechova and Venton, 2008; Pajski and Venton, 2013). Although a hand held accelerometer to measure tremor was not used in this patient shown in Fig. 13, the rise in the ADO signal during and after DBS (Fig. 13E) was visually observed to correlate with a marked reduction in tremor.

### 6.3. Translational importance on new large animal DBS models

Large animal models provide a necessary bridge between the fundamental discoveries made in small animal models and the translation into clinical practice. The preferred large animal model in neuroscience has been the non-human primate due to the higher cognitive function and behavioral similarities to the human. The rhesus macaque, for example, is a highly conserved animal model when anatomy is compared to human. The Atlas of the Rhesus Monkey Brain (Saleem, 2007), combined with high-precision stereotactic head frame and high-resolution MRI coil allows translational DBS studies in this large animal model (Min et al., 2014).

There are also known similarities between porcine and human biology that have led to the proposal to use the porcine model as an excellent way to study human disease (Lind et al., 2007). Easy to get and maintain, the domestic pig (*Sus scrofa*) is proving to be an economically viable alternative to the expensive non-human primate, and thus is becoming an increasingly popular animal for neuroscience research. Several characteristics make the pig an excellent model for mock human DBS surgery: (1) the pig has a gyrencephalic cortex, which is more similar to the human and non-human primate structure than that of commonly used lissencephalic rodent brains (Hofman, 1985, 1988); (2) the adult pig brain (~160 g) is comparable in size to that of the rhesus monkey (~100 g) and baboon (~140 g) and closer in size to the human brain (1300–1400 g) than the rat brain (~2 g) and mouse brain (~0.4 g) rodent brain; (3) a high-resolution pig brain atlas is available allowing for precision BG DBS studies in pigs to advance our understanding of the underlying mechanism (Félix et al., 1999; Saikali et al., 2010); (4) pig brain

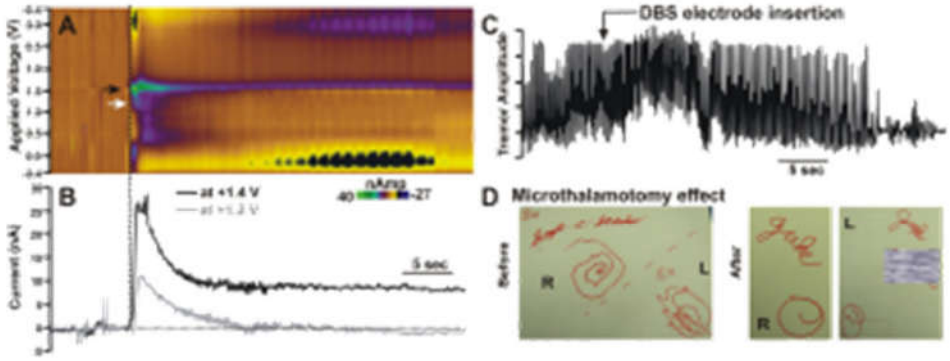


Fig. 12. Intraoperative FSCV recordings during monitoring of tremor in essential tremor patients. (A) FSCV color plot shows increases in oxidation current at +1.4 V (black arrow) and +1.2 V (white arrow) time-locked with the insertion of the DBS electrode into the ventral intermediate nucleus (VIM) of the thalamus ($n = 7$ patients). (B) Oxidation currents at +1.4 V (black) and +1.2 V (gray) plotted against time. (C) Representative tremor monitoring with a hand-held accelerometer shows tremor was decreased upon DBS electrode insertion. Time scale is the same as in (B). (D) Representative handwriting sample before and after DBS electrode implantation (L, left hand; R, right hand).

development is complete by ~5 months (Dobbing, 1964), which enables the use of younger pigs (20–50 kg) with adult-sized brains for easier mobilization and dissection during cranial surgery; (5) MPTP produces an effective pig PD model (Danielsen et al., 2000; Dall et al., 2002; Cumming et al., 2003); (6) several high-precision stereotactic head frames for pig neurosurgical studies have been developed establishing this system for DBS mechanistic studies (Bjarkam et al., 2009; Min et al., 2012); and (7) the pig genome has been decoded, which has revealed many key similarities between human and porcine genomes, further reinforcing the translational potential of this large animal model (Groenen et al., 2012). The advent of high-precision imaging tools such as functional magnetic resonance imaging (fMRI), combined with a recent increase in our understanding of cross-species neuroanatomical similarities among pig, human, and non-human primates highlight the potential of these large animal models to further our understanding of the mechanism behind DBS.

### 6.4. *Use of functional neuroimaging in BG-DBS*

Damage to the BG produces well-characterized changes that are related to movement disorders and motor deficits, including tremor, rigidity, and akinesia (Bhatia and Marsden, 1994; DeLong, 1983). Functional imaging is often used to indirectly monitor biochemical and anatomical changes within BG structures in movement and affective disorders due to its wide clinical availability and its global assessment of neural activity. Techniques including single photon emission computed tomography (SPECT), fMRI, and PET are used for this application. SPECT imaging has shown promise as a diagnostic tool for movement disorders revealing that changes in the caudate and putamen may help to differentiate early-stage PD from dystonia or essential tremor (Song et al., 2014). Other imaging studies, including PET, have been used to show decreased dopaminergic innervation within the BG in PD patients (Song et al., 2013). Longitudinal fMRI studies have also revealed heterogeneity in PD

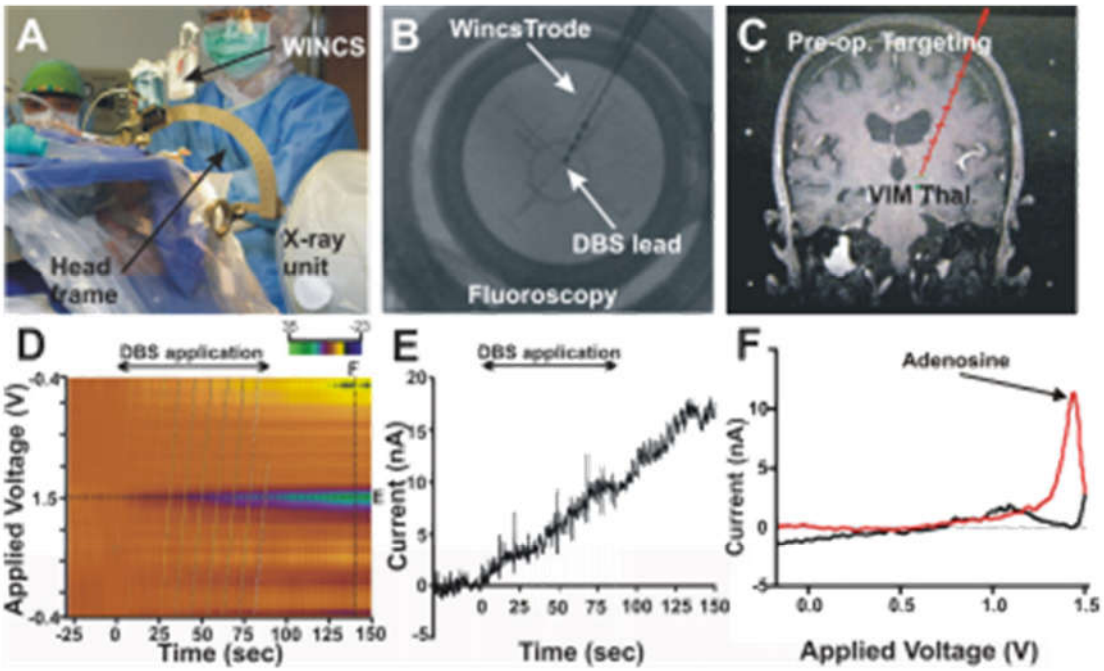


Fig. 13. Neurochemical changes evoked by DBS in the VIM of the thalamus in patients with essential tremor. (A) Surgical set-up. (B) X-ray of the position of the human CFM and DBS lead in patient's thalamus. (C) MR image of implantation trajectory. (D) Color plot shows the appearance of oxidation current at +1.4 V immediately upon application of DBS (135 Hz, 60 μs pulse width, 0.5–2.0 V, slowly increased). (E) Current versus time plot at +1.4 V following DBS. (F) Background subtracted cyclic voltammogram shows the oxidation peak of adenosine at +1.4 V.

patients. These latter studies have shown differential changes in BG structures when patient populations are presented with motor tasks whether they are responding or not responding to pharmacological therapy (Holiga et al., 2013). In addition to movement disorders, BG dysfunction is now accepted as playing a role in a variety of neuropsychiatric diseases, including TS (DeLong and Wichmann, 2010).

When mapping this dysfunction, fMRI studies in TS patients have shown a relationship between tic onset and paralimbic and sensory-association areas (Bohlhalter et al., 2006). fMRI has also revealed a role for cortico-BG network dysfunction in TS (Peterson et al., 1998; Worbe et al., 2010, 2012). Using diffusion tensor imaging (DTI), studies have also shown dysfunction in motor, associative, and limbic pathways (Neuner et al., 2009, 2010). Taken together, these studies show a role for neuroimaging in disease diagnosis and evaluating functionality of DBS for treating BG diseases.

As DBS is an effective treatment option for PD (Benabid et al., 1994, 2006; Benabid, 2003), its application has now been applied to other neurological and psychiatric disorders (Mayberg et al., 2005). The incomplete understanding of the therapeutic mechanisms of DBS and lack of objective methods to measure its central global effects inhibit the advancement of a more individualized approach to DBS therapy. The brain's dense wiring makes characterizing the effect of electrical stimulation on neuronal communication beyond a few synapses extremely challenging. Functional neuroimaging appears well suited to this task due to its wide clinical availability and its global assessment of neural activity. Many imaging studies in PD patients during STN DBS show modulation of motor and non-motor areas including the primary sensorimotor cortex, premotor cortex, SMA, dorsolateral prefrontal cortex, thalamus, BG, insular cortex, and contralateral cerebellum (Asanuma et al., 2006; Grafton et al., 2006; Haslinger et al., 2003; Kahan et al., 2012; Phillips et al., 2006; Stefurak et al., 2003). Other PET studies have implicated parietal and temporal cortices, classically defined as associative and limbic structures (Hershey et al., 2003; Le Jeune et al., 2010). These studies help to elucidate what makes DBS effective for treating motor and non-motor symptoms of PD.

Functional imaging studies of DBS have recently been aimed at identifying the circuitry elements that underlie effective, as opposed to ineffective, stimulation. For example, a recent tractography study of PD patients undergoing STN DBS identified a direct relationship between the positive clinical outcome and the targeting within white matter tracts that involve the cerebellum (Sweet et al., 2014). In a longitudinal SPECT study, a significant increase was shown in cerebral blood flow in the anterior cingulate/supplementary motor cortex in PD patients who responded to STN DBS treatment (Antonini et al., 2003). PET has shown that long-term effective STN stimulation of PD patients increases frontal motor/associative area blood flow compared to baseline (Sestini et al., 2005). A regional cerebral blood flow (rCBF) SPECT study reported a correlation between improved motor scores and an increase in rCBF in the pre-SMA and primary motor cortex in PD patients receiving STN DBS treatment (Paschali et al., 2013). Together, these studies suggest that neuroimaging biomarkers of effective DBS may exist for PD treatment.

Imaging has already identified structural and functional correlates of cognitive and affective deficits associated with PD (Kalbe et al., 2009; Kostic et al., 2010; Reijnders et al., 2010). In a case report in which STN DBS elicited several reproducible episodes of acute depressive dysphoria in PD patient, fMRI revealed increases in the superior prefrontal cortex, anterior cingulate, anterior thalamus, caudate and brainstem with widespread decreases in medial prefrontal cortex activation (Stefurak et al., 2003). Another case study identified STN DBS stimulation parameters which produced a hypomanic state in a PD patient. A PET investigation showed involvement of limbic and association cortex, including areas of the anterior cingulate gyrus and the ventral anterior nucleus of the thalamus (Mallet et al., 2007).

The fact that STN DBS can elicit cognitive and emotional side effects is unsurprising given our current understanding of the STN as a structure with anatomically defined subregions which connect to motor, associative and limbic structures (Benarroch, 2009). A recent clinical report showed that using model-based optimization of DBS stimulation parameters to avoid the current spreading to non-motor areas reduced cognitive and cognitive-motor impairments while maintaining therapeutic motor benefits in STN DBS PD patients (Frankemolle et al., 2010). These data suggest that anatomical target-placement decisions during human DBS surgery could be augmented by structural and functional neuroimaging techniques which intraoperatively assess the motor and non-motor networks affected by STN DBS.

## 7. Concluding remarks

The last decade has held impressive developments in understanding the mechanism of BG function and how targeting different brain sites can improve motor, cognitive and motivational aspects of BG diseases. However, we are still far from having the ability to fundamentally describe the mechanism behind therapeutically effective DBS. Deepened understanding of BG connectivity and the resultant computational modeling of functional motor, motivational and cognitive processes have emerged in the last decade. However, these models are still insufficient to support the idea that different striatal-GPi/SNr-thalamus-motor cortex neurons can initiate or prevent a particular movement or a sequence of movements that compose specific actions. Additionally, these studies have revealed paradoxical challenges to the current BG action-selection hypothesis. DBS has indeed emerged as a therapy with wide applications expanding from STN DBS to treat PD, to cover many neurological and psychiatric diseases; however, our fundamental understanding of BG DBS is limited in its current state. A great deal of effort from the neuroscience community will be required to advance BG DBS to the proposed level of understanding and clinical application.

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### 3.2. The rol of the basal ganglia in motivated behavior

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Claudio Da Cunha*, Alexander Gomez-A and Charles D. Blaha

# The role of the basal ganglia in motivated behavior

**Abstract:** The present paper reviews foundational and contemporary theories of motivated behaviors and the growing body of evidence that they require specific functional interactions within the basal ganglia. Such evidence suggests that unconditioned responses (UR), conditioned responses (CR), goal-directed actions and stimulus-response (S-R) habits are selected in the basal ganglia. Such selection depends on activation of striatal neurons by cortical and subcortical neurons encoding unconditioned stimuli (US), conditioned stimuli (CS), goals and neutral stimuli (S). These neurons project respectively to the medial nucleus accumbens (NAc) shell/olfactory tubercle, NAc core/lateral olfactory tubercle, dorsolateral striatum and dorsomedial striatum. The strength of these synapses is altered when the levels of extracellular dopamine in the basal ganglia undergo phasic increases or decreases, which signal outcomes that are, respectively, better or worse than expected. In addition, dopamine release in response to salient USs and to CSs with incentive salience increases the signal-to-noise ratio of corticostriatal neurotransmission, thus 'energizing' the performance of selected actions. Different actions can be selected in the striatum because the striatal neurons of the so-called direct and indirect pathways can respectively initiate and end actions through pallidum/nigral-thalamic projections to premotor and motor areas of the cortex. According to this view, the basal ganglia is thought to play a role in the action-selection processes needed for the expression of both declarative and procedural memories, but the memories of the contexts, predictive stimuli or neutral stimuli associated with free rewards or with an action's outcomes are stored elsewhere.

**Keywords:** action-selection; basal ganglia; decision-making; dopamine; motivated behavior; motivation.

*Corresponding author: Claudio Da Cunha, Department of Pharmacology, UFPR, 81.531-980 Curitiba PR, Brazil, e-mail: dacunha.claudio@gmail.com
Alexander Gomez-A: Department of Pharmacology, UFPR, 81.531-980 Curitiba PR, Brazil
Charles D. Blaha: Department of Psychology, University of Memphis, Memphis, TN 38152, USA

## Introduction

What are the reasons that someone behaves one way or another way? What motivates someone to dress in a particular way, to choose a type of shoe, a car or simply to choose a certain place for lunch? These questions have implications far beyond from what can be seen during performance of such behaviors. Previous experience with contexts, goals and the outcomes of actions are just some of the reasons. Here we review the accumulated evidence that action-selection of different motivated behaviors takes place in the basal ganglia. We start by reviewing historical and current theories of motivated behaviors. Next, the functional anatomy of the basal ganglia is reviewed along with evidence that the cortico-basal ganglia circuitry is dedicated to action-selection. Finally, we review current evidence for parallel processing in different regions of the basal ganglia for selection of unconditioned responses, conditioned responses, goal-directed behaviors and stimulus-response habits.

## Classic theories of motivated behavior

The term 'motivation' was developed by the German philosopher Arthur Schopenhauer (1788–1860). However, the meaning of this term had been contemplated long before. Plato (348–328 BC) and Aristotle (384–322 BC) both proposed that motivation includes three hierarchical levels: (i) a first or nutritional level, related to the essentials for maintaining life; (ii) a second or sensitive level, responsible for regulating pleasure and pain; and (iii) a higher level, exclusive to human beings, that includes choice, intentions and intellect (Reeve, 2009). René Descartes (1596–1650) maintained that mind, the thinking active entity, is separate from the body and that determination is the most important motivating force of the mind controlling the body's behavior (Descartes, 1949). These classics were followed by many other important theorists on the impact of motivation in behavior, including Charles

Darwin, William James, William McDougall, Sigmund Freud and Clark Hull (Reeve, 2009).

Hull, taken from Woodwoth (1918), described the term 'drive' as a power resultant from the body's needs. According to this view, motivation has a biological bases related to the body's needs (Hull, 1943). He maintained that drive energizes behavior without guiding it, a function reserved for habits. Habits are learned by the association between the response and the stimulus that triggers it. During habit learning, such association is reinforced by rewards and weakened by punishments contingent (that follow) to that response. Such conceptualization incorporates the 'law of effect' postulated by Thorndike (1911), according to which the likelihood of a response depends on its consequence: it will increase when reinforced by a rewarding stimulus and decrease when punished with an aversive stimulus. In this sense, rewards and punishments are conceptualized as stimuli that decrease or increase drive. In a simple example of this conceptualization, when a hungry dog eats food found in a trash container, this decreases drive (hunger), thus reinforcing the behavior of searching for food in that place. In summary, Hull's theory of how motivation drives action-selection can be expressed by three postulates: i) drive emerges from the body's needs; ii) drive energizes behavior; and iii) drive reduction produces learning (Reeve, 2009).

The acknowledgement of considerable limitations contributed to the decline of this theory. However, it was observed that some motifs can emerge without a corresponding biological need. For example, people with anorexia do not eat, despite a strong biological need for food. In addition, external sources can energize behavior; for example, in spite of not being hungry in the middle of the afternoon, most people would like the candy displayed in a shop window. Finally, in many cases, learning occurs without drive reduction, which implies that drive reduction is neither necessary nor sufficient for learning (Miller, 1951; Dickinson and Balleine, 2002).

As behavior does not occur in a vacuum, both drive (inherent in the subject) and context (what is outside the subject) constitute fundamental elements to understanding motivation. The subject is embedded in particular contexts, and interaction with these contexts gives rise to a number of behaviors, some of them mediated by the subject's will, whereas others are automatic responses or simple reflexes (Bolles, 1972; Latham and Pinder, 2005).

Some adaptive behaviors, especially those necessary for survival, are elicited by specific stimuli in an innate manner – independent of learning. Such responses will depend exclusively on the presence of the proper stimulus to be triggered. These responses are called reflexes, or unconditioned responses, and constitute a basic form of behavior that provides instant adjustments that facilitate the welfare of the subject (Staddon, 2003). We can also learn how to predict the imminent occurrence of a biologically important stimulus and anticipate response to it. Such learning, known as classicical or Pavlovian conditioning, occurs when the biologically relevant stimulus is repeatedly preceded by a neutral stimulus, as initially demonstrated by Ivan Pavlov (1849–1936) during his studies with dogs. He observed that the salivation response occurred naturally when the dog came into contact with food. A stimulus of this kind was called 'an unconditional stimulus' (US) by Pavlov, as the response was not tied to a previous experience of the subject with that stimulus. The response to a US was called an 'unconditioned response' (UR). After learning, the predictive stimulus was called a conditioned stimulus (CS) because now the response becomes conditional to the CS presentation. Accordingly, such a response was called a conditional response (CR) (Pavlov, 1927). In the context of motivated behavior, we can say that specific responses can be motivated either by unconditioned or conditioned stimuli. Neutral stimuli can also acquire the property of motivating a behavior when it is paired with a CS, a learning process known as second order conditioning (Rizley and Rescorla, 1972).

Burrus Skinner (1904–1990) also studied the type of learning that follows Thorndike's law of effect, but is different from Hull in that the emphasis is placed on the reinforcement property of appetitive stimuli, i.e., in the relationship between the response and its consequence. Skinner used a method of analysis of behavior that did not need to take into account any kind of mental state to explain how this operant or instrumental learning occurs. Therefore, this approach does not consider 'motivation', understood as an internal state, as a factor necessary to explain how instrumental learning occurs. He used the terms reinforcement and punishment to refer to stimuli that increase or decrease the frequency of a response that follows it (Skinner, 1938; Staddon, 2003).

An instrumental response is performed in the presence of a certain stimulus that precedes the response and is followed by the rewarding stimulus that reinforces the occurrence of this response. As the discriminative stimulus and the rewarding stimulus occur in close temporal contiguity, it is possible that they become associated by classical conditioning. Sometimes a particular context works as a discriminative stimulus during instrumental

learning. In this case, the context may acquire rewarding properties by a Pavlovian conditioning process. Thereafter, the discriminative stimulus or the context (CS) become predictors of reinforcement and determine the response. This hypothesis was widely studied by Hull (1930, 1931) and later by Spence (1956). They assumed that in the process of instrumental conditioning, the subject learns to present the instrumental response in the presence of the discriminative stimulus or of the context and, additionally, acquire the expectation that the reward is imminent. This expectation is learned through classical conditioning and also motivates the instrumental response. The mechanism proposed by Hull and Spense to explain the association between the stimulus and the reward was the substitution of stimuli. This hypothesis states that the CS acquires the motivational properties of the US.

Other theorists have addressed the interactions between classical and instrumental conditioning with different proposals. One of these proposals is the 'two-processes theory', which attributes an important role to emotional states generated by classically conditioned stimuli on the motivation of instrumental behavior (Rescorla and Solomon, 1967). It is similar to Hull's proposal to the extent that classical conditioning is important to motivate instrumental behavior. However, it does not consider that classical conditioning involves learning of specific responses or might contribute to general motivation (Rescorla and Solomon, 1967). In this theory, a CS comes to induce not a general, but a particular type of motivation that is specifically related to the US with which it was paired. Thus, the CS will not necessarily trigger a particular response, but a motivational state that can affect performance of different responses, depending on the context in which it occurs. For example, if the emotional state is fear, the resulting responses may be freezing, fleeing, defensive behaviors, screaming, etc., depending on the distance between the animal and a predator (Blanchard and Blanchard, 1988). During instrumental learning, these emotional states are conditioned to either contextual or discriminative stimuli. Later, the emotional state evoked by these CSs can motivate the performance of different kinds of instrumental responses. In other words, the two-processes theory predicts that the performance of an instrumental response can be altered by the presence of a CS according to the emotional state associated with it. In this way, a CS can decrease or increase performance, depending on the emotion that it evokes being similar or opposite to the emotion that is motivating the instrumental response (Bolles, 1970).

## Contemporary theories of motivated behavior

Most old theories involved in Pavlovian and instrumental conditioning were developed to describe behavioral changes that occur during learning without considering any emotional or cognitive cause for such changes. The sentence 'a response is reinforced' is used to report that the frequency of that response increased, without considering any emotional or cognitive cause. The term 'motivated behavior' came from studies intended to investigate the emotional factors involved in the actions that occur in response to stimuli with hedonic properties. Contemporary researchers of motivated behavior assimilated the concepts of Pavlovian and instrumental conditioning and coined new terms and concepts that included the emotional aspects of this phenomenon (Ikemoto and Panksepp, 1999).

In modern studies of motivated behaviors (Wise, 2008; Dalley and Everitt, 2009; Wilson et al., 2009; Humphries and Prescott, 2010; Schmidt et al., 2010; Shin et al., 2010; Alcaro and Panksepp, 2011; Flagel et al., 2011; Smith et al., 2011), the concepts of reinforcement and CS were incorporated into the concepts of incentive reward and motivation. The word reward incorporates the meaning that the rewarding stimulus has a hedonic value, i.e., it causes a change in the subject's emotional state and that this change is implicated in the behavioral change that follows the stimulus presentation. Saying that a subject received a free reward or that it was rewarded because of its behavior, implies that the subject was pleased by the presentation of the rewarding stimulus, i.e., the stimulus has a positive hedonic value.

Contemporary theorists of motivated behavior also distinguish primary motivation as involved in CRs and URs from appetitive stimuli and secondary or incentive motivation as determinant of instrumental responses to stimuli that signals the availability and location of an appetitive stimulus. Escape behaviors are also innate responses motivated by painful and other aversive stimuli (Mogenson et al., 1980; Ikemoto and Panksepp, 1999). Stimuli are distinguished according to the phase of motivation in which behaviors take place. Behaviors motivated by natural stimuli (USs) are classified as preparatory or appetitive, consummatory and post-consummatory (Di Chiara, 1995; Ikemoto and Panksepp, 1999). Incentive stimuli motivate preparatory behaviors and rewarding stimuli motivate consummatory and post-consummatory behaviors (Bolles et al., 1975; Bindra, 1978). Rewarding stimuli are USs recognized by sensory modalities

specialized in detecting proximal stimuli – tactile, taste, proprioceptive and visceral. They provide the final goals of attending to biological needs, such as feeding, drinking and breeding, essential to the survival of a species (Di Chiara, 1995). Incentive stimuli are detected by sensory modalities (e.g., vision, hearing and smell) specialized in distal stimuli that signal the location of rewarding and threatening stimuli. They are instrumental for the goal of getting a reward or avoiding a punishment, but they are not themselves the goal of such motivated behaviors. Neutral stimuli can acquire incentive properties by a process called instrumental incentive learning in which the subject faces the rewarding or threat-removing outcomes of an action. This process is recognized as different from Pavlovian conditioning in which a neutral stimulus acquires the property of eliciting conditioned emotional responses (Pavlovian CRs), but not instrumental incentive responses (Rescorla and Solomon, 1967; Dickinson and Balleine, 1994; Di Chiara, 1995). However, a neutral stimulus can also acquire the property of eliciting an approach response to an appetitive US through a type of Pavlovian conditioning called Pavlovian incentive learning (Dickinson and Balleine, 2002).

Incentive stimuli have activational value (they 'energize' the response, what corresponds to the 'wanting') and positive motivational valence (they determine the direction – approach or avoidance – of the response). Together these properties determine the intensity and nature of typical incentive responses of approach or avoidance to a rewarding stimulus or a threatening stimulus, respectively. Therefore, incentive stimuli are involved in both positive and negative reinforcement. For avoidance to take place, safety stimuli – incentive stimuli associated with safe responding – must be acquired (Mackintosh, 1974; Di Chiara, 1995).

Pavlovian incentive learning reflects the acquisition of motivational properties by CSs through their association with appetitive and aversive stimuli (Dickinson and Balleine, 2002). During Pavlovian conditioning, a neutral stimulus gains incentive salience, which means that this stimulus (CS) can now motivate approach and consummatory actions directed to USs (Berridge, 2007). According to these concepts, USs present incentive salience even to naive subjects. Pavlovian incentive learning can generate approach behaviors to a CS that predicts the proximity or availability of an appetitive stimulus (Ikemoto and Panksepp, 1999). Although the influence of appetitive CSs are modulated by primary motivational states, they exert a general motivational influence on appetitive behavior. By contrast, aversive CSs inhibit appetitive behaviors. Instrumental incentive learning determines the incentive value assigned to outcomes of goal-directed instrumental actions. This incentive value, and its control by primary motivational states, has to be learned through experience of the hedonic reactions elicited by the outcome (Dickinson and Balleine, 2002).

Dickinson and Balleine (1994) proposed that instrumental behavior can be controlled by either a neutral stimulus (just as proposed by Hull) or by the goal of getting a reward or avoiding a punishment, i.e., by the consequences of an action. The former kind of instrumental behavior is called S-R habit, and the latter goal-directed action (Yin and Knowlton, 2006). They can be conceptually distinguished because goal-directed actions, but not S-R habits, are motivated behaviors dependent on drive – the biological needs of the subject. S-R habits, on the other hand, are triggered by a neutral stimulus, independent of any type of motivation. The drive can be altered by the alteration of the physiological state of the animal. A hungry animal that is bar-pressing for food in an action-outcome manner has its behavior controlled by an outcome (food delivery) that reduces this drive (hunger). Therefore, the performance of this action will be reduced if the animal were previously fed. Such a procedure is called outcome devaluation – the hedonic value of the outcome (food delivery) is lower when the animal is sated than when it is hungry. However, if this instrumental behavior is triggered by a specific stimulus or context, it is not affected by devaluation of the outcome (Balleine and Dickinson, 1992; Dayan and Balleine, 2002).

Defining an action as 'goal-directed' means that its performance is mediated by the knowledge of the relation between the action and its outcome, which, at least in human beings, is the product of an expectation or belief. In addition, it is necessary that the subject represents the result of the action as a goal itself. Objective criteria for determining whether instrumental behaviors are goal-directed are operational. The first criterion involves acquisition of a behavior that is sensitive to the contingency established between the action and its outcome, thus allowing distinction from responses elicited by Pavlovian CSs. The second criterion (the goal) aims to certify whether the action performance is itself a goal for the subject (Dickinson and Balleine, 1994). Dickinson and Balleine rescued the concept of cathexis from Tolman (1959), defined as the connection between a potential goal and a related motivational state. This motivational state *per se* does not appear to directly determine the target value, unless there is prior experience that facilitates the association between the motivational state and the outcome (Balleine, 1992).

The next point of interest lies in the consequences of the instrumental action (the outcome), assuming that the state has an important motivational role in goal-directed behaviors. It seems that the subject tends to learn about the value of an outcome through direct experience, the process that is referred to above as instrumental incentive learning. As a result of it, experimental procedures that potentially affect the resulting hedonic value of the outcome, such as motivational changes and flavor-aversion conditioning, do this only when the subject has had the opportunity to learn the incentive that can be re-experienced by an instrumental action. This form of incentive learning can be clearly distinguished from the learning process by which the value of the outcome, once acquired, gains control over the instrumental performance (Balleine, 1992).

Finally, motivational states can interact with incentive learning, determining the reaction of the subject to the outcome. As in the example mentioned above, the subject values the food more when it is hungry. However, this does not imply an absolute control of the action performance by the motivational state. Previous experience of the subject with the outcome seems to be relevant. In conclusion, the influence of motivational states on goal-directed actions is apparently indirect and mediated by learning – what, in the words of Dickinson and Balleine 'release goal-directed actions from the tyranny of primary motivation' making room for socially-regulated values (Dickinson and Balleine, 1994).

A growing body of evidence suggests that it is in the basal ganglia, especially in the neural circuitry loop that feeds the nucleus accumbens (NAc), that salient, rewarding and aversive stimuli motivate specific behaviors to occur (Mogenson et al., 1980; Alexander et al., 1986; Albin et al., 1989; Gurney et al., 2001; Frank and Claus, 2006; Balleine et al., 2007; Nicola, 2007; Da Cunha et al., 2009; Isoda and Hikosaka, 2011). In the next section, we will review the functional anatomy of the basal ganglia and how it operates to translate different kinds of motivation into URs, CRs and goal-directed actions.

## The basal ganglia architecture

The basal ganglia consist of a group of subcortical nuclei that process information received from all areas of the cerebral cortex and send it back to the frontal cortex and other brainstem structures involved in the control of motor and emotional responses. Figure 1 offers an overview of the basal ganglia architecture that is organized into three

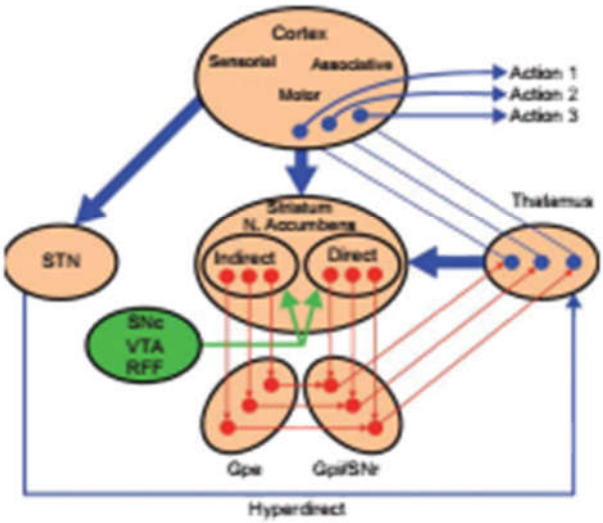


**Figure 1** Simplified depiction of the main pathways of the basal ganglia.
Green arrows indicate dopaminergic projections. Blue arrows indicate excitatory glutamatergic projections and red arrows indicate inhibitory GABAergic projections. GPe, globus pallidus externus; GPi, globus pallidus internus; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata; STN, subthalamic nuclei. Based on Albin et al., 1989.

levels: (i) an input station, formed by the striatum and subthalamic nuclei (STN); (ii) An output station, formed by the pallidum and the substantia nigra pars reticulata (SNr); and (iii) A modulatory station, formed by the substantia nigra pars compacta (SNc), retrorubral field (RRF) and ventral tegmental area (VTA). In addition, cortico-basal ganglia processing occurs in three parallel loops that are fed by different cerebral structures and project to limbic, associative and motor regions of the frontal lobe (Alexander et al., 1986). These loops are partially overlapped, thus allowing input integration, and follow a spiral pattern of projections that allows inputs to the limbic and associative loops to affect emotional and motor responses (Albin et al., 1989; Haber and Knutson, 2010).

The input station of the basal ganglia is formed by the striatum and the STN. Nearly 95% of striatal neurons are comprised of GABAergic medium spiny projection neurons that are kept under strong tonic inhibition by GABAergic and cholinergic interneurons (Kawaguchi et al., 1995). The STN is formed mostly of glutamatergic projection neurons (Parent and Hazrati, 1995b). The dorsal striatum and STN receive glutamatergic inputs from the thalamus, sensorimotor, associative and limbic areas of the neocortex and projections from subcortical limbic areas (Parent and Hazrati, 1995a,b; Ikemoto, 2007). The ventral striatum receives inputs from associative and limbic areas of the prefrontal cortex and from the piriform cortex, amygdaloid complex,

hippocampal formation and lateral hypothalamus (Swanson and Cowan, 1975; Ikemoto, 2007). Corticostriatal projections follow a divergent pattern that is most densely concentrated into a region of the striatum, with a gradual decrease in projection density to neighboring regions. In addition, tiny ramifications of the projections from each part of the cortex broadcast the same information to a broader field scattered throughout almost the entire striatum (Haber, 2003; Haber and Knutson, 2010).

Different areas of the striatum receive projections from the sensorimotor, associative and limbic cortex in rodents. The dorsolateral striatum receives projections from the sensorimotor cortex, the dorsomedial striatum receives projections from the associative cortex and the ventral striatum receives projections from neocortical and subcortical limbic structures (Parent and Hazrati, 1995a). In primates, the dorsal striatum (neostriatum or caudoputamen) is formed by the caudate nucleus and the putamen that are separated by the internal capsule (Alexander et al., 1986; Ikemoto, 2007; Haber and Knutson, 2010). In rodents, this anatomical separation does not exist, but it is considered that the dorsomedial and dorsolateral parts of the rodent striatum correspond approximately to the primate caudate nucleus and putamen, respectively (Yin and Knowlton, 2006; Balleine and O'Doherty, 2010). The ventral striatum is formed mostly by the core and shell parts of the NAc (Swanson and Cowan, 1975) and by the olfactory tubercle (Ikemoto, 2007).

The input station of the basal ganglia projects to various output nuclei via hyperdirect, direct and indirect pathways. (i) In the hyperdirect pathway, information received from the neocortex by the STN are sent 'hyperdirectly' to the output station, bypassing the striatum. (ii) The direct pathway is formed by direct projections from the striatum to the output station. (iii) The indirect pathway is formed by projections from the striatum to the external part of the pallidum (GPe), which in turn projects to the output nuclei, the SNr and the internal part of the pallidum (GPi, named as entopeduncular nucleus in rodents). Less dense bidirectional fibers interconnect the GPe and the STN (Alexander et al., 1986; Albin et al., 1989; Parent and Hazrati, 1995a,b; Nambu et al., 2002a).

The output station of the basal ganglia is formed by GABAergic neurons of the GPi and SNr that project to the thalamus (Parent and Hazrati, 1995a). Such projections are mostly segregated in the associative, limbic and motor loops:

- In the motor loop, projections from the dorsolateral striatum (putamen and caudal part of the caudate nucleus) in primates are directed to the SNr and GPi. These nuclei project to the oral part of the ventrolateral nucleus of the thalamus (VLo), the lateral medial subdivision of the ventrolateral nucleus of the thalamus (l-MLm), the magnocellular part of the ventral anterior thalamic nucleus (VAmc) and the dorsal medial part of the paralamellaris nucleus, a subnucleus of the thalamus (MDpl), which in turn project mostly to the primate supplementary motor cortex (Alexander et al., 1986).
- In the associative loop, projections from the dorsomedial and central striatum (head of the caudate nucleus and anterior putamen) are directed to the SNr and GPi in primates. These nuclei project to the ventral anterior part of the parvocellular nucleus of the thalamus (VApc) and the dorsal medial part of the parvocellular nucleus of the thalamus (MDpc), which in turn project to the dorsolateral prefrontal cortex (Alexander et al., 1986; Haber and Knutson, 2010).
- The limbic loop is more complex. The NAc core of primates projects to the ventral anterior part of the magnocellular nucleus of the thalamus (mVAmc), the dorsal medial part of the magnocellular nucleus of the thalamus (MDmc) and the medial dorsal part of the posteromedial part of the nucleus of the thalamus (PMmd), which in turn project to the lateral orbitofrontal and anterior cingulate cortex (Alexander et al., 1986). In rodents, the medial parts of the NAc core/shell and olfactory tubercle project to the ventral pallidum, and this in turn projects to the prelimbic, infralimbic and agranular insular cortices. The medial parts of the NAc shell and olfactory tubercle also project to the ventral pallidum and send direct and indirect projections to the lateral hypothalamus and closely connected brainstem regions, thus affecting visceral and emotional processes (Ikemoto, 2007; Haber and Knutson, 2010; Humphries and Prescott, 2010). Some signals from the ventral pallidum eventually reach primary motor and premotor areas of the cortex through polysynaptic pathways, thus providing a mechanism for motivation to affect action-selection. This is the basis of limbic/motor integration (Ikemoto, 2007).

The concept of a modulatory station for the basal ganglia comprises intrinsic and extrinsic modulators. The projection neurons of the striatum are kept under strong GABAergic and cholinergic modulation by striatal interneurons. Depending on the pattern of inputs that the medium spiny neurons receive from cortical neurons, their resting membrane potentials oscillate between down (hyperpolarized) and up (near to the firing threshold) states (Stern et al., 1997). Intrinsic and extrinsic neurons release several neurochemicals that modulate

corticostriatal neurotransmission, such as dopamine, serotonin, noradrenaline, nitric oxide, endocannabinoids, adenosine and opioid peptides. Most of these increase the signal-to-noise ratio of cortico-striatal neurotransmission by depolarizing the medium spiny neurons that are in the 'up state' and hyperpolarizing those that are in the 'down state' (Lewis and O'Donnell, 2000). Mechanisms of signal-to-noise improvement in the cortico-striatal neurotransmission also include increasing the release of glutamate in fibers under high frequency of firing and decreasing it in those under low frequency of firing (Hernandez-Lopez et al., 1987, 2000; West and Grace, 2000; Fredholm et al., 2005; Sesack and Grace, 2010). In addition, dopamine and other intrinsic modulators (e.g., endocannabinoids and adenosine) also play a role in synaptic plasticity of cortico-striatal neurotransmission (Di Filippo et al., 2009; Lovinger, 2010).

Dopamine, released from midbrain dopaminergic neurons, is the most abundant of the neuromodulators present in the striatum. The midbrain dopaminergic neurons are organized in the RRF, SNc and VTA, corresponding respectively to the A8, A9, and A10 groups (Prensa et al., 2009). All nuclei of the basal ganglia receive dopaminergic projections from these midbrain nuclei. However, only the role of the dopaminergic projections to the striatum is somewhat understood. These midbrain nuclei also send GABAergic projections to the striatum, but their role remains unclear. Projections from midbrain dopaminergic neurons follow a gradient in which dopaminergic neurons of the more medial parts of the midbrain (e.g., VTA) project mostly to the ventral striatum and those located in more lateral and posterior parts of the midbrain (SNc and RRF) project mostly to the dorsal striatum (Voorn et al., 2004; Ikemoto, 2007; Haber and Knutson, 2010). The midbrain dopaminergic nuclei receive strong GABAergic projections from the striatum and more modest glutamatergic and cholinergic projections from the pedunculopontine and laterodorsal tegmentum. They also receive afferents from the superior colliculus, rostromedial mesopontine tegmentum, lateral hypothalamic and lateral preoptic areas, periaqueductal gray and reticular formation (Forster and Blaha, 2003; Dommett et al., 2005; May et al., 2009; Sesack and Grace, 2010).

## Action-selection in the basal ganglia

As outlined above, the frontal lobe is the major neocortical target of the basal ganglia. Such architecture suggests that the roles of the basal ganglia are closely related to the roles of the frontal lobe itself: motor control, motor planning and executive functions (planning, working memory, attention, problem solving, verbal reasoning, behavioral inhibition, mental flexibility, multi-tasking and initiation and monitoring of action). Here we will focus on the role of the basal ganglia in action-selection of motivated behavior as suggested in a growing body of literature (Robbins, 1976; Cools, 1980; Mogenson et al., 1980; Alexander et al., 1986; Albin et al., 1989; Mink, 1996; Gurney et al., 2001; Frank and Claus, 2006; Yin and Knowlton, 2006; Balleine et al., 2007; Nicola, 2007; Da Cunha et al., 2009; Isoda and Hikosaka, 2011; Redgrave et al., 2011).

Motor actions are programmed in premotor and motor areas of the frontal cortex (Graziano, 2006) and motor nuclei of the brainstem (Takakusaki et al., 2004; McHaffie et al., 2005). The motor programs of the cortex can be selectively activated by neurons of motor nuclei of the thalamus, which are held under tonic GABAergic inhibition by neurons of the output stations of the basal ganglia (GPi and SNr) (Kropotov and Etlinger, 1999). Such inhibition can be removed or increased by the three pathways communicating with the input and output stations, as mentioned above (Alexander et al., 1986; Albin et al., 1989). According to the 'center-surround model' proposed by Nambu and co-workers (2002b), when a voluntary movement of the limbs is about to be initiated, the hyperdirect, direct and indirect pathways are sequentially activated to cancel competing programs while the selected program is initiated and finalized at the proper time. The hyperdirect pathway is in charge of cancelling competing programs. It is formed by neurons of the STN that can activate large areas of the GPi/SNr, thus increasing their inhibition over large areas of the thalamus (Nambu et al., 2002b). In contrast, striatal neurons of the direct pathway project to a limited number of neurons of the GPi/SNr, supposedly those in control of specific motor programs that are activated by specific cortico-thalamic neurons. Because these neurons are GABAergic they can selectively remove the inhibition of cortico-thalamic neurons, thus initiating this or that action. The indirect pathway can restore such inhibition by inhibiting neurons in the GPe that keep the GPi/SNr under tonic inhibition. By this mechanism, the indirect pathway can finalize or prevent specific actions from occurring (Albin et al., 1989).

This model of basal ganglia organization places the input station (striatum) as the site in which action-selection occurs (Kropotov and Etlinger, 1999; Gurney et al., 2001; Nicola, 2007). In a recent article, we reviewed evidence that projection neurons from the dorsolateral striatum (putamen) encode actions of body parts directed to

objects (Da Cunha et al., 2009). Specific striatal neurons are reported to fire in response to the approach of an object to a body part (Hikosaka et al., 1989; Graziano and Gross, 1993; Nagy et al., 2006) and to the touch of that object (Graziano and Gross, 1993; Flaherty and Graybiel, 1994; Nagy et al., 2006) or by the movement of that body part (Flaherty and Graybiel, 1994). As these experiments were done in anesthetized animals, we proposed that such neurons fired, not because the object approached a specific body part, but because that specific body part was approaching the object. We called this hypothesis 'the mosaic of broken mirrors model' because it proposes that objects and body parts' actions encoded in the neocortex are 'mirrored' by striatal neurons in a broken and repetitive manner (Da Cunha et al., 2009). Different studies present evidence for the representation of body parts in the putamen as in a broken mosaic (Flaherty and Graybiel, 1994) or in a somatotopic organization (Graziano and Gross, 1993; Gerardin et al., 2003; Obeso et al., 2008).

## Roles of different regions of the striatum in selection of motivated behaviors

Recent studies suggest that URs and CRs, goal-directed actions and S-R habits are selected in the regions of the striatum that belong respectively to the limbic, associative and motor loops. Here we review evidence in support of this view and of further segregation. According to such evidence, URs are selected mostly in the NAc shell and medial olfactory tubercle, whereas CRs are selected in the NAc core and lateral olfactory tubercle. In contrast, goal-directed actions and S-R habits are selected in the dorsolateral striatum (caudal parts of the caudate nucleus and putamen of primates). There is evidence for the involvement of both the NAc core and dorsomedial striatum (head of the caudate nucleus and rostral putamen in primates) in selection of goal-directed actions.

### The role of the NAc shell in selection of unconditioned responses

As reviewed in the first section of this paper, URs are elicited by specific USs, independent of previous learning. Most of these URs are directed to biologically relevant stimuli that are themselves rewarding or aversive. They involve approach/avoidance motor responses that are under the control of the lateral hypothalamus and visceral responses under the control of the autonomic and neuroendocrine systems – systems that are themselves under the control of the hypothalamus. The medial parts of the NAc shell and olfactory tubercle are the only regions of the ventral striatum that send direct projections to different subnuclei of the hypothalamus, including the lateral hypothalamus (Heimer et al., 1991; Stratford and Kelley, 1999; Ikemoto, 2007). Therefore, the medial NAc shell/olfactory tubercle is in a position to select the proper motor and emotional responses to USs (Meredith et al., 2008).

A growing body of evidence supports the hypothesis that URs organized in the lateral hypothalamus can be elicited by inhibition of sub-regions of the NAc shell. Inhibition of different sub-regions of the NAc shell with the GABA-A agonist muscimol elicits an intense feeding response (similar to that observed after stimulation of the lateral hypothalamus) and induces Fos expression in a great number of cells in the lateral hypothalamus. In addition, injection of a glutamate NMDA receptor antagonist into the lateral hypothalamus suppresses this NAc shell-mediated feeding behavior (Stratford and Kelley, 1999). Moreover, inactivation of the rostral part of the NAc shell with GABA-A receptor agonists or glutamate AMPA/kainate receptor antagonists induces responses similar to those elicited by appetitive USs. In contrast, infusion of the same drugs into more caudal sites of the NAc shell suppresses appetitive behaviors and induces responses similar to those elicited by aversive USs (Reynolds and Berridge, 2008; Faure et al., 2010b). In addition to eating (Maldonado et al., 1995; Stratford et al., 1998; Reynolds and Berridge, 2001, 2002; Baldo et al., 2005), such appetitive responses include positive valence orofacial reactions to taste (Reynolds and Berridge, 2002) and drinking behaviors (Stratford et al., 1998). The responses similar to those elicited by aversive USs include negative valence orofacial reactions to taste (Reynolds and Berridge, 2002) and species-specific fearful/defensive behaviors, such as distress vocalizations (Reynolds and Berridge, 2001), escape attempts (Reynolds and Berridge, 2001) and defensive treading. Consistent with these findings, subpopulations of neurons in the NAc of rats undergo increased or decreased firing activity in response to intraoral infusion of a sucrose solution (Krause et al., 2010; Roitman et al., 2010) and abrupt licking when the NAc is electrically stimulated (Krause et al., 2010). Furthermore, different subjective emotional responses were also reported by patients with major depressive disorders under deep brain stimulation with electrodes implanted in different sites in the NAc. These responses include anxiety, dizziness,

sensation of warmth and 'flushing,' signs of increments in mood, sensation of energy, alertness, laughing, calmness and talkative behavior (Machado et al., 2009).

Activation of dopamine receptors is needed following the inactivation of the NAc shell with glutamate receptor antagonists to elicit appetitive or aversively-motivated URs (Faure et al., 2008). Such effects seem to be mediated by activation of both the D1 and D2 dopamine receptors in direct and indirect GABAergic accumbal output pathways (Nicola, 2007), which might contribute to an increase in the signal-to-noise ratio of signals, as in what occurs in the dorsal striatum (see above). Selection of autonomic responses to USs may contribute to 'drive' states related to positive and negative affect. Release of dopamine in the medial NAc shell/olfactory tubercle is said to induce a high action-arousal state, defined as a mind state that energizes the organism for interactions with the environment, resulting in invigoration of behaviors of approach to biologically important stimuli (USs) or escape from danger (Ikemoto and Panksepp, 1999). This can explain the behavioral stimulant effect (e.g., increase in reward-seeking and other exploratory behaviors) (Pijnenbu and Vanrossu, 1973; Ikemoto and Panksepp, 1999; Di Chiara et al., 2004; Ikemoto, 2007) and increment of mood (Nestler and Carlezon, 2006) caused by drugs that increase the extracellular concentration of dopamine in the NAc. These findings are in line with the hypothesis that meso-striatal dopamine systems are part of the neuronal mechanisms that allow organisms to organize behaviors that are essential to sustaining life (Panksepp, 1982; Ikemoto and Panksepp, 1999).

## The role of the NAc core and shell in selection of conditioned responses

As outlined above, during Pavlovian conditioning, a previously neutral CS that is paired with an appetitive or aversive US acquires a corresponding positive or negative valence. This permits the CS to automatically elicit approach and consummatory CRs in anticipation of presentation of the US in a manner that is not dependent on the consequences of these responses.

In addition to the NAc (Ikemoto and Panksepp, 1999; Di Chiara, 2002; Belin et al., 2009; Faure et al., 2010b; Berridge, 2012), many other limbic structures, including the basolateral complex of the amygdala (Gallagher and Holland, 1994; Vazdarjanova and McGaugh, 1999; White and McDonald, 2002; Blundell et al., 2003; Yin et al., 2008), the hippocampus (Holland and Bouton, 1999), the orbitofrontal cortex (Gallagher et al., 1999; Izquierdo et al., 2004), the anterior cingulate cortex (Buchanan and Powell, 1982; Parkinson et al., 2000) and the cerebellar interpositus nucleus (Thompson and Steinmetz, 2009), have been proposed to play key roles in Pavlovian conditioning. However, there remains some contention as to what specific roles each of these structures play.

It is also controversial as to what critical roles the NAc core or shell play in Pavlovian conditioning. Some studies suggest that the NAc shell plays a role when the CS is a context (Riedel et al., 1997; Bossert et al., 2007; Ito et al., 2008; Chaudhri et al., 2010; D'Souza et al., 2011; Bossert et al., 2012) and the NAc core plays a role when the CS is a discrete cue (Bossert et al., 2007; Chaudhri et al., 2010). However, the opposite pattern or lack of effects have been reported in other studies (Parkinson et al., 1999; Levita et al., 2000; Pezze et al., 2001; Cassaday et al., 2005; Chaudhri et al., 2009; Kelsey et al., 2009; Edwards et al., 2011). In contrast, Bradfield and McNally (2010) proposed that what determines the involvement of the core and shell regions of the NAc in Pavlovian conditioning is, respectively, the poor or good predictive quality of the CS.

According to Ikemoto (2007), the meso-ventromedial striatal dopamine system, comprising the midbrain dopaminergic neurons that target the medial parts of the NAc shell and olfactory tubercle and these target areas, plays an important role in the aspects of incentive learning related to acquisition and consolidation of stimulus–outcome association (which corresponds to the CS-US association). In contrast, the meso-ventrolateral striatal dopamine system, comprising the midbrain dopaminergic neurons that target the NAc core and the lateral parts of the NAc shell and olfactory tubercle, plays a role in the selection of adaptive responses based on the learned CS-US association. Another possibility to explain the evidence that supports Ikemoto's view is that the CS-US association is learned and stored in the other abovementioned brain structures (Gallagher and Holland, 1994; Da Cunha et al., 1999; Holland and Bouton, 1999; Vazdarjanova and McGaugh, 1999; White and McDonald, 2002; Blundell et al., 2003; Yin et al., 2008), which in turn project to the NAc where it is associated with selection of a proper CR.

Berridge and other influential researchers addressed their studies to elucidate what aspects of Pavlovian conditioning depend on the meso-accumbal dopamine system – learning, incentive motivation or pleasure (Belin and Everitt, 2008; Berridge et al., 2009). Berridge (2012) defines (Pavlovian) incentive learning as the associative process that gives incentive value to arbitrary cues, such as a Pavlovian CS that is associated with a rewarding US. Incentive motivation is defined at the moment of performance and

results from the integration of what has been learned (that a US is cued by a CS) and the neurobiological state at the moment in which the CS is re-encountered (e.g., appetite states, satiety states, drug states). From this integration arises the 'wanting,' i.e., the desire of getting a rewarding US signaled by that CS. The last component – the pleasure or 'liking', is the subjective appreciation of the hedonic property of that US. These authors maintain that the midbrain dopaminergic projections to the NAc (particularly to the NAc shell) are critical for the incentive salience that strongly modulates the wanting, but is not needed for learning the CS-US association or for determining the hedonic appreciation of the US – the liking. The body of evidence for the role of NAc dopamine in the wanting, but not the liking and for learning of the CS-US association is quite strong. The findings of these authors argue in opposition of the proposal that the phasic release of dopamine in the striatum is a prediction-error or teaching signal that guides learning, a hypothesis that is supported by extensive electrophysiological evidence (Schultz, 2007).

These two views are not necessarily in contradiction if the type of learning strengthened by phasic dopamine release is not the CS-US association, but the CS-CR or the CS-instrumental response associations (Da Cunha et al., 2009). There is compelling evidence that the CS-US memory traces are consolidated in the basolateral complex of the amygdala when the CS is a discrete cue (Gallagher and Holland, 1994; Vazdarjanova and McGaugh, 1999; White and McDonald, 2002; Blundell et al., 2003; Vianna et al., 2004; Yin et al., 2008) and in the hippocampus when the CS is a context (Phillips and Ledoux, 1992; Maren et al., 1997; Holland and Bouton, 1999; Burgess et al., 2002; Vianna et al., 2004). As both the hippocampus and basolateral amygdala send glutamatergic projections to the NAc (see above), it is reasonable to posit that the midbrain projections to the NAc medial shell can generate either intense appetitive motivation to eat or intense actively fearful motivation, depending on whether the current environment is comfortable and familiar or overstimulating and aversive (Berridge, 2012). In other words, interruptions in glutamate signals coming from the basolateral amygdala and hippocampus (signaling the cues and context that signal a US) can trigger approach/avoidance responses toward the US due to the connections of the NAc with the lateral hypothalamus and ventral pallidum. Selection of the proper response can be improved by the release of dopamine, which increases the signal-to-noise ratio in glutamatergic synapses in the NAc. This may explain the wanting effect (Berridge, 2012) and the 'invigoration of approach' (Ikemoto and Panksepp, 1999) attributed to NAc dopamine. The same dopamine can also increase other action-selection processes in response to a CS previously paired with an appetitive US. This may explain the action-arousal property of striatal dopamine proposed by Ikemoto (2007). Finally, although striatal dopamine might not improve CS-US learning, as advocated by Berridge (2012), there is compelling evidence that the phasic release of dopamine in the NAc signals prediction errors and improves CS-UR associations by altering the strength of glutamatergic synapses. In this sense, the NAc is a site of learning, not of the CS-US, but of the CS-CR association (Dombrowski et al., 2012).

## Roles of the striatum in selection of instrumental actions

It remains controversial whether the ventral striatum plays a role in learning and performance of instrumental actions. Smith-Roe and Kelley (2000) reported that rat learning of actions instrumental to getting food is deeply delayed by the pre-training administration of D1 receptor antagonists into the NAc core. The same effect was observed in rats that received post-training injections of a protein synthesis inhibitor in the same site (Hernandez et al., 2002; Jonkman and Everitt, 2011). These findings are apparently in contradiction with the results of other studies reporting that excitotoxic lesions of the NAc core produced no effect on instrumental learning (Corbit et al., 2001; Ito et al., 2004). Independent of this controversy, it is well accepted that the release of dopamine in the NAc shell in response to a stimulus with incentive salience (a CS previously paired with a rewarding US) can invigorate instrumental performance directed to the same reward (Lovibond, 1983; Di Chiara, 2002), a phenomenon known as Pavlovian-to-instrumental transfer (PIT) (Trapold et al., 1968; Hall et al., 2001). In addition, release of dopamine in the NAc core seems to invigorate instrumental responses in the environment where conditioning occurred, a phenomenon called action-arousal in conditioned contexts (Ikemoto, 2007).

Early evidence for a role of the dorsal striatum in motor functions appeared more than 200 years ago and became well established in the first half of the twentieth century. However, only more recently has a role of the basal ganglia in cognitive functions been generally accepted (see White, 2009 for a review). The hypothesis that the dorsal striatum is the core structure in one of the multiple memory systems in the brain arises from studies with patients that, due to lesions in the hippocampal formation, had lost the ability to form memories that could be reported in a declarative manner but conserved the capacity to learn things

that could be expressed by a motor procedure (Scoville and Milner, 1957; Cohen and Squire, 1980). The multiple memory systems theory (McDonald and White, 1994; Packard and Knowlton, 2002) received extensive support from studies with models of declarative and procedural memory in animals and patients with lesions (Packard et al., 1989, 1992; Packard and White, 1990; Packard and McGaugh, 1992; McDonald and White, 1993; McDonald and White, 1994; Knowlton et al., 1996; Squire and Zola, 1996; Aggleton and Brown, 1999; Da Cunha et al., 2001; Packard and Knowlton, 2002; Schroeder et al., 2002), pharmacological manipulations (Izquierdo et al., 1992; McDonald and White, 1994; Packard and McGaugh, 1996; Izquierdo et al., 2006), genetic manipulations (Aggleton and Brown, 1999; Lobo et al., 2007; Ardayfio et al., 2008; Bach et al., 2008; Leea et al., 2008; Yu et al., 2009) and deep brain stimulation (Schumacher et al., 2011) in the hippocampus and dorsal striatum, as well as from studies showing activation of these areas (Aosaki et al., 1994; Jenkins et al., 1994; Aggleton and Brown, 1999; Jog et al., 1999; Maguire et al., 2000; Guzowski et al., 2001).

Studies from our and from other laboratories also provided support to add other nuclei of the basal ganglia to the procedural memory system. These include nuclei such as the SNc (Mitcham and Thomas, 1972; Routtenberg and Holzman, 1973; Staubli and Huston, 1978; Delacour et al., 1977; Hicks et al., 1979; Nikolaus et al., 1997; Matsumoto et al., 1999; Da Cunha et al., 2001, 2006, 2007; Gevaerd et al., 2001a,b; Miyoshi et al., 2002, 2012; Perry et al., 2004; Ferro et al., 2005; Tadaiesky et al., 2008; Ho et al., 2011), the pedunculopontine tegmental nucleus (Steckler et al., 1994; Brown et al., 1999; Satorra-Marin et al., 2006; Andero et al., 2007; Wilson et al., 2009; Bortolanza et al., 2010; Lester et al., 2010), the pallidum (Jahanshahi et al., 2000) and the subthalamic nucleus (Hicks et al., 1979; Jahanshahi et al., 2000; van Wouwe et al., 2011). It is important to stress that the influence of these other nuclei on learning and memory may not only derive from their relationships with basal ganglia circuitry, but also from their modulatory influences on thalamocortical neuronal activity.

Once it was well established that dorsal striatum and hippocampus encompass the core structures of declarative and procedural memory systems, the focus of research moved to the question of what is the nature of the information encoded in each of these memory systems. In humans, the declarative memories were defined as those that store information about facts (episodic memory) and concepts (semantic memories). Further studies showed that it is the episodic memories that can be critically impaired in patients with lesions restricted to the hippocampal formation (Cabeza et al., 1997; Aggleton and Brown, 1999). The main features, which can be modeled in animal models of episodic memory, are the encoding of information about what, where and when specific events occurred and information that can be flexibly used in different contexts (Eichenbaum, 2008). Non-spatial tasks that model the relational and flexible aspects of declarative memories include the social transmission of food preference (Bunsey and Eichenbaum, 1995; Vale-Martinez et al., 2002) and the human (Diamond, 1990), monkey (Meunier et al., 1993) and rat versions of the delayed non-matching-to-sample task (Clark et al., 2001). Learning of all these tasks is impaired by lesions in the hippocampal formation and closely related structures.

The rodent models that better assimilate the 'where' and 'flexible' nature of declarative memories demands that the animal learn to navigate in a maze in a flexible manner (e.g., departing from different locations) to get a reward in a specific location. The Morris water maze (Morris et al., 1982) and the 8-arm radial maze (Olton et al., 1979) are examples of models that have been extensively used in these studies. Variations of the same tasks in which the animal learns how to get the same reward, but using an S-R strategy have been used as models of procedural memory tasks. In these variations, the animal learns to approach a cue that, despite being placed in different locations at each trial, always signals the current location of the reward (Packard and White, 1991; Da Cunha et al., 2006). Learning to navigate in these mazes following a place or a response (of approaching the cue) strategy is considered, respectively, as a rodent model of declarative and procedural memories.

Double dissociation studies in which lesions or inactivation of the hippocampus or dorsal striatum impaired, respectively, place and response learning were taken as evidence that the navigation action was under the control of the declarative or procedural memory system (Packard and White, 1991; Packard and McGaugh, 1996; Da Cunha et al., 2006). However, this interpretation could not accommodate recent findings that lesions in the dorsomedial parts of the striatum impair place learning (Devan et al., 1999) and that some striatal neurons fire when the animal approaches a specific place (Mizumori et al., 2004). Some authors have tried to solve this inconsistency by proposing that the dorsomedial striatum is part of the 'spatial/declarative memory system' (McDonald et al., 2004). However, if this were the case, rats with double lesions in the dorsolateral striatum and dorsal hippocampus should be as impaired in learning how to navigate by a spatial strategy as rats with lesions restricted to the hippocampus (that are mildly impaired) and those

with lesions restricted to the dorsolateral striatum (that are not impaired at all). We tested these predictions, but found that rats with these double lesions were deeply impaired in navigating in a Morris water maze using spatial or cue strategies (Miyoshi et al., 2012). Such findings suggest that both memory systems based on the hippocampus and dorsolateral striatum are needed for navigation using both strategies and that the multiple memory system theory needs to be reformulated.

In addition, experiments with monkeys have shown that declarative tasks are learned quickly, whereas S-R habit (procedural) tasks are learned slowly (Fernandez-Ruiz et al., 2001). However, lesions in the dorsal striatum of rats impaired hippocampal-dependent tasks, which are learned quickly by control rats, such as odor discrimination memory tasks. Such dorsal-striatum-lesioned rats were also impaired in learning other tasks learned more slowly by control rats, such as object and pattern discrimination tasks (Broadbent et al., 2007).

The main problem with the hypothesis that response vs. place navigation models capture the key properties of the declarative and procedural memory systems is the assumption that both the hippocampus and the dorsal striatum hold control over navigation behavior. This goes well with the current evidence that the main role of the dorsal striatum is to select motor actions that result in rewarding outcomes (Da Cunha et al., 2009). However, there is no support that the hippocampus and associated cortex has direct access to the motor nuclei bypassing the basal ganglia. Therefore, we propose to keep the well-supported idea that the hippocampal formation encodes and stores contextual [e.g., spatial, relational, i.e., stimulus-stimulus association (S-S)] information organized in episodes, but to replace the idea that the hippocampus holds control over motor actions for the (also well-supported) hypothesis that the striatum uploads information from the hippocampus and other areas of the brain and uses it to select actions to approach a place in which the subject received a reward. According to this view, the answer to the question posed above is that the episodic memory system based on the hippocampus stores memories about relations among stimuli (S-S) that are encoded as contexts or episodes, whereas the procedural memory system, based on the dorsal striatum, stores information about how to select instrumental actions in response to cue or contextual stimuli that result in rewarding outcomes [stimulus-response-outcome associations(S-R-O)].

The next relevant question is whether different subregions of the striatum store S-R and R-O (also as action outcome; AO) associations. As reviewed above, the instrumental responses (actions) selected on the basis of S-R or (A-O) contingencies are named S-R habits and goal-directed actions, respectively (Dickinson and Balleine, 2002). Currently, the most accepted view is that learning and performance of instrumental goal-directed actions and S-R habits in rodents depends, respectively, on the dorsomedial and dorsolateral parts of the striatum (Yin et al., 2004, 2006; Redgrave et al., 2010; Dezfouli and Balleine, 2012). Evidence for this comes from experiments showing that the behavior of bar-pressing for appetitive rewards is sensitive to outcome devaluation in rats after lesion or inactivation of the dorsolateral striatum (Yin et al., 2004, 2006), but not in rats with a lesion in the dorsomedial striatum, or in controls trained under schedules that favor S-R habit learning (Yin et al., 2004). In contrast, lesions or inhibition of the posterior dorsomedial striatum have the opposite effect, favoring learning and expression of S-R habitual responding, which is insensitive to outcome devaluation and A-O contingency degradation (Yin et al., 2004, 2005a,b), without impairing the ability of rats to discriminate either between actions or between outcomes (Yin et al., 2005b). Further evidence was provided by studies in rats with partial depletion of dopamine in the dorsolateral striatum as a result of methamphetamine treatments (Son et al., 2011), lesions of the SNc with 6-OHDA (Faure et al., 2005) followed by systemic injection of D1 or D2 agonists (Faure et al., 2010a) or infusion of D1 or D2 antagonists into this brain region (Boschen et al., 2011; Wietzikoski et al., 2012). A recent study suggested that the role of the dorsolateral striatum on S-R habits also depends on information uploaded from the central nucleus of the amygdala (Lingawi and Balleine, 2012).

The dorsolateral striatum is in receipt of strong projections from the sensorimotor cortex, but receives very few projections from limbic and associative areas (Parent and Hazrati, 1995a). Therefore, it is in position to associate stimuli to responses that can be automatically triggered by them. In contrast, the dorsomedial striatum receives projections from the dorsolateral prefrontal and limbic cortex, including the hippocampus and amygdala, regions that encode the value of the outcome as well as goals (Parent and Hazrati, 1995a; Ikemoto, 2007). This may explain why lesions and other manipulations of the rodent dorsomedial striatum affect performance of instrumental goal-directed actions.

As mentioned above, neurons in the putamen of primates and in the dorsolateral striatum of rats respond to visual and tactile stimulation when objects approach them and also to movement of the animals to locations in which they were previously rewarded (Graziano and Gross, 1993; Berke et al., 2009). Striatal neurons also respond to touch or movement of specific body parts (Graziano and Gross, 1993;

Flaherty and Graybiel, 1994; Gerardin et al., 2003; Tang et al., 2007). In the 'the mosaic of broken mirrors model', we propose that these automatic responses of approach to an object or location result from activation of specific striatal neurons of the direct pathway or by inhibition of neurons of the indirect pathway to the output stations of the basal ganglia (Da Cunha et al., 2009; Kreitzer and Berke, 2011).

In summary, although some controversies remain, the pieces of evidence accumulated so far support the view that instrumental actions are selected in the dorsal striatum – selection of goal-directed actions dependent on the dorsomedial striatum and S-R habits dependent on the dorsolateral striatum.

## Concluding remarks

After all, what motivates someone to behave in this way or that way? According to the current view, this depends on the type of behavior being discussed. URs are automatically triggered by stimuli important for the survival of the subject (e.g., food and harmful or threatening USs) or the preservation of its species (e.g., sex-related USs). CRs are not innately triggered by a CS, but depend on previous learning that predicts the imminence or proximity of a US. In addition, CRs are not motivated by the goal of getting an appetitive US or avoiding an aversive US – it is rather an involuntary response in anticipation of the US. However, many instrumental actions are motivated by the goal of approaching/consuming an appetitive US or avoiding an aversive US. Like the CRs, the goal-directed actions are not innate, but depend on learning about the relationship between specific actions and outcomes. Finally, the instrumental behaviors called S-R habits are not performed with the goal of achieving specific outcomes, but rather as automatic responses to a neutral stimulus that was previously paired with the action that resulted in appetitive outcomes or in avoidance of aversive outcomes. Therefore, the difference between a habit and a goal-directed action is that the former is automatically triggered by a discriminative stimulus, whereas the latter is motivated by a goal. S-R habits are also different from CRs, which are learned by simple exposure to paired CS-US stimuli that are presented independent of the subject's response. Therefore, according to the current learning theories, the motivation to perform different motor behaviors depends on how they are linked to USs, CSs, outcomes and discriminative stimuli. Incentive learning theories propose the physiological and/or emotional state (e.g., hunger, thirst, and satiety) as an additional variable to modify the direction and intensity of a specific motivated behavior.

The body of evidence reviewed here points to the basal ganglia as the core system in action-selection. Therefore, the next critical question is, 'how does the basal ganglia select actions based on emotional states, USs, CSs, goals and discriminative stimuli'? According to the current anatomical models of basal ganglia circuitry, specific actions can be initiated by neurons of the direct pathway (striatum-SNr/GPi) and ended or avoided by striatal output neurons of the indirect pathway (striatum-GPe-SNr/GPi), whereas performance of concurrent actions are prevented by activation of the hyperdirect pathway (cortex-STN-SNr/GPi). Striatal neurons of the direct and indirect pathways are activated by cortical and subcortical neurons encoding USs, CSs, goals and neutral stimuli. Learning how to respond to specific stimuli or goals in an adaptive manner depends on alterations in the strength of the synapses between these cortical/subcortical neurons and striatal neurons of the direct and indirect pathways. Such alterations occur when phasic increases or decreases in extracellular striatal dopamine occur in response to discrepancies between expected and obtained rewards (prediction errors). Striatal dopamine also 'energizes' performance of adaptive actions by increasing the signal-to-noise ratio of corticostriatal neurotransmission in a manner that increases the likelihood of firing in the striatal neurons that are more active due to inputs of information relevant to action-selection. Phasic increases in striatal dopamine also occur in response to salient USs or CSs with incentive salience.

Finally, the next question addressed in this review is, 'are there specific regions in the basal ganglia dedicated to selection of actions based on specific emotional states, USs, CSs, goals and neutral stimuli'? A growing body of evidence supports a functional compartmentation hypothesis that the limbic, associative and motor cortico-basal ganglia loops are, respectively, involved in action-selection of UR/CRs, goal-directed actions and S-R habits. Studies addressing the role of the different sub-regions of the striatum support the view that selection of URs depends on the medial NAc shell and olfactory tubercle, selection of CRs depends on the NAc core and lateral olfactory tubercle, selection of goal-directed actions depends on the dorsomedial striatum of rodents (anterior caudate nucleus of primates) and selection of S-R habits depends on the dorsolateral striatum of rodents (putamen of primates).

Such a view of how different kinds of motivated behaviors are selected implies that, instead of encoding, storing and expressing all aspects of procedural memories, as proposed by the multiple memory systems theory, the role of the basal ganglia is restricted to selecting those actions needed to express both declarative and procedural memories. According to this view, selection of the actions used

to express a spatial memory, for example, occurs in the basal ganglia, but the memory *per se* of a given location in an environment (independent of the actions needed to go there) is encoded and stored elsewhere, possibly in the hippocampal formation and related brain areas. In the same way, expression of an emotional memory learned by Pavlovian conditioning depends on the basal ganglia only for the selection of the response conditional to the CS presentation, but the memory of the CS-US association is stored elsewhere, possibly in the basolateral amygdala (for discrete CSs) or in the hippocampus (for contexts).

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Claudio Da Cunha, has aimed in his research to understand how the brain learns to select and initiate proper actions based on environmental cues (habits), outcome predictions (goal-directed actions), primary motives (unconditioned responses) or secondary motives (Pavlovian conditioned responses). In his lab they use *in vivo* electrochemical and microdialysis techniques combined with lesion and pharmacology behavioral studies in freely moving rats to test the hypothesis that action-selection depends on the functioning of the cortico-basal ganglia circuitry and its modulation by midbrain dopaminergic neurons. Such a hypothesis has strong implications for normal learning of procedural memories and abnormal learning and/or action selection processes that contribute to symptoms of Parkinson's and Huntington's disease, schizophrenia, drug abuse and other neuropsychiatric disorders.

Gonzalo Alexander Gomez Acosta, is currently working on his PhD thesis in Professor Da Cunha's lab. In his current work he is using *in vivo* electrochemical recording techniques to test how the release of dopamine in the nucleus accumbens during the presentation of a pair of conditioned and unconditioned stimuli is correlated with the prediction error related to the magnitude, duration, and probability of an appetitive or an aversive stimulus that are presented following presentation of a conditioned stimulus.

Charles D. Blaha, is interested in a systems neuroscience approach to understanding the neurobiological bases of incentive-motivated behaviors, neuropsychiatric disorders and autism spectrum disorders using state of the art *in vivo* electrochemical recording techniques. His program of research has involved elucidating receptor mechanisms and neuronal circuitry in the cerebellum, hindbrain and midbrain that are important targets for therapeutic drugs and for mediating the actions of the neurotransmitters acetylcholine, glutamate and several neuropeptides that critically control forebrain dopaminergic neurotransmission. His research also involves the development of new neurochemical recording procedures to improve the therapeutic success of deep brain stimulation in individuals suffering neurological disorders such as Parkinson's disease.

## 3.3. Diazepam inhibits phasic and tonic dopamine release in the nucleus accumbens

Alexander Gomez-A[1], Suelen L. Boschen[1,2], Adam H. Sugi[1], Amanda M. Fiorenza[1], , Danielle Beckman [2], Sergio T. Ferreira[2], Kendall Lee[3], Charles D. Blaha[3], Claudio Da Cunha[1]*

[1]Departamento de Farmacologia, Universidade Federal do Paraná, Curitiba 81.530-980, PR, Brazil.
[2]Institute of Biophysics Carlos Chagas Filho & Institute of Medical Biochemistry Leopoldo de Meis, Federal University of Rio de Janeiro
[3]Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, 55905, USA
* Corresponding author.

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**Abstract**

Diazepam is a benzodiazepine receptor agonist with anxiolytic and addictive properties. Microdialysis studies have shown that while most addictive drugs increase dopamine concentration in the nucleus accumbens, benzodiazepines cause the opposite effect. In the present study we used 20 min sampling *in vivo* microdialysis *and* sub-second fast-scan cyclic voltammetry to show that diazepam (1-3 mg/kg, i.p.) caused a dose-dependent decrease in tonic and phasic dopamine release in the nucleus accumbens of urethane anesthetized mice. This effect was prevented by administration of the benzodiazepine receptor antagonist flumazenil. No significant effects on measures of dopamine re-uptake were observed. These results suggest that the pharmacological effects of benzodiazepines might have a dopaminergic component. In addition, this study provides a likely mechanism by which benzodiazepines are claimed by some researchers as effective in the treatment of addiction by other drugs of abuse such as cocaine, amphetamines, and opioids.

**Keywords**

Dopaminergic neurons, electrochemistry, ventral tegmental area, nucleus accumbens core, GABA, anxiolytic, anticonvulsant.

Decades ago, the drugs used to treat anxiety (e.g. benzodiazepines and barbiturates) and psychosis (e.g., *chlorpromazine*, haloperidol, sulpiride) were named as minor tranquilizers and major tranquilizers, respectively[1]. Later on it was established that these two classes of drugs present quite different mechanisms of action and therapeutic properties. Benzodiazepines (BZs) are agonists of the central type BZ receptors linked to the γ-aminobutyric acid ($GABA_A$) receptor and are used as anxiolytics[2]. The typical antipsychotic drugs are antagonists of the D2 dopamine (DA) receptors[3]. In the current study, using *in vivo* microdialysis and fast-scan cyclic voltammetry (FSCV) to make 20 min and sub-second measures of tonic and phasic dopamine release, respectively, in the nucleus accumbens (NAc), we present evidence that BZs may also act as indirect DA antagonists by decreasing both tonic and phasic release of DA from meso-accumbal neural terminals.

Urethane anesthetized mice had a carbon-fiber FSCV recording electrode placed in the NAc and a stainless steel stimulating electrode placed in the ventral tegmental area (VTA). The VTA and NAc are brain nuclei rich in dopaminergic neurons and DA terminals, respectively[4]. After the electrochemical recording signal stabilized (did not decay by more than 20% per hour), 4 trains of electric stimulation 3 min minutes apart were applied in the VTA under the following conditions: baseline (before any drug administration) and 5 min after the administration of vehicle, the BZ receptor agonist diazepam (DZP 1, 2, or 3 mg/kg i.p), and then the BZ receptor antagonist flumazenil (FLU 2.5 mg/kg, i.p.). These drugs were administered sequentially in the same animals, but independent groups of mice received the different doses of DZP. A second control group of mice was submitted to the same protocol but received drug injections in a different order: baseline, vehicle, 2.5 mg/kg FLU, and 2 mg/kg DZP. Another control group received 3 injections of vehicle at the same time that the other groups received vehicle, DZP or FLU. At the end of this procedure, the 1 mg/kg DZP group also received an i.p. injection of the dopamine transporter (DAT) inhibitor nomifensine (20 mg/kg, i.p.) and electrically evoked DA release was monitored 5, 8 and 11 min later.

All stimulating electrodes were located in the VTA (Figure 1A) and all recording electrodes were located in the NAc core (Figure 1B). All microdialysis probes were also located in the NAc, at least 50% in the core part (Fig 1C).

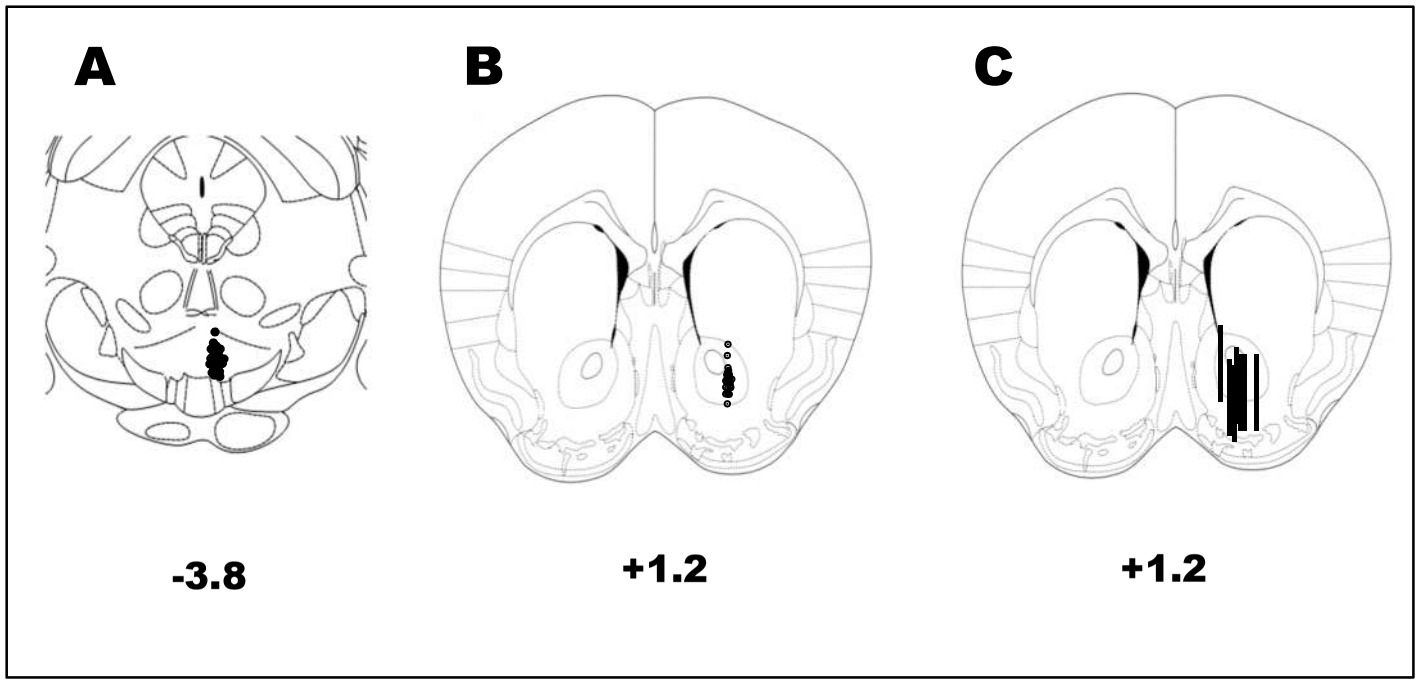



Figure 1. Schematic drawing of coronal sections showing the locations of the electrode and probe tips according to the mouse brain atlas of Paxinos and Franklin (2005). The approximate AP distances (mm) from the bregma are indicated. (A) Site of the stimulating electrodes in the mouse ventral tegmental area. (B) Site of the recording electrodes in the mouse nucleus accumbens. (C) Site of the microdialysis probes in the nucleus accumbens.

Cyclic voltammograms and corresponding pseudocolor plots show clear DA oxidation peaks occurring between +0.65 V and +0.79 V and a reduction peak between -0.20V and -0.36V (versus the Ag/AgCl reference electrode) with relatively low currents in other potentials. On average, the oxidation of 0.5 μM DA at an electrode with 100 μm exposed tip caused a current of 4.2 ± 0.3 nA. The average length of the carbon-fiber electrodes used measured 87 ± 18 μm.

The voltammograms obtained *in vivo* have oxidation and reduction currents peaks in the same range as those observed in the flow cell calibration of the electrodes. Individual examples of FSCV measurements of DA release in the NAc evoked by electrical stimulation of the VTA are shown in Figure 2. The selected examples are representative of the recordings obtained from all animals. Background noise, defined as the variance of oxidation current measured between -65 and 5 s before the electric stimulation, was 0.04 ± 0.02 nA and did not vary significantly among groups ($F(4,23) = 0.73$; $p = 0.58$). Data from 31 out of 444 electrically evoked DA signals were discarded because they overlapped with obvious stimulation artefacts. The remaining data were averaged by animal and the composite data of all animals were used for statistical tests.

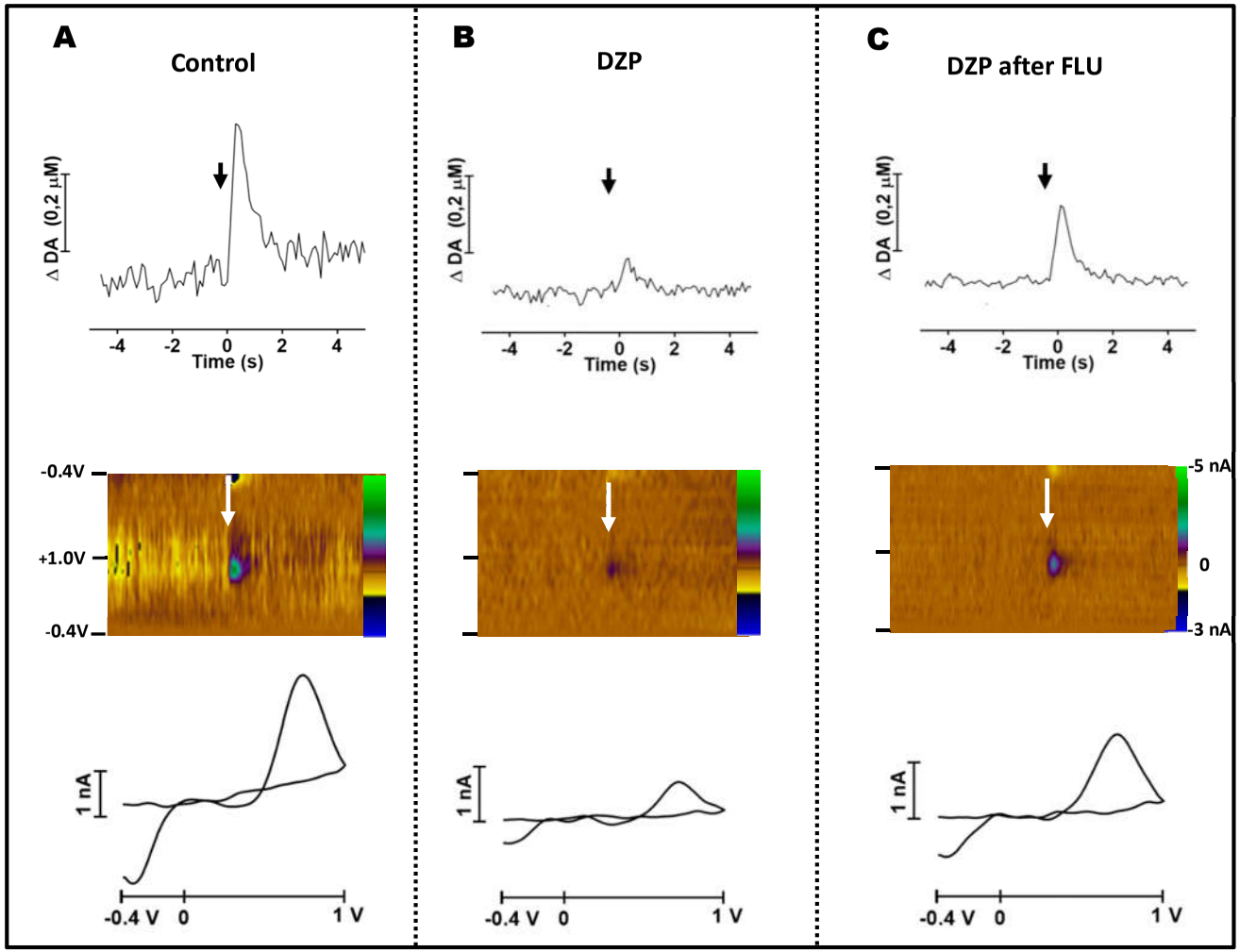



Figure 2. Individual examples illustrate the effect of the i.p. administration of 2 mg/kg diazepam and 2.5 mg/kg flumazenil on DA release in the nucleus accumbens evoked by electrical stimulation of the ventral tegmental area in urethane anesthetized mice. DA was monitored by background-subtracted FSCV at carbon-fiber microelectrodes. From top to bottom are shown concentration versus time traces, pseudo-color plots and cyclic voltammograms taken at the peak oxidation current. The arrows indicate when the electrical stimulation occurred.

As shown in Figure 3, i.p. administration of the DAT blocker nomifensine (20 mg/kg) did not change the potentials at which dopamine oxidizes or reduces (Figure 3A and 3C). In addition, nomifensine administration caused significant time-dependent increases in the amount of DA released (calculated from the height of the oxidation peak; Fig 3D), increases in decay half-life ($T_{1/2}$) (Figure 3E) and decreases in the decay rate constant (K) (Figure 3F). These findings support the use of the FSCV oxidation current as a measure of variation of extracellular DA release in the present study[5].

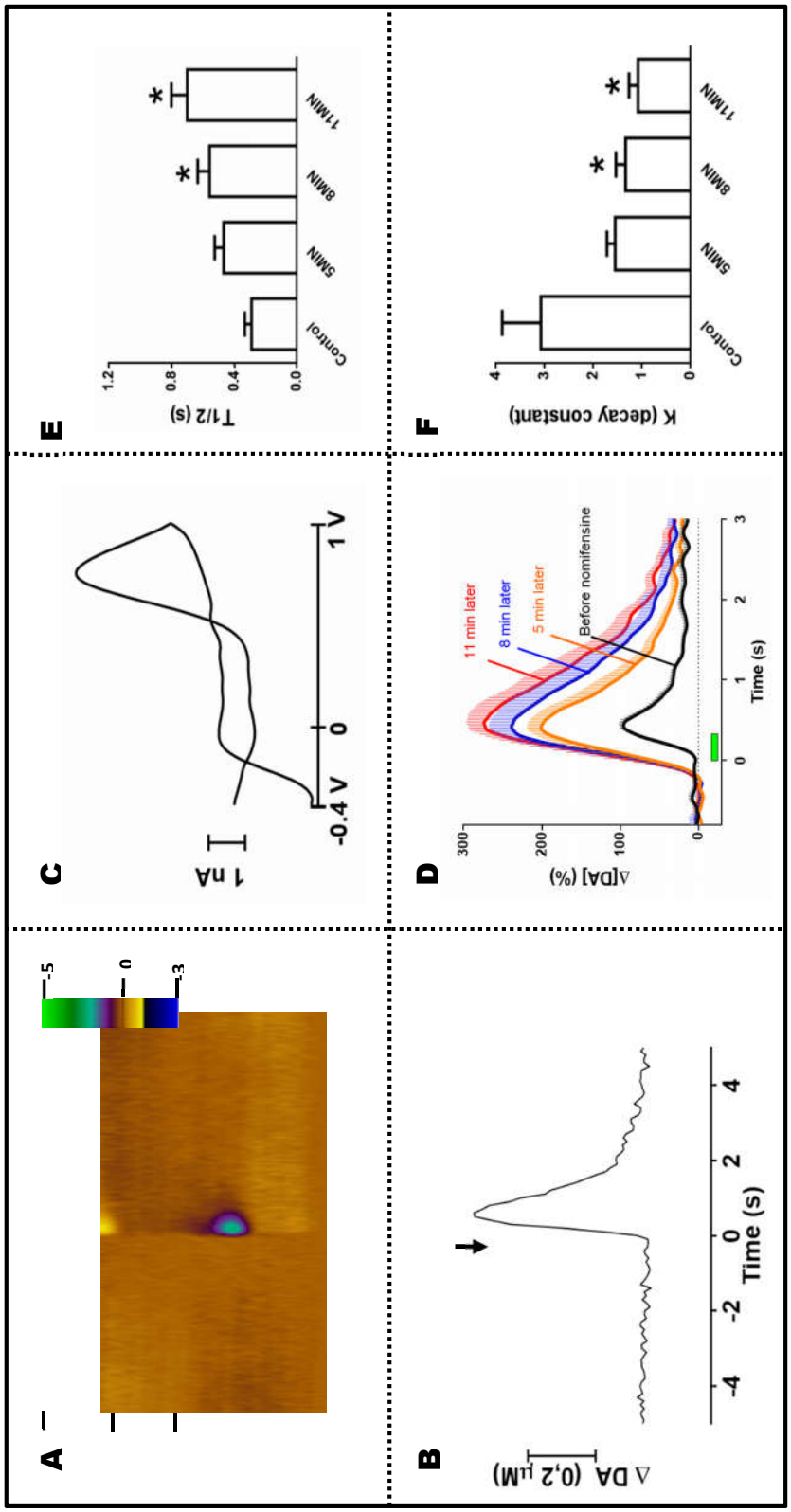



Figure 3. Effect of the i.p. administration of 20 mg/kg nomifensine on electrically-evoked dopamine release recorded by FSCV. Mice (N = 5) were anesthetized with urethane and the release of DA in the nucleus accumbens evoked by the electric stimulation of the VTA was monitored by background-subtracted FSCV at carbon-fiber microelectrodes. Data are expressed as mean ± SEM. One-way ANOVA showed a significant drug-treatment effect for the T1/2 ($F(3,16)=5.81$; $p < 0.01$) and for K decay constant measures ($F(3,16)=4.40$, $p < 0.05$). * $p < 0.05$, Dunnett test.

Figure 4A shows the average height of the peaks (Δ[DA]) and Figures 4B-D show the temporal variation of the DA concentration in response to the VTA stimulation. Average $T_{1/2}$ and K values are shown in Supplemental Table 1. Mice in the control group received 3 injections of vehicle at the same time that the mice in the other groups received vehicle, DZP or FLU. Data from the same animals were used for the control group shown in the Figures 4D-F, Supplemental Figure 1, and Supplemental Table 1.

As shown in Figure 4A, the height of the DA peaks (Δ[DA]) in the control group did not significantly decrease during the 1-hour duration of the experiment ($F(3,24) = 1.17$, $p = 0.34$, one-way ANOVA). This control is important to show that any observed decrease in the peak heights in the groups treated with DZP was not caused by electrode desensitization. Figure 4A also shows that DZP caused a dose-dependent and significant reduction in the size of the peaks. A repeated-measures two-way ANOVA showed a non-significant drug treatment factor ($F(3,19) = 1.82$, $p = 0.18$), a significant time effect ($F(3,57) = 17.1$, $p < 0.001$), and a significant interaction between these factors ($F(9,57) = 2.12$, $p < 0.05$). Dunnett's post-hoc tests showed that DZP at 2 and 3 mg/kg, but not at 1 mg/kg, caused a significant reduction in the DA peak height ($p < 0.05$). Post-hoc tests also showed that 2.5 mg/kg FLU reversed the effect of DZP at 2 mg/kg, but not at 3 mg/kg ($p < 0.05$, Figure 4A). Supplemental Figure S1 shows that 2 mg/kg DZP preceded by 2.5 mg/kg FLU did not cause a significant decrease in electrically-evoked DA release.

The shape of the DA peaks (notably, the descending trace corresponding to re-uptake of the neurotransmitter) shown in Figure 4B-D and in Supplemental Figure S1B-D) suggests that DZP did not affect DA re-uptake. This was confirmed by the analysis shown in Supplemental Table 1. While nomifensine caused a significant and time-dependent increase in the $T_{1/2}$ and corresponding decrease in the K (Figure 3), these factors were not significantly affected by any dose of DZP (Supplemental Table 1).

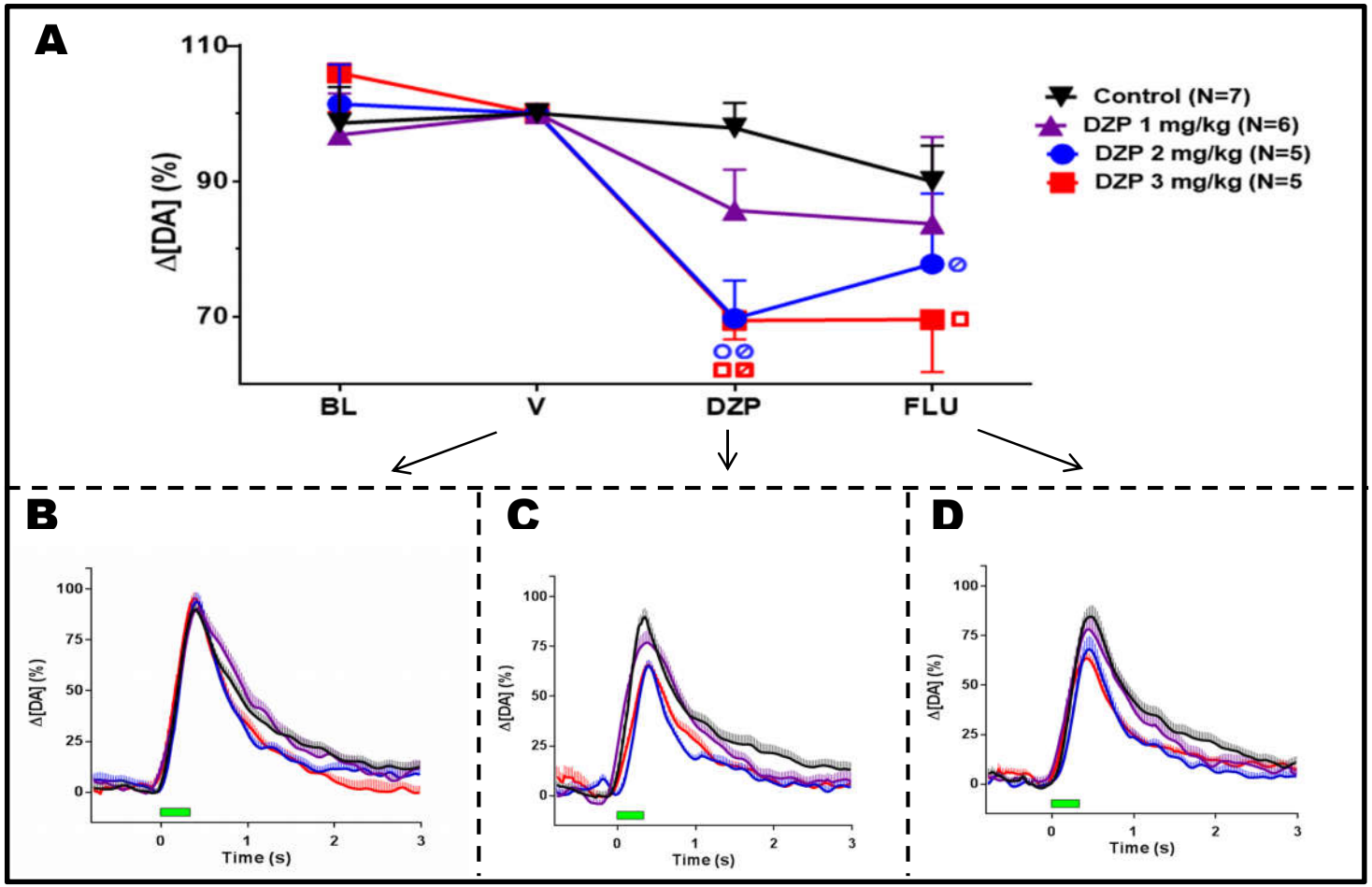



Figure 4. Effect of diazepam (DZP) on dopamine release. Mice were anesthetized with urethane and the release of DA in the nucleus accumbens evoked by the electric stimulation of the VTA was monitored by background-subtracted FSCV at carbon-fiber microelectrodes. (A) Four peaks of evoked DA release were monitored in the following order: under baseline (BL) condition (before the injections), 5 min after the injection of vehicle (V), DZP and 5 min after the injection of 2.5 mg/kg flumazenil (FLU). The mice of the control group always received vehicle when the mice of the other groups received vehicle, DZP, and FLU. The average concentration versus time traces recorded after injection of V (B) DZP (C), and FLU (D) are shown in the lower panels. Drug were injected i.p. The green bar indicates the duration of the electric stimulation. Data are expressed as mean ± SEM percent of the baseline. , $p < 0.05$ compared to the control group at the same time; , $p < 0.05$ compared to the same group at the previous time (Dunnett test after one-way ANOVA).

Figure 5 shows that the tonic concentrations of DA measured in the microdialysis samples also were significantly reduced by the i.p. administration of 2 mg/kg DZP and that this effect is reversed by the i.p. administration of 2.5 mg/kg FLU. A repeated-measures two-way ANOVA showed a non-significant drug treatment factor ($F(1,5) = 1.40$, $p = 0.29$), a significant time effect $F(10,50) = 2.62$, $p < 0.05$), and a significant interaction between these factors ($F(1,50) = 4.50$, $p < 0.001$). Dunnett's post-hoc tests showed that DZP caused a significant reduction in tonic DA concentration ($p < 0.05$). These post-hoc tests also showed that 2.5 mg/kg FLU significantly reversed this reduction ($p < 0.05$).

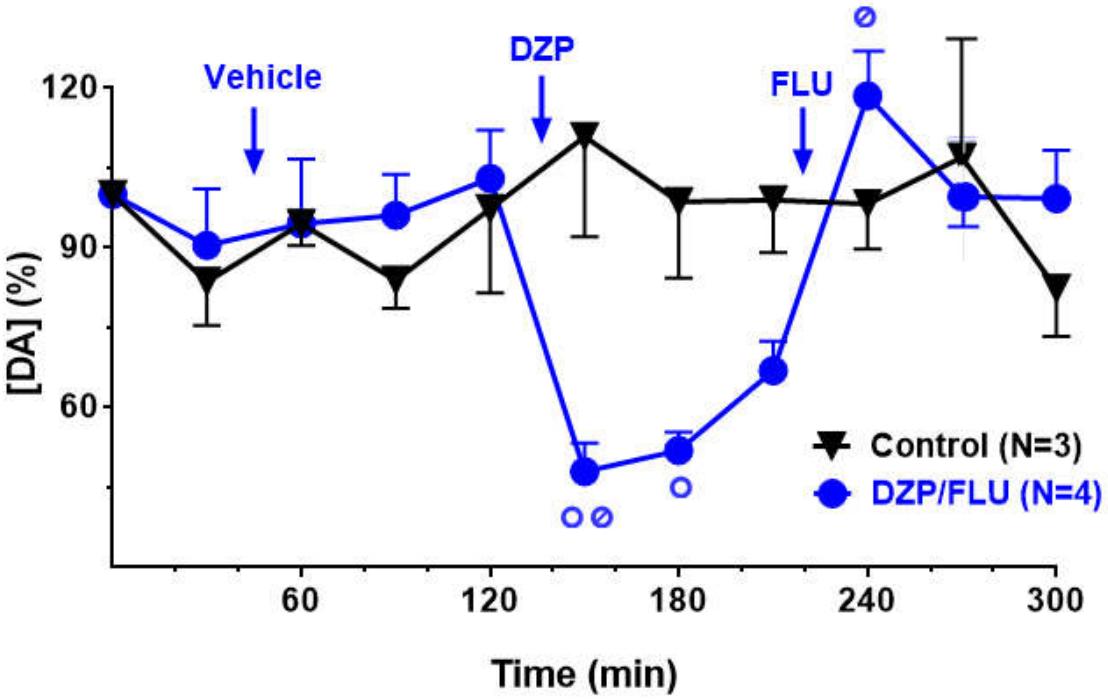



Figure 5. Effect of diazepam on variation of tonic levels of dopamine in the mouse nucleus accumbens. Mice were anesthetized with urethane and microdialysis samples were collected every 30 min and DA concentration were measured by HPLC-EC in the following order: under baseline (BL) condition (before the injections); after the injection of 2 mg/kg diazepam (DZP), and after the injection of flumazenil (FLU). The mice of the control group always received vehicle when the mice of the other groups received diazepam and flumazenil. Data are expressed as mean ± SEM percent of the baseline. $p < 0.05$ compared to the control group at the same time; $p < 0.05$ compared to the same group at the previous time (Dunnett test after repeated measure two-way ANOVA).

BZ drugs increase the affinity of GABA for certain subtypes of $GABA_A$ receptors, causing hyperpolarizing inhibition mediated by increase of the postsynaptic membrane conductance to $Cl^-$ ions[2]. In the present study we present evidence that BZs also affect DA neurotransmission in the NAc. More specifically, we showed that the BZ receptor agonist DZP, used at doses that cause anxiolytic-like effects in rodents[6], decreased the electrically-evoked release of DA in the NAc. The reversal of this effect by the BZ antagonist FLU[7] suggests that the effect of DZP on DA release was mediated by $BZ/GABA_A$ complex receptors.

The α1 subunit of the $GABA_A$ receptor (necessary for BZ binding) is expressed in GABAergic neurons of the NAc that project to the VTA[8] and in GABAergic interneurons of the VTA[9]. However, $GABA_A$ receptors expressing the α1 subunit are not expressed in the dopaminergic neurons of the VTA[9]. This pattern of BZ receptor distribution would be seen as supporting the hypothesis that, rather than decreasing DA release in the NAc (as shown in the present study), BZs would increase DA release in the NAc by disinhibiting GABAergic neurons that make synaptic contact with the DA neurons of the VTA. However, no direct evidence has been provided that acute administration of a BZ increases DA release in the NAc. On the contrary, in addition to the present study all microdialysis studies have shown that DZP[10] and other BZs[11-14] decreased extracellular DA levels in the NAc. The mechanism underlying this phenomenon remains unclear.

This is the first time that a suppressive effect of a BZ on DA release was shown by using well controlled FSCV recording. We also used *in vivo* microdialysis to confirm that DZP decreases DA release in the NAc. However, in microdialysis studies samples were collected at intervals of 20-30 min while in the FSCV recording used in this study changes in extracellular DA release were measured every 100 ms. Microdialysis measures tonic variations in extracellular levels of DA which can vary in the time scale of minutes to hours due to alterations in the synthesis, metabolism, and tonic firing rate of DA neurons[5]. However, this temporal resolution is not enough to measure changes in DA release due to relatively rapid phasic activation or inhibition of DA neurons in response to salient, rewarding, or aversive stimuli[15, 16].

Another advance of the present study is that FSCV recording of DA release allowed measures of the kinetics of both DA release and DA re-uptake. Our results clearly showed that DZP decreased DA release without affecting DA re-uptake. The lack of significant difference among groups was not due to low sample size or poor quality of the

data as using the same method, we were able to detect significant differences caused by the DAT inhibitor nomifensine on $T_{1/2}$ and K during the re-uptake phase of the DA peaks.

In the present study, DZP was injected systemically. Thus, it is possible that DZP affects DA release in the NAc by acting in other sites of the brain. However, a microdialysis study by Gruen et al.[17] showed that intra-striatal infusion of the BZ receptor antagonist, Ro15-1788 or the $GABA_A$ receptor antagonist SR 95531 increased the extracellular concentration of DA and that this effect was blocked by co-administration of DZP or GABA. In addition, Takada et al.[18] showed that the BZs midazolam and flunitrazepam decreased extracellular DA in the dorsal striatum. Furthermore, an amperometry study reported that the infusion of the $GABA_A$ receptor blocker picrotoxin into the rat amygdala caused a phasic increase in DA concentration[19].These findings suggest that BZs act locally at the BZ/$GABA_A$ complex receptor to decrease tonic DA in the striatum. However, two other microdialysis studies reported that local infusion of the BZs DZP (at a dose similar to those used in the present study) and flurazepam decrease extracellular DA in the NAc, but not in the dorsal striatum[10, 11]. Based on our current findings it seems plausible that proximity of the tip of the microdialysis probes to the NAc in the Gruen et al.[17] and Takada et al.[18] studies might explain the differences between their results[17,18] and those of the other studies[10, 11].

The addictive property of BZs is mediated by the same subunit of the BZ/$GABA_A$ receptor complex involved in their anxiolytic effect, which limits the therapeutic use of BZs[2, 20]. However, as discussed above, while other drugs of abuse such as cocaine, amphetamine, and opioids increase DA release in the NAc[21] , BZs cause the opposite effect. This makes BZs candidates to treat abusive use of opioids and psychostimulants as shown in animal[22-25] and human[26] studies.

The VTA-NAc pathway plays a critical role in motivation[4, 15]. Therefore, the decrease in DA release in the NAc as shown in the present study, might impact the motivational dimension of anxiety, affecting the response to psychostimulant drugs[27] and to stressful stimuli such as novelty, physical and social stress[28]. In other words, the present study suggests that the anxiolytic properties of the BZs might have a dopaminergic component.

**Methods**

Twenty-eight adult Swiss mice (20-40 g) from the colony of the Universidade Federal do Paraná were used for the FSCV recordings. An additional 7 mice were used in the microdialysis experiment. They were housed in groups of 5 in polypropylene cages (41x34x16 cm) with sawdust bedding under a 12 h/12 h light/dark cycle (lights on 7:00 am) and controlled temperature (22 ± 2 ˚C). Food and water were available ad libitum. After surgery the animals were housed individually. All procedures were in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the institutional Ethics Committee for Animal Experimentation of the Universidade Federal do Paraná (protocol number 638), and are consistent with the Brazilian law (Bil#11.794/8 October 2008).

Each mouse was anesthetized with urethane (1.5 mg/kg, i.p) and mounted in a stereotaxic frame (David Kopf Instruments, Tujunga, CA). A scalpel was used to make a 1 cm midline incision exposing the skull bone surface, which was cleaned using the scalpel and sterile cotton swaps. A stainless steel burr (David Kopf Instruments) was used to drill 2 circular openings of 2 mm diameter above the NAc in the left frontal bone and above the VTA in the parietal bone. The openings were centered in the following stereotaxic coordinates, according to the Atlas of Paxinos and Franklin[29]: NAc, AP +1.2 mm, ML +1.2 mm; VTA, AP -3.8 mm, ML +0.2 mm. An Ag/AgCl wire reference electrode was inserted 0.5 mm into a smaller hole drilled in the right parietal bone and fixed to the bone with dental cement.

Fast-scan cyclic voltammetry recording. The stimulating electrode was lowered into the VTA in steps of 0.1 mm until the highest evoked DA response was recorded, between the following DV range below dura: 3.4 - 4.1 mm. This procedure was repeated to optimize the location for the recording electrode in the NAc core: 3.2 - 4.0 mm. FSCV measurements were obtained with a Wireless Instantaneous Neurotransmitter Concentration Sensor (WINCS, Mayo Clinic, Rochester, MN) system and processed by the WINCSware with MINCS software (version 2.10.4.0, Mayo Clinic). Every 100 ms, a triangular waveform potential of -0.4 V to +1.0 V to -0.4 V was applied at 300 V/s to the carbon-fiber recording electrode versus the Ag⁄AgCl reference electrode. Oxidative and reductive currents were continuously sampled at 100 ksamples/s, 944 samples/scan. The digital output was filtered with a Butterworth low pass filter (800 Hz, 3 poles). The triangular waveform potential was applied to the electrode for 10 min before recording commenced in order to condition the electrode. Next, trains of 20 biphasic pulses (0.5 ms

per pulse, 600 μA, 60 Hz) were applied to the stimulating electrode every 180 s via a programmable optical isolator pulse generator (MINCS, Mayo Investigational Neuromodulation Control System, Mayo Clinic, MN). Data of 4 evoked peaks during baseline, vehicle, DZP and FLU were collected for each animal. Background-subtracted cyclic voltammograms were obtained by subtracting voltammograms collected during stimulation from those collected up to 3 s before the stimulation. Voltammetric responses were viewed as pseudo-color plots with the abscissa as voltage, the ordinate as acquisition time, and the current encoded in color. Temporal responses were determined by monitoring the current at the peak oxidation potential for DA in successive voltammograms. Current values were converted to concentration based on calibration curves obtained after the experiments with the electrodes immersed in known concentrations of DA in a flow cell. Change in DA concentration (ΔDA) was measured by subtracting the higher and lower values of current in the optimal voltage for DA oxidation (from +0.65 to +0.75 V) recorded between 3 s before and 3 s after the electrical stimulation. $T_{1/2}$ (time required for DA signal to decay 50% compared to the initial value) and K (kinetic decay rate constant) were calculated by modeling the descending part of the evoked DA peaks to a one phase exponential decay equation (Y=(Y0 - Plateau)* exp(-K*X) + Plateau).

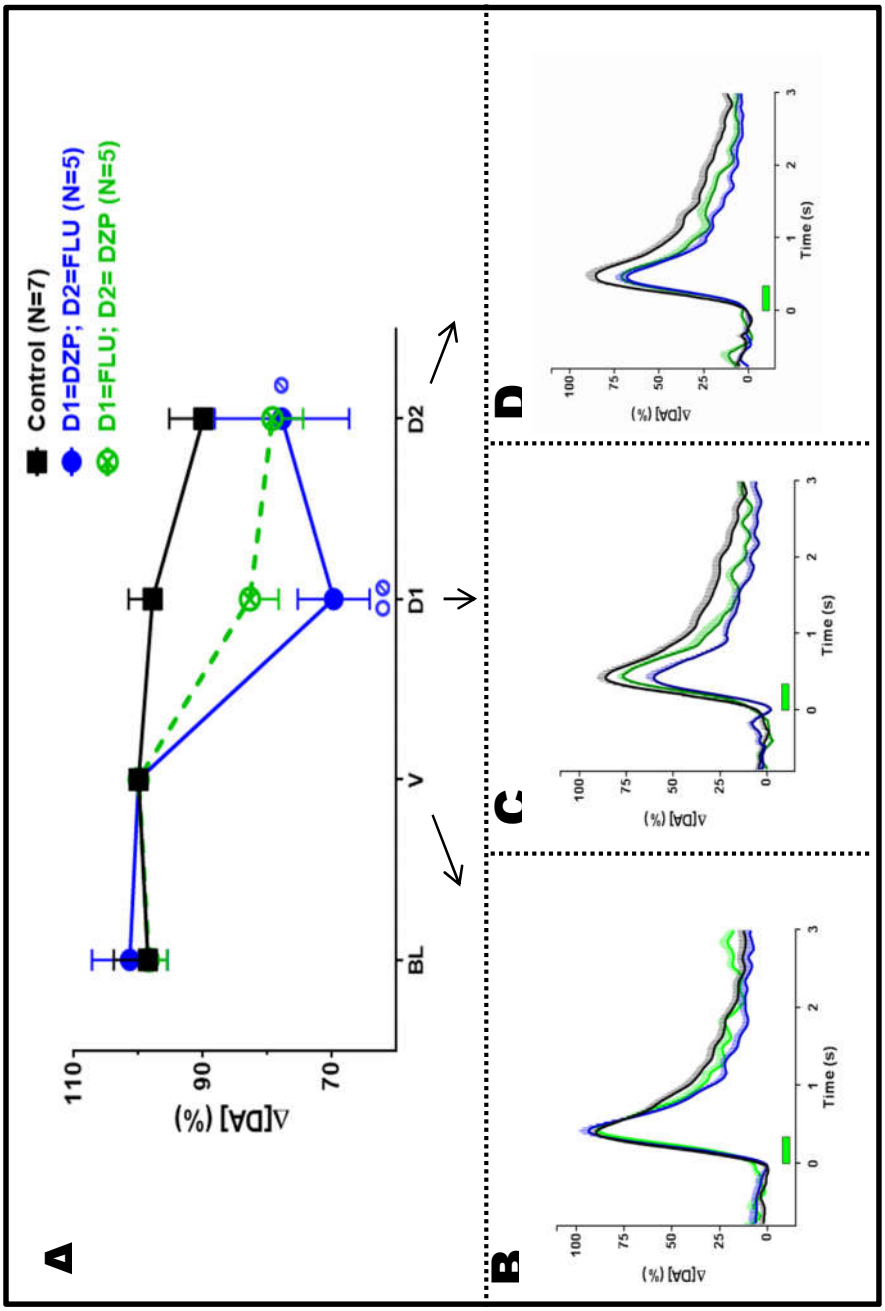
Microdialysis monitoring. Mice were anesthetized with urethane (1.5g/Kg, ip.) and placed in a stereotaxic frame, where the cranium was exposed and a burr hole was drilled targeting the NAc at +1.2 mm from bregma, +0.8 mm from midline; -3.8 mm from skull surface, according to the mouse atlas of Paxinos and Franklin[29]. A concentric microdialysis probe (0.24 mm o.d.; permeability 6 kDa; Cuprophan; AgnTho's, Lidingö, Sweden) with active membrane lengths of 2 mm was inserted unilaterally into the NAc via a polyurethane guide cannula (shaft o.d. 0.5 mm; shaft length 8 mm; AgnTho's, Lidingö, Sweden) and perfused for 30 minutes to stabilize. Dialysate samples were taken every 20 min. Two dialysate samples were taken in basal conditions; 3 dialysate samples were obtained after vehicle i.p. administration; 3 dialysate samples post 2.0 mg/kg diazepam i.p.; and 3 dialysates samples after 2.5 mg/kg flumazenil i.p. Control group had the same procedure except for vehicle i.p. administration at the three moments of injection. The full experiment lasted 5 hours per mouse. The microdialysis probe was perfused with Ringer's solution (in mM: NaCl, 145.0; KCl, 2.7; CaCl2, 1.2; MgCl2, 1.0, pH 7.4) at a constant rate of 2 μL/min. All microdialysis samples were collected into polyethylene tubes containing 20 μL of 0.1 M perchloric acid solution (Merck, Darmstadt, Germany) and 0.06% sodium

metabisulfite (Sigma–Aldrich), and stored at -86 ºC until high-performance liquid chromatography with electrochemical detection (HPLC-ED) analysis. Isocratic separation was performed on a reverse phase LC-18 column (4.6 mm x 250 mm; Sigma-Aldrich) using 20 mM Na2HPO4, 20 mM citric acid, 10% methanol, 0.12 mM $Na_2EDTA$

Histology. The brains were fixed for 10 days in 4% formaldehyde and transferred to a solution of 30% sucrose, 4% formaldehyde solution where they were left for 2 more days. Coronal slices of 50 µm thickness were stained with cresyl violet and compared to the mouse atlas of Paxinos and Franklin[29] to locate damage along the electrode length (DV, and ML coordinates). Electrodes tip locations (DV coordinate) were estimated by how far down the electrode was lowered.

Statistical analysis. Significant differences among DZP-FLU and FLU-DZP groups were calculated by repeated measure two-way ANOVA followed by the Dunnet *post-hoc* test and were considered significant when $p < 0.05$. Effect of the administration of nomifensine on dopamine release was calculated using a one-way ANOVA followed by the Dunnet *post-hoc* test. All statistical data analysis was conducted using Prism for Windows, version 6.01 (GraphPad Software Inc., La Jolla, CA).

Supplemental Material




Supplemental Figure 1. The administration of flumazenil (FLU) prevents the depressive effect of diazepam (DZP) on dopamine release. Mice were anesthetized with urethane and the release of DA in the nucleus accumbens evoked by the electric stimulation of the VTA was monitored by background-subtracted FSCV at carbon-fiber microelectrodes. (A) Four peaks of evoked DA release were monitored in the following order: under baseline (BL) condition (before the injections), 5 min after the injection of vehicle (V), diazepam (DZ) and 5 min after the injection of flumazenil (FLU). The mice of the control group always received vehicle when the mice of the other groups received vehicle, diazepam, and flumazenil. (B) The previous protocol was repeated with other mice, but flumazenil was injected before diazepam. The average concentration versus time traces recorded after the diazepam injection (C) and after the flumazenil injection (D) are shown in the lower panels. Variations in DA concentration after the injection of vehicle were considered to be 100%. Drug were injected i.p. Data are expressed as mean ± SEM percent of the baseline. A two-way ANOVA showed a non-significant drug treatment effect ($F(2,14) = 2.93$ $p = 0.09$, a significant time effect ($F(3,42) = 13.8$, $p < 0.001$) and a significant interaction ($F(6,42) = 2.63$, p

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**Conclusões gerais**

A principal contribuição do meu trabalho de tese foi a padronização da técnica de voltametria cíclica de varredura rápida (FSCV) para o registro de dopamina *in vivo* em animais anestesiados no Laboratório de Fisiologia e Farmacologia do Sistema Nervoso Central do Departamento de Farmacologia da UFPR. Esta conquista foi muito importante por várias razões: a primeira delas esta relacionada com a própria tecnologia. Conseguir registrar um evento neuroquímico *in vivo*, em tempo real é uma ferramenta poderosa no objetivo de compreender melhor o funcionamento do cérebro. Conseguir padronizar a voltametria cíclica de varredura rápida em animais anestesiados é o primeiro passo para padronizá-la para o seu uso com animais acordados (*head-fixed* e *freely moving*) o que abre a possibilidade de responder a perguntas mais complexas sobre a relação entre cérebro e comportamento com aplicações práticas para a neuropsicofarmacologia comportamental.

A segunda razão é o reconhecimento. Este é o primeiro experimento realizado usando voltametria cíclica de varredura rápida para registros cerebrais no Brasil e possivelmente na América Latina (até onde o nosso conhecimento permite), o que coloca o nosso Laboratório, o nosso Departamento e obviamente o Brasil como um dos poucos no mundo com resultados positivos usando esta técnica. Enquanto estivemos envolvidos com o esforço e seus percalços no desenvolvimento dessa técnica pudemos também interagir com dois grupos dos Estados Unidos que estão entre os poucos que desenvolveram e dominam essa técnica. Como fruto dos nossos estudos sobre esse tema, publicamos com o grupo do Dr. Charles Blaha (hoje na Mayo Clinic) dois trabalhos de revisão em revista científicas de alto impacto. A Revisão que publicamos em 2012 na revista Reviews in the Neuroscience (fator de impacto 3.3) já recebeu 13 citações no ISI e 14 citações na Scopus. O paper que publicamos em 2015 na revista Neuroscience and Biobehavioral Reviews (fator de impacto 8.8) já recebeu 2 citações no ISI e 5 citações do Scopus. O outro grupo com o qual interagimos é liderado pela Dra. Donita Robinson

(University of North Carolina) que me contratou para trabalhar como p'os-doc em seu laboratório a partir de março de 2016.

Em relação aos resultados do nosso estudo, além da padronização, nós atingimos todos os objetivos propostos no início do trabalho. Conseguimos observar os efeitos do diazepam na liberação evocada de dopamina no NAc e, a partir desse resultado, propor que os efeitos das benzodiazepinas no tratamento da ansiedade e no tratamento da adição podem ter um componente dopaminérgico. Também conseguimos determinar a efetividade da voltametria para estudar a cinética de liberação e recaptação da dopamina e do efeito do diazepam e da nomifensina. As diferenças significantes sobre os parâmetros de recaptação que observamos após a administração de nomifensina, mas não após de DZ, confirmaram que esse último não alterou a cinética da recaptação da DA, mas também que, usando voltametria, esses parâmetros são passíveis de medição.

Os percalços que enfrentamos na implantação dessa técnica limitaram nossa produção de papers de resultados. Deixamos, porém dois estudos iniciados e que serão finalizados pelos colegas de laboratório e enviados para publicação: um sobre a padronização de registros de FSCV em animais *head-fixed* e outro estudo com registro em tempo real de liberação de dopamina no núcleo accumbens durante o teste de *tail-flick* em camundongos *head-fixed*. Participei também intensamente no treinamento e acompanhamento dos experimentos de dois mestrandos: Bernardo Firmino e Daniele Ramos. Desse trabalho resultou um outro estudo sobre o papel da substância negra compacta sobre o aprendizado associativo com motivações apetitiva e aversiva. Esse trabalho vai ser submetido a publicação assim que for concluído um último experimento envolvendo FSCV.

Finalmente, o nosso trabalho abre as portas para novos estudos que visem determinar os efeitos locais das BZ na liberação evocada de DA e a sua relação com o

comportamento em animais acordados além de outras possibilidades tanto em animais "head-fixed" como "freely-moving". O futuro está servido!

Em relação com as revisões publicadas e incluídas neste trabalho de tese, as principais conclusões são:

Os GB constituem um sistema central na seleção de ações. Para levar a cabo esta função, os GB usam elementos tais como os estados emocionais dos sujeitos, os eventos do seu contexto (Estímulos Incondicionados, Estímulos Condicionados, Estímulos Discriminativos, recompensas), os objetivos e as motivações por traz desses objetivos. O funcionamento anormal dos GB deriva numa série de condições onde os processos dependentes desse funcionamento podem ser severamente danificados como no caso da doenca de Parkinson ou Hantington entre outras. Entre as posibilidades de tratamento para estas doenças, a Estimulação Cerebral Profunda tem mostrado importantes avanços. Os estudos feitos com sujeitos animais e humanos tem permitido elucidar alguns dos possíveis mecanismos pelos quais a ECP funciona no tratamento dessas doenças. Contudo, ainda se está longe de descrever totalmente o mecanismo por traz da efetividade da ECP, sendo necessário aumentar os esforços da comunidade neurocientífica para conseguir uma maior compreensão das suas bases neurobiológicas e as suas aplicações clínicas.

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