Neuromodulation of cognitive-behavioral control

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Discussion

The research included in this dissertation investigated the biological underpinnings of cognitive-behavioral control—both to gain further insight into its underlying mechanisms and to evaluate the efficacy of potential enhancement techniques. Rather than repeating the conclusions of each chapter, which are already summarized in the Introduction's Overview section, this Discussion will instead highlight three important lessons that can be gathered by comparing and contrasting some of the chapters' findings.

First, the study on color vision and cognitive control presented in Chapter Two suggested that better color vision is associated with processing goals in a parallel, overlapping rather than serial, step-by-step manner. This was assessed using an action-cascading (also known as multitasking) paradigm, in which participants are given either no time, i.e., 0 ms, to prepare for a task-switch (the SCD0 condition) or are given 300 ms to prepare for a task-switch (the SCD300 condition). It is traditionally thought (Stock et al., 2014; Verbruggen et al., 2008) that the former condition gives participants a choice between a serial or parallel strategy, because they must decide whether to first finish fully processing the previous goal (i.e., serial processing) or already start processing the next goal simultaneously (i.e., parallel processing). In contrast, the 300 ms interval in the SCD300 condition is thought to enforce a serial, step-by-step manner of goal-activation by offering ample time to finish processing of the first goal before indicating the nature of the second goal. The traditional interpretation of the paradigm's results, then, is that longer reaction times in the SCD0 as compared to SCD300 condition indicate a more parallel goal-activation strategy. That is, the relatively worse performance in the SCD0 condition is thought to result from parallel processing that allows different goals to interfere with each other, accounting for longer reaction times. In other words, longer reaction times in the SCD0 condition as compared to the SCD300 condition are thought to reflect a parallel processing strategy that is associated with a more flexible but interference-prone cognitive control mode.

However, a different interpretation is also conceivable. Consider that the 300 ms interval in the SCD300 condition gives participants 'a lot' of time (in the context of neural processing) to switch between different goals. In contrast, the SCD0 condition gives very little time to switch between goals. As such, rather than indicating parallel and interference-prone processing, longer reaction times in the SCD0 condition might reflect an inability to switch under time pressure—meaning that longer reaction times in this condition are actually diagnostic of greater cognitive stability rather than flexibility. This alternative interpretation converges on a study relating color vision to response conflict (Colzato, Sellaro, et al., 2014). There it is suggested that individuals with good color vision (who had longer SCD0 than SCD300 reaction times in Chapter Two) actually have a more stable and interference-resistant cognitive control mode. This is concluded based on the finding that they demonstrate a smaller congruency effect in the Simon paradigm, which indicates a superior ability to ignore task-irrelevant information. Taking together this report and Chapter Two, these findings highlight that it is crucial to consider alternative interpretations of results. An important step in doing so is to use and contrast different experimental paradigms, as in this particular example the action-cascading and Simon paradigms.

The second important lesson from this dissertation lies in the contrasting results of Chapters Six and Seven. In both cases, studies are presented that aim to investigate the role of dopamine in a brain stimulation technique called transcranial direct current stimulation (tDCS). Previous studies have demonstrated that a genetic predisposition toward higher or lower prefrontal dopaminergic signaling determines the cognitive-behavioral response to tDCS when stimulation is applied *during* task performance (Nieratschker et al., 2015; Plewnia et al., 2013). Chapter Six aimed to extend this finding by investigating whether dopamine also plays a role in tDCS when stimulation is applied *before* task performance. Indeed, this chapter reports that individuals who received L-tyrosine supplementation—which modestly enhances dopamine activity—responded differently to tDCS in terms of working memory performance than those who were supplemented with a placebo. Subsequently, Chapter Seven investigated whether this pattern of results can be replicated not using a dopaminergic manipulation but instead using baseline, pre-existing individual differences in dopamine activity. To investigate this, participants were genotyped to estimate prefrontal dopaminergic signaling (as in previous studies on tDCS), and underwent the same stimulation protocol of Chapter Six. Contrary to the previous chapter and previous studies, these individual differences did not predict different responses to the tDCS for individuals with higher as compared to lower prefrontal dopaminergic signaling. Considering this and previous findings, Chapters Six and Seven suggest that (i) dopamine might differentially affect tDCS depending on whether stimulation is applied during or before task performance, and (ii) tDCS is affected in different ways by a manipulation of dopamine activity (as in Chapter Six) and baseline differences in dopamine (as in Chapter Seven). The latter point has the broader implication that researchers should be careful when generalizing results from manipulation of a neurotransmitter system to naturally-occurring differences in activity of that system—something that is a common practice in cognitive neuroscience research.

The third and final lesson lies in the apparent contrast between Chapters Nine and Ten. Both chapters investigate the effect of a presumed increase in neural inhibition on response selection. In Chapter Nine neural inhibition is enhanced using a technique called transcutaneous (through the skin) vagus nerve stimulation (tVNS). This technique is often used to treat epilepsy patients, as it can enhance the release of the inhibitory neurotransmitters GABA and noradrenaline. Because of the increase in these neurotransmitters, intracortical inhibition is stronger, presumably making it easier for the brain to select the appropriate response among competing response alternatives. Consistent with this idea, tVNS enhanced response selection by preventing a slowing of response speed on certain trials in the serial reaction time (SRT) task. However, Chapter Ten reports on a different technique to enhance neural inhibition and demonstrates that this impairs rather than enhances response selection processes. In this chapter, tDCS is used to stimulate the cerebellum, which exerts an inhibitory tone over the primary motor cortex. As such, excitatory stimulation of the cerebellum strengthens this inhibition, thereby decreasing excitability of the motor cortex. Chapter Ten reports that this stimulation produces an increase in reaction times on the SRT task, consistent with the idea that inhibition of the motor cortex hinders the initiation of responses. In sum, Chapter Nine reports that increased neural inhibition enhances response selection whereas Chapter Ten reports that this impairs response selection.

These findings highlight that regional specificity might play an important role in the effects of neural inhibition on response selection. Indeed, previous studies have demonstrated that higher GABA concentration (associated with stronger inhibition) in some but not other regions predicts better response selection ability (Boy et al., 2011; Dharmadhikari et al., 2015; Sumner et al., 2010). These regions include, for example, the dorsolateral prefrontal cortex, the thalamus and striatum. In contrast, excitatory tDCS directly applied to the motor cortex (which presumably decreases inhibition) has also been reported to enhance response selection (Nitsche, Schauenburg, et al., 2003). Based on these studies, it is conceivable that tVNS might have enhanced response selection by promoting GABA activity in for example thalamic and striatal regions, whereas the inhibitory effects of cerebellar tDCS mainly targeted the primary motor cortex and led to an impairment in response selection ability. However, the important lesson to take away in this case is that in order to better understand and predict the effects of stimulation techniques such as tVNS and cerebellar tDCS, it is crucial to investigate how and which brain regions are affected by the different techniques.

In conclusion, the biological underpinnings of cognitive-behavioral control are highly complex, involving many different neurotransmitters and their interactions, as well as various different brain regions that contribute differentially to control. This dissertation has shown that it is possible to non-invasively estimate individual differences in neural chemistry and use them to predict performance on various experimental tasks. Furthermore, it demonstrated that some but not all available techniques for manipulation of neural chemistry and inhibition can enhance performance. Better understanding how and why these techniques work is an endeavor that is sure to stimulate research in many more years to come.

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Summary in Dutch

Nederlandse samenvatting

Zonder het door te hebben leveren mensen dagelijks uitzonderlijke prestaties. We navigeren een steeds complexere en uitdagende wereld door gebruik te maken van onze verfijnde vaardigheid om habituele neigingen te overkomen. Bovendien kunnen we ons handelen zorgvuldig plannen, uitvoeren en aanpassen om zodoende de doelen te behalen die we voor onszelf stellen. Er wordt gerefeerd naar dit vermogen tot doelgericht gedrag—vaak beschouwt als een kenmerk van de superioriteit van de mens boven andere diersoorten—als ‘cognitieve controle’ of ‘executive functie’. Dit zijn bijzonder vage, meestal synonieme concepten die meer dienen als een parapluterm voor veel verschillende processen dan dat ze refereren naar één functie. Tientallen jaren aan neuropsychologisch onderzoek zijn gewijd aan het begrijpen van cognitieve controle en zijn deelprocessen, de manier waarop het geïmplementeerd is in het brein, en hoe we de effectiviteit kunnen beïnvloeden—en mogelijk verbeteren. Deze vraagstukken dragen het onderzoek dat gepresenteerd wordt in deze dissertatie. Het onderzoek in deze dissertatie betreft voornamelijk de overkoepelende vragen van hoe chemische processen in het brein cognitieve controle mogelijk maken en beïnvloeden, en of we deze biologische onderleggingen van doelgericht gedrag non-invasief kunnen meten en manipuleren.

Cognitieve controle

Wat betreft het definiëren en operationaliseren van cognitieve controle is deze dissertatie geïnspireerd door twee invloedrijke en zeker niet wederzijds-exclusieve theoretische kaders. Het eerste kader is gerepresenteerd in het werk van Miyake et al. (2000), dat zich focuste op het identificeren van drie belangrijke executieve functies en het bepalen van hun onderscheidbaarheid. Miyake et al. veronderstellen dat cognitieve controle uit drie hoofdfuncties bestaat, namelijk *inhibition* (i.e., het vermogen om prepotente/dominante responsen te weerhouden), *updating* (i.e., het vermogen om werkgeheugen representaties vast te houden en bij te werken), en *shifting* (i.e., het vermogen om te wisselen tussen doelen en taken). Een belangrijke bevinding van Miyake et al. is dat deze functies (maar) middelmatig gecorreleerd zijn met elkaar, wat impliceert dat dit scheidbare processen zijn die gevoelig zijn voor verschillende manipulaties. In lijn met dit idee laten cognitieve trainingsstudies zien dat het trainen van een van deze functies zelden gegeneraliseerde effecten heeft op de andere functies. Echter onderstreept de middelmatige correlatie van deze functies ook het feit dat executieve functies een gedeelde onderlegging hebben—waarop straks wordt teruggekomen—en dat hun effectiviteit afhangt van elkaar (zie Diamond, 2013).

Het tweede theoretische kader betreft in mindere mate specifieke cognitieve functies en stelt in plaats daarvan voor dat er verschillende cognitieve controle 'modi' of 'staten' zijn die beïnvloeden hoe de eerdergenoemde functies opereren. Met name wordt gedacht dat controle modus varieert van (i) een meer stabiele setting die het vasthouden van doelen ondersteunt en hen beschermt tegen afleiding, tot (ii) een meer flexibele setting die ontkoppeling van en wisselen tussen doelen en taken bevordert (Cools & D'Esposito, 2011; Goschke, 2003; Hommel, 2015). Elke controle modus is in verschillende situaties voordelig, maar heeft ook noemenswaardige nadelen. Hoewel een stabiele controle modus het navolgen van een specifiek doel toelaat, brengt dit het risico met zich mee dat iemand te rigide is om zich aan te passen aan een verandering in de omgeving. In tegendeel, een flexibele controle modus laat het efficiënt wisselen tussen doelen toe, maar kan iemand ook afleidbaar maken wanneer dit wisselen niet selectief gebeurt. Zodoende vereist adaptieve cognitieve controle een balans tussen de tegenstrijdige vereisten van cognitieve stabiliteit en flexibiliteit, wat ook wel bekend staat als de *cognitieve control paradox* of de *paradox van de flexibele geest*.

Er is grote compatibiliteit tussen deze twee theoretische kaders van cognitieve controle. Bijvoorbeeld, Miyake et al. (2000) rapporteren noemenswaardige individuele verschillen in prestaties op taken die de drie voorgestelde executieve functies meten, en deze verschillen zijn mogelijk het gevolg van individuele variabiliteit in cognitieve controle modus. Dat wil zeggen, iemand met een meer stabiele controle modus zou plausibel beter zijn in het inhiberen van handelingen uitgelokt door afleidende, taak-irrelevante stimuli, terwijl iemand met een meer flexibele controle modus beter is in het updaten van hun werkgeheugen representaties en het wisselen tussen doelen en taken. Dit idee wordt ondersteund door verschillende studies (bijvoorbeeld, Colzato, Ozturk, & Hommel, 2012; Colzato, Sellaro, Samara, & Hommel, 2015; Colzato, Szapora, Lippelt, & Hommel, 2017; Fischer & Hommel, 2012; Fröber & Dreisbach, 2017). De vraag *waarom* sommige individuen superieure inhibitievermogen of cognitieve flexibiliteit vertonen betreft nog een overeenkomst tussen deze twee theoretische kaders en de gedeelde biologische onderlegging van executieve functies waar eerder naar verwezen werd: dopamine activiteit in het brein.

Dopamine

Er wordt gedacht dat de neurotransmitter dopamine in grote mate individuele verschillen in cognitieve controle modus en de efficiëntie van de drie grote executieve functies bepaalt. Dopamine wordt vaak een neuro*modulator* genoemd vanwege zijn wijdverspreide, complexe effecten op neurale activiteit (Nieoullon, 2002; Seamans & Yang, 2004). In plaats van het volgen van een 'meer is beter' regel, volgt de relatie tussen dopamine activiteit en cognitieve prestatie vaak een karakteristieke omgekeerde-U relatie (Cools & D'Esposito, 2011; Cools, 2006; Goldman-Rakic, Muly, & Williams, 2000). Dat wil zeggen, een middelmatig niveau van dopaminerge activiteit is veelal geassocieerd met optimale prestatie, terwijl zowel lagere als hogere dopamine activiteit gepaard gaat met suboptimale prestatie.

Hoewel dopamine wellicht het best bekend is bij de algemene bevolking voor zijn rol in beloning, de ervaring van plezier, en verslaving, is het moeilijk om zijn belang bij cognitieve controle te overdrijven. Om dit belang te begrijpen is het noodzakelijk om een onderscheid te maken tussen twee dopaminerge paden in het brein die op verschillende wijze bijdragen aan cognitieve controle. Dit zijn (i) het mesocorticale pad dat projecteert naar cingulate en prefrontale cortex, en (ii) het nigrostriatale pad dat projecteert naar de basale ganglia. Kort gezegd wordt gedacht dat dopaminerge activiteit in het eerste pad cognitieve stabiliteit ondersteunt terwijl activiteit in het tweede pad cognitieve flexibiliteit ondersteunt (Cools & D'Esposito, 2011; Cools, 2006).

In meer detail, binnen de prefrontale cortex (PFC) moduleert dopamine cognitieve controle via twee verschillende families van receptoren: de D1-achtige en D2-achtige receptoren. Zoals uiteengezet in de *dual-state theory* van PFC functie (Durstewitz & Seamans, 2008) leidt dopaminerge stimulatie van prefrontale D1-achtige receptoren tot het inhiberen van vuren van neuronen in een lage, spontane activatiestaat terwijl het vuren van neuronen in een hoge, persistente activatiestaat wordt bevorderd. Dit verhoogt de corticale signaal-tot-ruis ratio en faciliteert de stabiliteit van mentale representaties in PFC. Aan de andere kant, activatie van D2-achtige receptoren leidt tot een algehele vermindering in inhibitie van PFC neuronen, wat hun spontaan vuren faciliteert en daarmee flexibele maar ook storingsgevoelige representaties bevordert (Robbins, 2005; Seamans, Gorelova, Durstewitz, & Yang, 2001; Seamans & Yang, 2004; Trantham-Davidson, Neely, Lavin, & Seamans, 2004). Zodoende wordt aangenomen dat dopamine in de PFC de balans tussen een stabiele en flexibele controle modus moduleert door middel van de ratio tussen D1 en D2-achtige receptor activatie.

Binnen de basale ganglia bevordert dopamine flexibele controle via een *input-gating* mechanisme dat bepaalt of de PFC open is voor nieuwe informatie. Het *prefrontal-cortex basal-ganglia working memory model* (Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, & O'Reilly, 2006; O'Reilly, 2006) stelt voor dat *phasic* dopamine activiteit in de basale ganglia een zogenaamde poort opent naar de PFC, wat corticale representaties vatbaar maakt voor updaten en storing, terwijl een gebrek aan dopamine activiteit in de basale ganglia zorgt dat de poort dicht blijft en daarmee corticale representaties beschermd zijn tegen afleiding (zie ook Braver & Cohen, 2000). Belangrijk is dat dopaminerge stimulatie van D1-achtige receptoren in de basale ganglia het doorlaten van informatie faciliteert terwijl D2 receptoren dit tegengaan, en een verhoogd *tonic* dopamine niveau in de basale ganglia leidt voornamelijk tot stimulatie van D1 over D2 receptoren (Hazy et al., 2006; O'Reilly & Frank, 2006; van Schouwenburg, Aarts, & Cools, 2010). Het gevolg hiervan is dat hogere niveaus van dopamine in de basale ganglia flexibiliteit bevorderen door toegang van informatie tot de PFC te faciliteren. Tegelijkertijd verhoogt dit echter ook het risico dat taak-irrelevante informatie interfereert met het vasthouden van informatie van in PFC, waardoor niet alleen flexibiliteit maar ook afleidbaarheid wordt verhoogd.

Samengevat is dopamine bijzonder belangrijk bij het begrijpen van cognitieve controle. Via regio-specifieke effecten in corticale en subcorticale netwerken kan het cognitieve processen meer stabiel of flexibel maken, en zodoende de effectiviteit van *inhibition*, *updating* en *shifting* beïnvloeden. Echter zou het nalatig zijn om te impliceren dat dopamine de enige neurotransmitter is dat van belang is bij cognitieve-gedragsmatige controle. Het is bekend dat andere neurotransmitters ook een belangrijke rol spelen, zoals noradrenaline (Robbins, 2005), serotonine (Cools, Roberts, & Robbins, 2008), en glutamaat en GABA (de la Vega et al., 2014; Munakata et al., 2011). Daarom zullen de laatste hoofdstukken van deze dissertatie de focus verschuiven naar de laatste twee neurotransmitters, glutamaat en GABA, en onderzoeken hoe manipulatie van deze neurotransmitter system controle beïnvloeden.

Glutamaat en GABA

Als de primaire exciterende en inhiberende neurotransmitters, respectievelijk, spelen glutamaat en GABA een belangrijke rol in de controle over handelingen. Kort gezegd wordt gedacht dat glutamaat en GABA (en met name de balans tussen de twee) bepalend zijn voor het niveau van intracorticale inhibitie, wat vervolgens het vermogen beïnvloedt om een specifieke representatie of handeling te kiezen uit verschillende alternatieven (de la Vega et al., 2014; Munakata et al., 2011). Dit kan van invloed zijn op alledaagse situaties zoals het kiezen welk woord te gebruiken in een zin of een besluit te nemen wanneer er niet een duidelijk beste optie is.

Kort gezegd, hogere niveaus van glutamaat (en omgekeerd, lagere GABA-niveaus) onderdrukken de competitie tussen representaties in PFC, waardoor de kans groter is dat alternatieve, wellicht zelfs taak-irrelevante concurrenten actief worden. Dit kan resulteren in het kiezen van de verkeerde handeling, of het proces van het kiezen van de juiste handeling vertragen. In tegendeel, meer competitie (als gevolg van lagere glutamaat en/of hogere GABA niveaus) heeft het tegenovergestelde effect door de activatie van concurrerende responsen te onderdrukken (de la Vega et al., 2014; Jocham, Hunt, Near, & Behrens, 2012). Verschillende studies hebben dit model van actie selectie binnen het brein bevestigd, bijvoorbeeld door te laten zien dat hogere GABA concentraties in zekere regionen voorspellend zijn voor snellere (Dharmadhikari et al., 2015) en meer accurate (Haag et al., 2015) responsen in de Simon taak, een klassieke respons-interferentie taak (Hommel, 2011).

In het kader van dit model van actie selectie en inhibitie in het brein zullen de laatste drie hoofdstukken in deze dissertatie onderzoeken hoe een veronderstelde verhoging of verlaging van neurale inhibitie een effect heeft op respons selectie. Dit wordt onderzocht door gebruik te maken van het *serial reaction time* (SRT) paradigma (Abrahamse & Noordzij, 2011), waarin men een sequentie van knoppen snel moet indrukken. Deze sequentie kan willekeurig zijn, of een ingebedde *second-order conditional* (SOC) sequentie bevatten. Terwijl een willekeurige response sequentie sterk berust op een stimulus-georiënteerde, reactieve modus van controle, is het in een SOC-sequentie mogelijk om kennis van de vorige twee responsen te gebruiken om te anticiperen wat de volgende respons zal zijn. Zodoende laten SOC sequenties een meer plan-georiënteerde, proactieve modus van controle toe (Tubau, Hommel, & López-Moliner, 2007) die steeds snellere en accurate responsen toelaat. Zodoende is het mogelijk om met de SRT-taak te onderzoeken hoe response selectie, inhibitie van irrelevante responsen, en de impliciete formering van response sequentie structuren gevoelig zijn voor een verandering in het niveau van neurale inhibitie.

Overzicht

Deze dissertatie kan worden onderverdeeld in drie overkoepelende thema's. Het eerste deel (Hoofdstukken 1-2) presenteert een literatuur review en een empirische studie die focussen op non-invasieve markers van individuele verschillen in dopamine functie en of het mogelijk is cognitieve controle prestatie te voorspellen op basis van deze verschillen. Het tweede deel (Hoofdstukken 3-7) verschuift van deze correlationele aanpak naar milde experimentele manipulaties van het dopaminerge systeem en hun geassocieerde veranderingen in cognitieve controle, zoals besproken in twee literatuur reviews en twee empirische studies. Als laatst betreft het derde deel (Hoofdstukken 8-10) drie empirische studies die verschillende methoden gebruiken om neurale inhibitie te manipuleren om zodoende de effecten op actie selectie te onderzoeken.

Hoofdstuk Een presenteert een uitgebreide review van literatuur die het spontane oog knipper gehalte (*eye blink rate*; EBR) gebruikt als indirecte marker van dopaminerge activiteit. Zoals besproken in dit hoofdstuk is er veel literatuur die een positieve relatie aantoont tussen EBR en dopaminerge activiteit. Kort gezegd laten farmacologische studies zien dat dopamine agonisten en antagonisten respectievelijk EBR verhogen en verlagen, en klinische populaties gekenmerkt door hypo-actieve dopamine activiteit vertonen lage EBR terwijl populaties gekenmerkt door hyper-actieve dopamine activiteit een hoge EBR vertonen. Met name interessant is de bevinding dat EBR in gezonde individuen de cognitieve prestatie op verschillende experimentele paradigma's kan voorspellen. In lijn met het idee dat EBR vooral geassocieerd is met dopaminerge activiteit in de basale ganglia, voorspelt hogere EBR meer cognitieve flexibiliteit zoals gemeten, bijvoorbeeld, op paradigma's van taak-wisselen en divergent denken.

Aangezien er al omvangrijke literatuur is over EBR als marker van dopaminerge activiteit zal **Hoofdstuk Twee** een studie presenteren dat focust op een ander aspect van onze ogen dat mogelijk dopaminerge activiteit voorspelt. Met name blijkt dat kleurenvisie, i.e., het vermogen om kleuren te onderscheiden, voorspellend is van individuele verschillen in dopamine en gerelateerde cognitieve functies. Dit werd onderzocht door het testen van kleurenvisie en prestatie op een *action cascading* (ook bekend als *multitasking* of taak-wisselen) paradigma. *Action cascading* refereert naar het vermogen om verschillende doelen achter elkaar uit te voeren en tussen doelen te wisselen. Dit kan gedaan worden in een meer seriële, stap-voor-stap wijze waarbij het volgende doel pas geactiveerd wordt wanneer het vorige doel volledig is afgerond, of in een meer parallelle, overlappende wijze waarbij verschillende doelen tegelijkertijd geactiveerd worden. *Action cascading* is gerelateerd aan dopamine functie, aangezien een vorige studie heeft aangetoond dat individuen met een genetische predispositie voor meer dopamine D2 receptor activiteit (wat met name prevalent is in de basale ganglia) de neiging hebben om doelen in een meer parallelle wijze te verwerken. De resultaten in Hoofdstuk Twee laten zien dat, op vergelijkbare wijze, individuen met goede kleurenvisie presteren op een manier die consistent is met een meer parallelle dan seriële modus van doelen verwerken. Dit suggereert onder voorbehoud dat goede kleurenvisie met name voorspellend is van de dopamine D2 receptor en cognitieve flexibiliteit. Een discussie van deze interpretatie, en een alternatief perspectief, wordt uiteengezet in de Discussie sectie van deze dissertatie.

Hoewel markers als EBR en kleurenvisie ons in staat stellen om veronderstelde individuele verschillen in dopamine functie te onderzoeken, is deze aanpak correlationeel van nature en kan daarom niet een causale rol van dopamine in de onderzoeksresultaten bevestigen. Daarom zullen de volgende hoofdstukken focussen op een milde maar effectieve methode om dopaminerge activiteit te manipuleren. In **Hoofdstuk Drie** wordt een uitgebreide review gepresenteerd met betrekking tot de cognitief-gedragsmatige effecten van het toedienen van het voedingssupplement L-tyrosine, wat de biochemische voorloper is van dopamine. Aangezien tyrosine omgezet kan worden in dopamine in het brein, hebben veel studies onderzocht of tyrosine supplementatie gunstige effecten heeft op cognitieve processen die gemoduleerd worden door dopamine. Inderdaad, het is aangetoond dat tyrosine de drie executieve functies uiteengezet door Miyake et al. (2000) kan verbeteren, dat wil zeggen *inhibition* (Colzato, Jongkees, Sellaro, van den

Wildenberg, & Hommel, 2014), *task-switching* (Steenbergen, Sellaro, Hommel, & Colzato, 2015), en met name werkgeheugen (Colzato, Jongkees, Sellaro, & Hommel, 2013; Jongkees, Sellaro, et al., 2017; Thomas, Lockwood, Singh, & Deuster, 1999). Noemenswaardig is het feit dat de effecten van tyrosine enkel betrouwbaar lijken te zijn wanneer men blootgesteld wordt aan een externe stressor zoals hitte, kou, of lawaai, of een interne stressor zoals hoge cognitieve belasting. Daarom wordt voorgesteld dat tyrosine een '*depletion reverser*' is, aangezien het alleen effectief is in omstandigheden waarin prestatie normaliter verslechterd zou zijn door de uitputting van cognitieve middelen, motivatie, of dopamine niveaus.

Hoofdstuk Vier dient als uitbreiding van het vorige hoofdstuk, door te benadrukken dat de effecten van tyrosine waarschijnlijk afhankelijk zijn van individuele verschillen in dopamine functie. Inderdaad wordt vaak geobserveerd dat het effect van een dopaminerge manipulatie staat-afhankelijk is en verschillend is voor hen met een laag of hoog baseline dopamine niveau. Doorgaans worden individuen met een lager dopamine niveau omhooggeschoven op de omgekeerde-U-curve die dopamine aan cognitieve prestatie relateert wanneer hen een verhoging in dopamine activiteit wordt toegediend. In tegendeel, individuen met een hoger dopamine niveau zouden als gevolg hiervan omlaag schuiven naar de rechterzijde van de curve. Voor laag en hoog baseline niveau individuen zou dit respectievelijk leiden tot een geobserveerde toename en afname in cognitieve prestatie in vergelijking met baseline[2]. Dit is waarom de korte review in Hoofdstuk Vier verschillende mogelijke markers van individuele verschillen in dopamine functie voorstelt die wellicht de effectiviteit van tyrosine supplementatie voorspellen. Deze markers zijn onder andere EBR en kleurenvisie zoals onderzocht in eerdere hoofdstukken, en genetische markers van dopamine functie in PFC of basale ganglia. Een recente studie heeft een van deze hypotheses bevestigd door aan te tonen dat tyrosine supplementatie meest effectief was in individuen met een

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[2] Echter moet worden opgemerkt dat een dergelijk patroon van resultaten ook verklaard kan worden door het fenomeen 'regressie naar het gemiddelde' (zie Barnett, van der Pols, & Dobson, 2005). Toekomstige studies moeten deze alternatieve verklaring in acht nemen, wat in de huidige literatuur zelden wordt gedaan.

genetische predispositie naar lagere dopamine activiteit in de basale ganglia (Colzato et al., 2016), van wie verondersteld wordt dat ze de meeste ruimte hebben om omhoog te schuiven op de curve die dopamine activiteit relateert aan prestatie.

Hoofdstuk Vijf presenteert een van de empirische studies van tyrosine supplementatie die onderdeel uitmaakt van de review in Hoofdstuk Drie. Dit hoofdstuk onderzoekt met name de effectiviteit van tyrosine supplementatie bij het verbeteren van inhibitievermogen, waarvan bekend is dat het afhangt van dopamine activiteit. Dit is onderzocht door gebruik te maken van het *stop-signal* paradigma, waarbij proefpersonen een simpele geforceerde-keuze reactietijd taak zo snel mogelijk uitvoeren tenzij een stopsignaal aangeeft dat ze hun respons moeten inhouden. Door te variëren wanneer het stopsignaal verschijnt is het mogelijk om te schatten hoe veel tijd iemand nodig heeft om hun respons succesvol te inhiberen. Zoals verwacht laten de resultaten zien dat proefpersonen sneller waren in het inhouden van hun respons na tyrosine supplementatie zoals vergeleken met een placebo. In tegendeel was respons executie niet beïnvloedt, wat onderstreept dat tyrosine supplementatie alleen effectief is in het verbeteren van prestatie op bijzonder uitdagende taken.

In **Hoofdstuk Zes** wordt een andere aanpak genomen tot dopaminerge manipulatie, door gebruik te maken van *transcranial direct current stimulation* (tDCS). Dit is een non-invasieve methode van hersenstimulatie waarvan bekend is dat het corticale excitabiliteit en neurale plasticiteit kan beïnvloeden. Er wordt gedacht dat tDCS niet direct maar indirect dopamine kan beïnvloeden door een effect op GABA, wat vervolgens een modulerende invloed heeft op dopaminerge activiteit. Hoewel er veel studies zijn die laten zien dat tDCS cognitieve prestaties kan beïnvloeden, is er ook veel twijfel over de betrouwbaarheid van deze effecten aangezien resultaten variëren tussen studies. Dit is waarschijnlijk deels te wijden aan methodologische verschillen tussen studies, maar er is ook gesuggereerd dat individuele verschillen in dopamine kunnen bijdragen aan variabiliteit in respons op tDCS (Wiegand, Nieratschker, & Plewnia, 2016). Er zijn enkele studies die dit idee ondersteunen. In acht nemend dat er een omgekeerde-U-curve is in de relatie tussen dopamine activiteit en cognitieve prestaties, hebben voorgaande studies laten zien dat het toepassen van exciterende (anodale) stimulatie bij individuen die al een hoog niveau van dopamine activiteit hebben leidt tot een afname in prestatie. Ook leidt het toepassen van inhiberende (kathodale) stimulatie bij individuen die al een laag niveau hebben van dopaminerge activiteit tot een afname in prestatie. Dit patroon van resultaten is waargenomen door een onderscheid te maken tussen individuen met een genetische predispositie naar hogere of lagere dopamine activiteit in de PFC. Echter is het belangrijk om te erkennen dat genetische studies enkel correlationeel bewijs kunnen leveren en niet kunnen spreken tot de causale rol van dopamine in de effecten van tDCS. Dat is waarom de studie gepresenteerd in Hoofdstuk Zes een meer experimentele aanpak zocht door tDCS te combineren met tyrosine supplementatie en het effect op werkgeheugen te testen, welke de meest onderzochte cognitieve functie is in tDCS studies. Zoals in het overgrote deel van voorgaande studies werd tDCS toegepast over de dorsolaterale PFC, welke een regio is dat belangrijk is voor cognitieve control en met name werkgeheugen. In lijn met de eerdergenoemde bevindingen met genetica, lieten de resultaten zien dat de combinatie van tyrosine met exciterende stimulatie leidde tot een afname in werkgeheugenprestatie. Deze bevinding ondersteunt het idee dat tDCS beïnvloedt kan worden door dopamine in het brein, en kan leiden tot een afname in prestatie wanneer deze wordt gecombineerd met een manipulatie die ook dopamine activiteit verhoogd.

Gezien het bewijs dat een rol voor dopamine in de effecten van tDCS ondersteund, onderzoekt **Hoofdstuk Zeven** of het patroon van resultaten uit het vorige hoofdstuk nagebootst kunnen worden met al-bestaande individuele verschillen in dopamine activiteit in plaats van een experimentele manipulatie daarvan. Als dit het geval blijkt, dan zouden dit en het vorige hoofdstuk de belangrijke implicaties hebben dat (i) dopamine een rol speelt in de effecten van tDCS en dat (ii) individuele verschillen in dopamine activiteit mogelijk bijdragen aan de variabiliteit in de effecten van tDCS. Om deze tweede hypothese te testen presenteert dit hoofdstuk een studie dat dezelfde experimentele opzet gebruikt als in Hoofdstuk Zes. In plaats van een tyrosine manipulatie, worden proefpersonen ditmaal gegenotypeerd voor het COMT Val^{158}Met polymorfisme, welke het niveau van dopaminerge activiteit in de PFC bepaalt. Vergelijkbaar met het patroon van resultaten dat werd geobserveerd in Hoofdstuk Zes, was hierbij de hypothese dat het toedienen van exciterende stimulatie bij hen met een predispositie voor hogere dopamine activiteit zou leiden tot een verslechtering van werkgeheugen prestatie. Opmerkelijk genoeg leverde de studie enkel nul-bevindingen. Dat wil zeggen, verschillende COMT polymorfismen waren niet geassocieerd met verschillende responsen op de tDCS. In combinatie met de bevindingen van het vorige hoofdstuk, impliceert dit dat resultaten van studies met farmacologische manipulaties (bijvoorbeeld tyrosine) enkel voorzichtig gegeneraliseerd moeten worden naar bevindingen met individuele verschillen (bijvoorbeeld het COMT-polymorfisme). In dit specifieke geval lijken *state* (i.e., een manipulatie van) en *trait* (i.e., baseline) verschillen in dopamine een verschillend effect te hebben op tDCS.

Hoofdstuk Acht maakt de overgang van dopamine naar het onderwerp van neurale inhibitie en respons selectie. De volgende hoofdstukken, elk op hun eigen manier, onderzoeken hoe een verondersteld toename of afname in neurale inhibitie een effect heeft op het vermogen om de juiste respons te selecteren uit verschillende alternatieven. In Hoofdstuk Acht wordt de eerste studie gerelateerd aan dit onderwerp gepresenteerd, waarbij gefocust wordt op het voedingssupplement glutamine. Zoals tyrosine de voorloper is van dopamine, is glutamine de voorloper van glutamaat en GABA. Dit zijn respectievelijk de voornaamste exciterende en inhiberende neurotransmitters en daarom kan supplementatie van glutamine mogelijk het niveau van neurale inhibitie beïnvloeden. Hoewel glutamine een populair supplement is dat vaak gebruikt wordt door bodybuilders, zijn de cognitief-gedragsmatige effecten ervan weinig onderzocht tot op heden. Om te onderzoeken of en hoe glutamine de response selectie beïnvloedt, werden proefpersonen gesupplementeerd met glutamine of een placebo en voerden zij vervolgens een SRT-taak uit, wat zowel *sensorimotor* (i.e., stimulus-georiënteerde) controle meet als impliciet sequentieel leren. De resultaten lieten geen effect zien van glutamine op motorische leerprocessen, maar zij die glutamine kregen maakten wel meer respons fouten, voornamelijk wanneer de taak vereiste dat ze wisselden van reageren met de ene naar de andere hand. Deze bevinding impliceert dat glutamine het niveau van glutamaat ten opzichte van GABA verhoogde, met als gevolg meer corticale excitabiliteit en response competitie tussen verschillende alternatieven. Deze vermindering in prestatie bleek alleen betrouwbaar wanneer men moest wisselen van hand gedurende de taak, wat indiceert dat de verhoogde corticale excitabiliteit ervoor zorgde dat de lateraliteit van de vorige respons interfereerde met die van de huidige respons. Dit is de eerste demonstratie dat glutamine de response selectie kan verhinderen via een veronderstelde afname in neurale inhibitie.

In **Hoofdstuk Negen** werd onderzocht of het tegenovergestelde ook bewezen kan worden. Dat wil zeggen, of een toename in neurale inhibitie de respons selectie kan verbeteren. Correlationeel bewijs voor dit idee bestaat al, aangezien studies hebben aangetoond dat individuen met hogere GABA-niveaus in striatale and thalamische gebieden beter zijn in het selecteren van de juiste respons uit verschillende concurrerende alternatieven. Om causaal bewijs te vinden voor dit idee werd in de studie in Hoofdstuk Negen gebruik gemaakt van transcutane (door de huid) vagus zenuwstimulatie (*transcutaneous vagus nerve stimulation*; tVNS), een non-invasieve methode van hersenstimulatie die het niveau van GABA in het brein kan verhogen. Deze manipulatie werd wederom gecombineerd met de SRT-taak, om te bepalen of tVNS respons selectieprocessen kan verbeteren. Vergelijkbaar met het vorige hoofdstuk was er geen verschil in impliciet sequentieel leren tussen hen die actieve (echte) of *sham* (placebo) stimulatie kregen. Echter, zoals verwacht verbeterde tVNS de response selectie. Om precies te zijn, actieve tVNS elimineerde een fenomeen vergelijkbaar met '*inhibition of return*', waarbij proefpersonen langzamer zijn wanneer de huidige respons dezelfde is als de respons op twee trials eerder. In andere woorden, terwijl zij die *sham* tVNS kregen wel deze *inhibition of return* vertoonde, ook wel het *reversal effect* genoemd, lieten zij die actieve tVNS kregen niet dergelijke respons vertraging zien. Deze bevinding valt samen met eerdere studies die suggereren dat tVNS, via een veronderstelde toename in GABA, een effectieve methode is om cognitief-gedragsmatige controle te verbeteren.

Als laatst werd in **Hoofdstuk Tien** neurale inhibitie gemanipuleerd met tDCS. Echter, terwijl voorgenoemde tDCS studies typisch direct gericht waren op PFC-regionen, werd in dit hoofdstuk tDCS toegepast op het cerebellum. Dit gebied is noemenswaardig voor het feit dat het tot wel 80% van alle neuronen in het gehele brein bevat, en het is bekend dat het een belangrijke rol speelt in het plannen, initiëren, en coördineren van beweging. Maar een klein aantal studies heeft tot op heden onderzocht of cerebellaire tDCS de respons selectie kan beïnvloeden, maar er is bewijs voor deze mogelijkheid afkomstig van een studie die laat zien dat cerebellaire tDCS een fenomeen genaamd cerebellaire-brein inhibitie (CBI) kan beïnvloeden. Dit refereert naar het feit dat het cerebellum een inhiberende werking heeft op de primaire motor cortex, en deze inhibitie kan versterkt worden door exciterende en verzwakt worden door inhiberende stimulatie van het cerebellum. Dit kan vervolgens beïnvloeden hoe moeilijk of makkelijk het is om beweging te initiëren. Om te onderzoeken of deze modulatie van CBI inderdaad zich vertaalt in een verandering in het vermogen om responsen te selecteren, kregen in Hoofdstuk Tien proefpersonen exciterende (anodale), inhiberende (kathodale), of *sham* (placebo) stimulatie over het cerebellum terwijl zij de SRT-taak uitvoerden. Zoals in de vorige hoofdstukken leek deze manipulatie niet direct een effect te hebben op impliciet motor sequentie leren, maar de exciterende stimulatie in vergelijking met de inhiberende en *sham* stimulatie beïnvloedde wel response selectie zoals bleek uit een algehele toename in reactietijd. Deze bevinding is consistent met het idee dat exciterende stimulatie van het cerebellum de CBI kan versterken en daarmee het vermogen beperkt om beweging te initiëren. Opmerkelijk is het feit dat deze studie ook een follow-up sessie 24 uur na de stimulatie bevatte, om te bepalen of de stimulatie gedurende de taak wellicht van invloed was op consolidatieprocessen die plaats vinden nadat de taak is afgerond. Deze follow-up liet een patroon van resultaten zien dat vergelijkbaar was met de vorige dag: zij die eerder exciterende stimulatie kregen lieten nog steeds verhoogde reactietijden zien, maar alleen wanneer zij twee verschillende response sequenties moesten uitvoeren in hetzelfde SRT-blok. Dit indiceert dat wellicht de exciterende stimulatie van het cerebellum van invloed was op hoe robuust proefpersonen de motor sequentie leerde, wat vervolgens alleen te merken was wanneer een niet-getrainde sequentie op dag twee interfereerde met de getrainde sequentie. Deze resultaten zijn een van de eerste die vaststellen dat cerebellaire tDCS een potentiele methode is om response selectie te moduleren, en zij suggereren dat de effecten gemedieerd worden door een verandering in de inhiberende werking van het cerebellum op de primaire motor cortex.

Om dit overzicht af te sluiten: de hoofdstukken in deze dissertatie bieden inzicht in of en hoe het mogelijk is om individuele verschillen in neurochemie onderliggend aan cognitief-gedragsmatige controle te meten. Daarnaast verkent het verschillende methoden voor het non-invasief manipuleren van deze biologische basis en levert het bewijs dat sommige van deze methoden veelbelovend zijn voor cognitief-gedragsmatige verbetering.

Curriculum Vitae

Bryant J. Jongkees was born on December 12, 1991 in Nieuwegein, the Netherlands. In 2010, he obtained his pre-university level high school diploma from the Oosterlicht College in Nieuwegein. Thereafter he studied Psychology at Leiden University, graduating (cum laude/with honors) from the Bachelor program in Psychology in 2013. Bryant then started the Research Master's program in Psychology, Cognitive Neuroscience track at Leiden University, during which he worked as a research assistant investigating the relationship between dopamine and goal-directed behavior. In 2015, he graduated (summa cum laude/with honors) from the Master program and immediately started a PhD at Leiden University. Under the supervision of Prof.dr. Sander Nieuwenhuis and Prof.dr. Lorenza Colzato, Bryant has investigated the effects of individual differences in and mild manipulation of several neurotransmitter systems on various cognitive functions including working memory, task-switching, and motor sequence learning. The results of his doctoral work are outlined in this dissertation.

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