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Two types of learning in healthy and pathological aging exemplified by Parkinson's disease

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Sarah Nadine Meißner

aus Heilbronn

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Aus dem Institut für Klinische Neurowissenschaften und Medizinische Psychologie
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1. Prof. Dr. Bettina Pollok

2. Prof. Dr. Christian Bellebaum

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Learning is the only thing the mind never exhausts,

never fears,

and never regrets.

Leonardo da Vinci

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List of Abbreviations

ACC	anterior cingulate cortex
DBS/THS	deep brain stimulation/Tiefe Hirnstimulation
DICS	dynamic imaging of coherent sources
DLPFC	dorsolateral prefrontal cortex
EoA	end of acquisition
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
FRN	feedback related negativity
GPe	external segment of the globus pallidus
GPi	internal segment of the globus pallidus
M1	primary motor cortex
MDS-UPDRS III	motor part of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
MEG	magnetoencephalography
PD	Parkinson's disease
PET	positron emission tomography
PMC	premotor cortex
RT	reaction time
SMA	supplementary motor area
SNc	substantia nigra pars compacta
SNr	substantia nigra pars reticulata
SQUID	superconductive quantum interference device
SRTT	serial reaction time task
STN	subthalamic nucleus
tACS	transcranial alternating current stimulation
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation

Summary

Learning is a driving force for successful adjustment to our environment. The present thesis concentrated on implicit motor sequence and feedback learning, both essential for proper functioning in daily life.

The acquisition of motor sequences occurs online during practice and is followed by motor consolidation describing stabilization of skills (i.e., reduced susceptibility to interference) as well as offline improvement (i.e., skill enhancement without further practice). Furthermore, working memory might contribute to this type of learning. At the neural level, motor sequence learning relies on distributed brain networks including cortico-basal ganglia circuits. In young adults, motor cortical beta oscillations are assumed to be of functional significance for this type of learning. In the light of an aging population, a better understanding of age-related changes takes on increasing relevance to ensure a self-determined life up until old age. Knowledge about changes across the adult life span is necessary to derive concepts for early detection and prevention of possible declines in old age. In the context of aging and its associated diseases, another line of research on motor sequence learning investigated patients with Parkinson's disease (PD), a neurodegenerative disorder associated with loss of dopaminergic neurons and pathological alterations in cortico-basal ganglia circuits including altered synchronization of beta oscillations. Considering this, it might not be surprising that motor sequence learning has been found to be diminished in patients with PD. But, whether pathological beta oscillations are indeed associated with impaired motor sequence learning in PD is yet to be determined. Similar to motor sequence learning, areas of cortico-basal ganglia circuits and the dopaminergic system in particular play a crucial role in feedback learning. This type of learning occurs by linking either own (active) or observed actions (observational) to accompanying outcomes (e.g., positive or negative feedback). Previous studies in PD patients suggest that whereas performance patterns in observational feedback learning may be similar to those in healthy older adults – at least in early stages of PD – active learning from feedback is altered and may vary with the dopaminergic state. Besides dopamine substitution, deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment option in advanced PD. Regarding active feedback learning, there is first evidence that this type of learning might be enhanced by STN-DBS. Whether STN-DBS also promotes observational feedback learning remains to be investigated. Disentangling influences of treatment methods such as DBS on

cognitive functions including feedback learning are of high relevance for both the improvement of therapy and the prognosis of therapeutic effects. As DBS is also considered as a treatment option for younger, working PD patients, alterations in cognitive functions due to STN-DBS might have considerable consequences for gainful employment and thereby quality of life.

The present thesis comprises three studies to contribute to the understanding of implicit motor sequence and feedback learning in healthy and pathological aging using PD as a prominent example. The investigation of motor sequence learning across the adult life span at the behavioral level (study 1) was complemented by the investigation of its underlying brain oscillations in healthy and pathological aging (study 2). Study 3 examined the effect of STN-DBS on feedback learning in PD patients. Healthy older adults served as control group.

Study 1 examined motor sequence acquisition and consolidation across the adult life span and explored whether working memory is associated with these processes. It revealed that young and older but not middle-aged adults showed acquisition of a motor sequence. Since the data suggest that older adults may adopt explicit learning strategies, one might argue that the decline in middle-aged adults reflects that implicit learning may become less effective while a compensatory strategy has not been successfully implemented yet. Immediately after acquisition, young and older adults were susceptible to interference. However, after an offline period of 1 hour, both showed stabilization of the newly acquired skill indicating consolidation. Additional offline improvement, which was not specific for sequence trials but rather represented general reaction time improvement, was only observed in young and middle-aged adults. These results give rise to the hypothesis that different forms of consolidation may be distinctly affected by aging. Working memory was not linked to motor sequence acquisition or consolidation, independent of age.

Study 2 investigated motor sequence learning in PD – representing a prominent example of pathological aging – as compared to healthy aging. Neuromagnetic activity was recorded using magnetoencephalography (MEG) to investigate the functional role of brain oscillations with a special emphasis on beta oscillations. PD patients exhibited diminished but basically preserved motor sequence acquisition as well as higher susceptibility to interference immediately after acquisition when compared to healthy adults. These differences were accompanied by less beta power suppression in motor cortical areas in PD patients supporting its significance in motor sequence learning. Interestingly, while reduced

susceptibility to interference may rely on successful acquisition in healthy adults, these two processes were found to be distinct in PD. Indirectly supporting this assumption, beta power suppression was found to promote reduced susceptibility to interference but was not beneficial for sequence acquisition in PD. Beyond beta activity, the study provided first evidence that motor cortical theta oscillations might be associated with susceptibility to interference, at least in an aging but healthy motor system.

Study 3 concentrated on active and observational feedback learning in PD patients and healthy older adults. The investigation of STN-DBS effects on feedback learning was the main focus of the study. Healthy older adults served as control group. The data revealed that STN-DBS facilitates active feedback learning which requires to link own actions to accompanying outcomes and that PD patients OFF but not ON STN-DBS showed worse active learning than healthy adults. Interestingly, when it came to the application of what had been learned during feedback trials, only more severely impaired patients benefited from STN-DBS. In addition to active feedback learning, the study provided first evidence that STN-DBS might also be beneficial for observational feedback learning when outcomes are required to be linked to actions of another person.

This thesis contributes to the understanding of implicit motor sequence and feedback learning in healthy aging as well as in PD representing a prominent example of pathological aging. The three studies revealed (i) preserved initial learning of a motor sequence probably due to compensatory explicit strategies as well as stabilization of the newly acquired sequence indicating consolidation in healthy older adults, (ii) diminished motor sequence learning in pathological aging such as PD associated with alterations in the modulation of beta and theta oscillations, and (iii) a beneficial effect of STN-DBS on feedback learning in PD patients which enhanced learning to a level similar to that in healthy older adults. Such knowledge about physiological and pathological changes as well as treatment effects is indispensable for the preservation of functionality in healthy aging as well as for a precise prognosis and optimization of treatment outcome in PD.

Zusammenfassung

Lernen ist eine wichtige Voraussetzung für die erfolgreiche Anpassung an unsere Umwelt. Die vorliegende Doktorarbeit befasst sich mit zwei unterschiedlichen Arten des Lernens, die essentiell für die Funktionsfähigkeit in alltäglichen Lebenssituationen sind: implizites motorisches Sequenzlernen sowie rückmeldungsbasiertes Lernen.

Das Erlernen motorischer Sequenzen findet insbesondere während des Trainings statt, das für gewöhnlich den Prozess der Konsolidierung nach sich zieht. Der Begriff der Konsolidierung umfasst neben der Stabilisierung neu angeeigneter Fertigkeiten (d.h., eine verringerte Interferenzanfälligkeit) auch eine Verbesserung der Fertigkeiten ohne weitere Übung, das sogenannte *offline improvement*. Es gibt Evidenz für die Annahme, dass Arbeitsgedächtnisprozesse zu motorischem Sequenzlernen beitragen. Auf neuronaler Ebene konnte gezeigt werden, dass motorisches Sequenzlernen neuronale Netzwerke wie etwa die Kortex-Basalganglien-Schleifen rekrutiert. Es wird weiterhin angenommen, dass bei jungen Erwachsenen insbesondere Beta-Oszillationen in motor-kortikalen Arealen von funktioneller Bedeutung für diese Art des Lernens sind. Vor dem Hintergrund einer alternden Bevölkerung ist das Verständnis altersbedingter Veränderungen relevant, um ein selbstbestimmtes Leben bis ins hohe Alter gewährleisten zu können. Kenntnisse über Veränderungen über die Lebensspanne hinweg sind wichtig, um Beeinträchtigungen im Alter früh zu erkennen und bilden somit die Grundlage präventiver Maßnahmen. Im Zuge des Alterns und damit einhergehenden Erkrankungen konzentrieren sich Studien zu motorischem Sequenzlernen unter anderem auf Patienten, die an Morbus Parkinson erkrankt sind. Morbus Parkinson ist eine neurodegenerative Erkrankung, die unter anderem mit dem Verlust dopaminerger Neurone sowie pathologischen Veränderungen der Kortex-Basalganglien-Schleifen einschließlich einer veränderten Synchronisation von Beta-Oszillationen einhergeht. In Anbetracht dessen mag es kaum überraschen, dass diese Patienten oftmals eingeschränktes motorisches Sequenzlernen zeigen. Ob pathologische Beta-Oszillationen für diese Beeinträchtigung verantwortlich sind, wurde bislang noch nicht untersucht. Ähnlich zu motorischem Sequenzlernen, spielen auch beim rückmeldungsbasierten Lernen Strukturen der Kortex-Basalganglien-Schleifen sowie das Dopamin-System eine wichtige Rolle. Diese Art des Lernens basiert auf der Verbindung von eigenen (aktiv) oder beobachteten Handlungen (beobachtungsgestützt) mit damit einhergehenden Konsequenzen (z.B. positive oder

negative Rückmeldungen). Interessanterweise zeigen Studien zu rückmeldungsbasiertem Lernen bei Morbus Parkinson, dass beobachtungsgestütztes Lernen zumindest in frühen Phasen der Erkrankung vergleichbar mit dem gesunder Probanden zu sein scheint, wohingegen aktives Lernen bei diesen Patienten verändert ist und in Abhängigkeit des dopaminergen Medikationsstatus zu variieren scheint. Neben der Dopamin-Substitution, ist die Tiefe Hirnstimulation (THS) des STN eine erfolgreiche Behandlungsmethode vor allem für Patienten mit fortgeschrittenem Morbus Parkinson. Bezüglich rückmeldungsbasiertem Lernen gibt es erste Evidenz, dass aktives Lernen durch Rückmeldung im Rahmen der STN-THS verbessert werden kann. Die Effekte auf beobachtungsgestütztes Lernen durch Rückmeldung wurden bisher nicht untersucht. Ein genaueres Verständnis möglicher Veränderungen kognitiver Leistung wie des rückmeldungsbasierten Lernens durch die THS ist von großer Bedeutung für eine Verbesserung der Behandlung sowie für eine Prognose bezüglich therapeutischer Effekte bei Morbus Parkinson. Da die THS zunehmend auch eine Behandlungsoption für jüngere, berufstätige Patienten darstellt, können Veränderungen kognitiver Funktionen beachtliche Auswirkungen auf die Erwerbstätigkeit und im Zuge dessen auch auf die Lebensqualität dieser Patienten haben.

Diese Doktorarbeit umfasst drei Studien, die zu einem besseren Verständnis des impliziten motorischen Sequenz- sowie des rückmeldungsbasierten Lernens bei physiologischem und pathologischem Altern am Beispiel des Morbus Parkinson beitragen sollen. Die Untersuchung motorischen Sequenzlernens im Verlauf des physiologischen Alterns (Studie 1) wurde durch die Charakterisierung neuronaler Oszillationen, die dem Sequenzlernen bei physiologischem und pathologischem Altern zugrunde liegen, ergänzt (Studie 2). Studie 3 befasste sich mit den Effekten der STN-THS auf das rückmeldungsbasierte Lernen bei Parkinsonpatienten. Gesunde ältere Erwachsene dienten hier als Kontrollgruppe.

Studie 1 untersuchte Prozesse der Akquisition und Konsolidierung einer motorischen Sequenz im Verlauf des physiologischen Alterns. Zudem wurde erfasst, ob das Arbeitsgedächtnis mit diesen Prozessen verbunden ist. Die Studie zeigt, dass junge und ältere Erwachsene im Gegensatz zu Erwachsenen im mittleren Alter eine motorische Sequenz erlernten. Die Daten weisen darauf hin, dass ältere Erwachsene möglicherweise explizite Lernstrategien anwenden. Daher besteht Grund zur Annahme, dass das beobachtete Defizit bei Erwachsenen im mittleren Alter darauf zurückzuführen ist, dass implizites Lernen weniger effektiv wird, kompensatorische Strategien aber noch nicht erfolgreich implementiert

wurden. Unmittelbar nach der Akquisition waren sowohl junge als auch ältere Erwachsene interferenzanfällig. Nach einer Pause von einer Stunde jedoch zeigten beide Altersgruppen eine Stabilisierung der Sequenz, was darauf hindeutet, dass eine Konsolidierung der motorischen Sequenz stattgefunden hat. Unspezifisches *offline improvement*, eine generelle Verbesserung der Reaktionszeiten, die nicht sequenz-spezifisch war, wurde hingegen nur bei Erwachsenen jungen und mittleren Alters beobachtet. Diese Befunde geben Grund zur Annahme, dass unterschiedliche Formen der Konsolidierung spezifisch durch Alterungsprozesse beeinflusst werden. Das Arbeitsgedächtnis war unabhängig vom Alter der Probanden nicht mit dem Erwerb oder der Konsolidierung der motorischen Sequenz verbunden.

Studie 2 diente der Beantwortung der Frage, ob und inwieweit pathologisches Altern am Beispiel des Morbus Parkinson mit Veränderungen motorischen Sequenzlernens einhergeht. Mittels Magnetenzephalographie (MEG) wurde die neuromagnetische Aktivität mit dem Ziel aufgezeichnet, die funktionelle Bedeutung von neuronalen Oszillationen – vor allem im Beta-Frequenzbereich – für diese Form des Lernens zu charakterisieren. Parkinsonpatienten zeigten im Vergleich zu gesunden Erwachsenen eingeschränktes Sequenzlernen sowie eine größere Interferenzanfälligkeit unmittelbar im Anschluss an die Akquisition. Diese Unterschiede wurden von einer geringeren Beta-Suppression bei Parkinsonpatienten begleitet, was deren Bedeutung für das Lernen motorischer Sequenzen unterstützt. Interessanterweise zeigte sich bei gesunden Erwachsenen ein korrelativer Zusammenhang zwischen der Akquisitionsleistung und der Interferenzanfälligkeit, wohingegen diese beiden Prozesse bei Parkinsonpatienten nicht miteinander korrelierten. Die Annahme distinkt ablaufender Prozesse bei Morbus Parkinson wurde weiterhin durch den Befund gestützt, dass eine stärkere Beta-Suppression bei Parkinsonpatienten förderlich für die Interferenzanfälligkeit, nicht aber für die Akquisitionsleistung war. Zusätzlich zu den Befunden im Beta-Frequenzband lieferte die Studie erste Evidenz für die Annahme, dass Theta-Oszillationen in einem alternden aber gesunden motorischen System mit Prozessen der Interferenzanfälligkeit verbunden sein könnten.

Studie 3 konzentrierte sich auf aktives und beobachtungsgestütztes Lernen durch Rückmeldung bei Parkinsonpatienten und gesunden älteren Erwachsenen. Hauptbestandteil der Studie war die Untersuchung der Effekte der THS auf rückmeldungsbasiertes Lernen. Ältere Erwachsene dienten als Kontrollgruppe. Die Daten zeigten, dass die THS aktives

rückmeldungsbasiertes Lernen, das auf der Verbindung von eigenen Handlungen mit damit einhergehenden Auswirkungen basiert, begünstig und dass Patienten im Stimulations-OFF nicht aber im Stimulations-ON schlechteres aktives Lernen zeigen als gesunde Erwachsene. Bei der Anwendung des durch die Rückmeldung Gelernten profitierten interessanterweise nur stärker beeinträchtigte Patienten von der THS. Zusätzlich zu diesen Ergebnissen des aktiven Lernens, liefert die Studie erste Hinweise darauf, dass die THS auch beobachtungsgestütztes Lernen durch Rückmeldung begünstigt.

Zusammengefasst trägt diese Arbeit zum Verständnis des impliziten motorischen Sequenzlernens und des rückmeldungsbasierten Lernens bei physiologischem und pathologischem Altern am Beispiel des Morbus Parkinson bei. Die drei Studien zeigen (i) initiales Lernen einer motorischen Sequenz – möglicherweise durch den Einsatz kompensatorischer expliziter Lernstrategien – sowie die Stabilisierung der neu angeeigneten Sequenz als eine Form von Konsolidierung bei gesunden, älteren Erwachsenen, (ii) vermindertes motorisches Sequenzlernen bei Patienten mit Morbus Parkinson, das vermutlich mit Veränderungen der Modulation von Beta- und Theta-Oszillationen einhergeht, sowie (iii) einen förderlichen Effekt der STN-THS auf rückmeldungsbasiertes Lernen bei Parkinsonpatienten, so dass diese Patienten eine Lernleistung ähnlich zu der gesunder Kontrollen zeigen. Das Wissen über solch physiologische und pathologische Veränderungen sowie behandlungsbezogene Einflüsse ist unverzichtbar, um die Funktionsfähigkeit bei physiologischem Altern zu erhalten sowie präzise Prognosen und eine Verbesserung des Behandlungserfolgs bei pathologischen Veränderungen zu ermöglichen.

1 Introduction

"Most of what we know about the world and its civilizations we have learned. Thus learning [and memory] is central to our sense of individuality" (Kandel and Hawkins, 1992, p.79). This citation from Eric R. Kandel and Robert D. Hawkins in its simplicity stresses the importance of learning. Learning is a driving force for successful adjustment to our environment and even for social progress (Kandel and Hawkins, 1992). The great interest in learning is reflected by the variety of academic disciplines engaged in this research field including, but not limited to, psychology, neuroscience, education, and philosophy. Although there is no agreed-upon absolute definition of learning, possibly owing to the breadth of interest, it is usually referred to as the process by which we acquire or modify knowledge about the world (Kandel et al., 2000). The term knowledge might concern information or facts but also skills or even values. In the studies of learning, it is not only of interest *what* we learn, but also *how* we learn. Traditionally, implicit (or non-declarative) and explicit (declarative) forms of learning have been distinguished which has been supported by case studies of amnestic patients with specific impairments of explicit learning (and memory) processes involving conscious participation (Schacter, 1987; Squire, 1992, 2004; Schacter and Tulving, 1994; Squire and Zola, 1996). Although a common universal definition is still lacking, implicit learning is often laxly defined as learning which occurs without being aware of what is learned (Frensch and Rünger, 2003). Explicit learning, on the other hand, utilizes conscious participation (reviewed by Squire, 1992). Although it has been questioned whether implicit and explicit learning are indeed completely distinguishable with independent underlying cognitive and neural systems (Ward et al., 2013) the concept of multiple learning (and memory) processes and systems is widely accepted and applied (e.g., see Squire, 2004).

One important field of interest in the learning literature refers to the acquisition of (motor) skills (e.g., grasping objects, practicing sports, driving a car, or playing a musical instrument) representing an important component of our everyday life. In the laboratory, experimental paradigms investigate explicit (e.g., Karni et al., 1995) or implicit motor learning (e.g., Robertson et al., 2004a) and usually measure either (i) the incremental acquisition of movement patterns, e.g. motor sequences or (ii) the capacity to modify previously learned movements to compensate for changes in the environment referred to as motor adaptation (for a review see Doyon and Benali, 2005). Similarly, learning of associative links between actions and corresponding outcomes (e.g., positive or negative feedback) referring to

feedback learning enables the successful adjustment to our environment. While positive consequences (e.g., reward or positive feedback) lead to increased frequency of a certain action, negative outcomes (e.g., punishment or negative feedback) usually result in reduced frequency of an action. Studies investigating neural correlates of these learning processes suggest that both motor sequence learning and feedback learning recruit distributed brain networks including cortico-basal ganglia circuits (reviewed by Doyon et al., 2009; Haber and Knutson, 2010). Furthermore, the dopaminergic system has been revealed to play an essential role in feedback-based learning (Haber and Knutson, 2010). Interestingly, Parkinson's disease (PD), a neurodegenerative disorder, is primarily associated with the loss of dopaminergic cells in the basal ganglia and pathological alterations within cortico-basal ganglia circuits (reviewed by Kalia and Lang, 2015). Therefore, the investigation of PD constitutes a fruitful line of motor sequence and feedback learning research.

The current thesis aimed to extend the knowledge about two types of learning, i.e. implicit motor sequence and feedback learning. As both types of learning underlie everyday behaviors and their successful adjustment to our environment, they are an essential aspect of life across the entire life span. Therefore, both implicit motor sequence and feedback learning were investigated in healthy as well as pathological aging taking the prominent example of PD, for which advanced age constitutes a major risk factor (Kalia and Lang, 2015). Non-invasive recordings of neurophysiological measures using magnetoencephalography (MEG) and the investigation of treatment effects in PD (i.e., deep brain stimulation (DBS) of the subthalamic nucleus (STN)) complemented behavioral data.

1.1 Implicit motor sequence learning

Motor sequence learning relates to the ability to acquire knowledge of sequences of events and actions and plays a pivotal role in various everyday activities. If one just thinks of typing, riding a bike or playing a musical instrument, it becomes apparent that these activities all make use of sequences of movements (Clegg et al., 1998). In motor sequence learning paradigms, participants typically learn such sequences of movements. Required motor responses in these tasks often involve button presses with fingers of the left and/or right hand on a response box (e.g., Doyon et al., 2002), finger to thumb opposition movements (e.g., Karni et al., 1995), arm movements (e.g., Doyon et al., 1996), or oculomotor sequential movements (e.g., Albouy et al., 2006). To assess learning, parameters such as decreases in reaction time (RT), movement time, and errors or changes in kinematics are measured. As

outlined above, sequential knowledge may be acquired explicitly or implicitly, that is with or without being aware of what has been learned or the fact that learning had occurred. The present thesis concentrates on learning under implicit conditions. The *Serial Reaction Time Task* (SRTT; Nissen and Bullemer, 1987) is an established measure for implicit motor sequence learning (Figure 1). Learning is usually reflected in a RT decrease over the course of the task. In the traditional variant, participants are *not* informed about the sequence of button presses embedded in the task and participants usually do not become aware of this sequential nature. However, if the applied sequence is presented extensively, explicit learning might be induced as well (Stadler, 1994). Moreover, the SRTT can be employed as a task assessing explicit learning by informing the participants about the repeatedly presented sequence prior to learning (Robertson et al*.,* 2004a).

The initial acquisition of motor sequences is usually characterized by relatively rapid improvements in performance (reviewed by Karni et al*.*, 1998). However, learning does not only occur during practice in so-called 'online' periods but also 'offline' without further training between sessions referred to as consolidation (Karni et al*.*, 1998; Robertson et al*.*, 2004b, 2005). The umbrella term consolidation describes different behavioral phenomena and is assumed to take mainly two forms: stabilization of skills reflected by reduced susceptibility to interference by an interfering task and further skill enhancement referred to as offline improvement (reviewed by Robertson et al*.*, 2004b). With regard to consolidation in implicit learning, several factors such as the length of the period between sessions have been identified as relevant (Janacsek and Nemeth, 2012). More specifically, previous studies suggest that gain in consolidation might increase with the length of the offline period (Press et al*.*, 2005) and that a 'critical time interval' of at least 1 to 4 hours – depending on task demands – must pass until enhancement of the newly acquired skill can be observed (Press et al*.*, 2005; Robertson et al*.*, 2005). In contrast, there is first evidence that improvement may be observable after a shorter break of only 10 minutes (Pollok et al*.*, 2014), suggesting that newly acquired motor skills may become stabilized relatively rapidly.

Over the last years, an area of research on motor sequence learning focused on disentangling the contribution of cognitive processes. Although several cognitive abilities including general fluid intelligence (Unsworth and Engle, 2005) and temporal processing (Ashe et al., 2006) have been suggested to play a role, working memory in particular has emerged as being substantially involved in acquiring motor sequences (reviewed by Seidler et al., 2012).

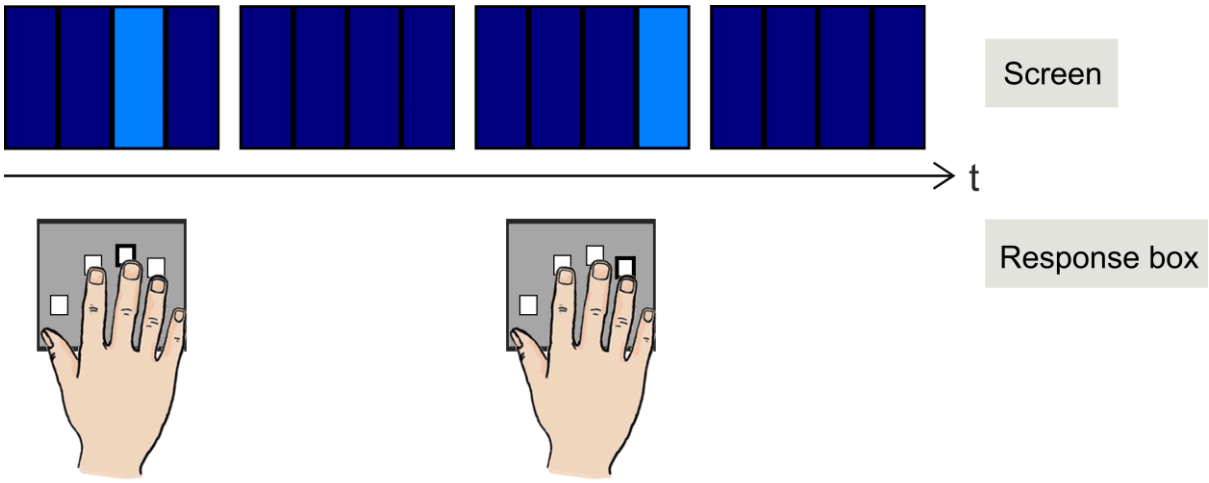

Figure 1: Serial reaction time task (SRTT). Sequence of events in two exemplary SRTT trials is depicted. The response keys are spatially mapped to four bars presented on the screen. Participants are instructed to press the corresponding button as soon as one of the bars changes from dark to light blue. Adapted and modified from Meissner et al. (*submitted*).

Working memory is considered as one fundamental prerequisite of almost every cognitive function and is suggested to constitute the interface between perception and attention, long-term memory, cognitive control and action planning (Wolf and Walter, 2008). It refers to a system with a limited capacity which temporarily stores and manipulates information (Baddeley and Hitch, 1974; Baddeley, 1992). Tasks used to investigate working memory not only make use of materials reflecting different working memory domains (e.g., verbal or visuospatial) but also differ with regard to mainly necessitated mental processes such as manipulation or rather pure maintenance (e.g., storage and matching) of information. In the context of motor sequence learning, it seems plausible that better working memory might lead to a 'larger window' opened to sequences, thereby making the process of learning easier (Frensch and Miner, 1994; Janacsek and Nemeth, 2013). Further, one might assume that performance on learning tasks comprising sequences of locations (e.g., the SRTT) might be linked to visuospatial rather than verbal working memory. In line with this, Bo and Seidler (2009) were able to show that individual differences in visuospatial working memory capacity were linked to learning of new sequences of finger movements. In that study, participants were explicitly instructed to learn a given sequence cued by boxes presented in a spatial array on the computer screen. This further supports the hypothesis that higher order cognition such as working memory contributes to motor sequence learning but only when intentional processing is emphasized (Unsworth and Engle, 2005). Contradictory to this assumption, in a follow-up study applying the SRTT, Bo et al. (2011) were able to show that implicit motor learning relies on working memory capacity as well. Interestingly enough,

verbal and visuospatial working memory were both related to performance improvement of young adults on the SRTT (Bo et al., 2011).

1.1.1 Neural substrates of implicit motor sequence learning

Neuroimaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have characterized the neural substrates of motor sequence learning in humans. Cortical and subcortical structures including primary motor (M1), premotor (PMC), supplementary motor (SMA), and dorsolateral prefrontal cortices (DLPFC), the basal ganglia (the striatum in particular) and the cerebellum have been suggested to play an important role in motor sequence learning (Grafton et al., 1995; Rauch et al., 1997; Destrebecqz et al., 2005; Ashe et al., 2006; Doyon et al., 2009; Hardwick et al., 2013; King et al., 2013). Doyon and colleagues assume that cortico-basal ganglia and cortico-cerebellar networks are involved in acquiring motor sequences, while consolidation may rather rely on cortico-basal ganglia circuits (e.g., Albouy et al., 2008; Doyon et al., 2009; King et al., 2013).

Evidence for the pivotal role of M1 within this network in implicit motor sequence learning comes from non-invasive brain stimulation studies (Pascual-Leone et al., 1994; Nitsche et al., 2003; Robertson et al., 2005; Tecchio et al., 2010; Krause et al., 2016). More specifically, anodal transcranial direct current stimulation (tDCS) – suggested to alter brain activity non-invasively by application of weak electrical currents – applied over the M1 facilitated both acquisition performance on the SRTT (Nitsche et al., 2003) and consolidation of a newly acquired motor sequence (Tecchio et al., 2010). Furthermore, Pascual-Leone and colleagues (1994) demonstrated by using transcranial magnetic stimulation (TMS) that implicit motor sequence learning leads to progressively larger motor cortical output maps until explicit knowledge is achieved. These findings support not only the importance of M1 for implicit motor sequence learning but additionally indicate relatively rapid functional plasticity of this area during motor learning. Long-term potentiation-like mechanisms, the modification of synaptic strength, have been proposed to play a major role in such plasticity associated with motor learning (Butefisch et al., 2000; Rioult-Pedotti et al., 2000; Ziemann et al., 2004; Jung and Ziemann, 2009).

1.1.2 Brain oscillations underlying implicit motor sequence learning

Synchronized brain oscillations represent a crucial mechanism for local and long-range neural communication in a temporally precise manner (Varela et al., 2001; Schnitzler and Gross,

2005). Such oscillations reflect rhythmic fluctuations of populations of neurons which are mainly characterized by their frequency, amplitude and phase. Classically, they are categorized into five frequency bands: delta (< 4 Hz), theta (4-7 Hz), alpha (8-12 Hz), beta (13-30 Hz), and gamma oscillations (> 30 Hz). Spectral power, which is probably the most frequently analyzed parameter of oscillations, is defined as the squared amplitude at a given frequency. At the macroscopic level, oscillations can be investigated non-invasively using electroencephalography (EEG) or MEG (Figure 2). The signals measured by EEG and MEG are generated by synchronized neuronal activity of thousands of neurons aligned in parallel (Hämäläinen et al., 1993). Whereas EEG measures electrical activity, MEG records small magnetic fields resulting from the electrical current occurring in the brain. The detection of these magnetic fields requires very sensitive sensors called superconductive quantum interference devices (SQUIDs) which are immersed in liquid helium at the temperature of 4 K (− 269 °C). MEG provides a very high temporal resolution in the range of milliseconds as well as a good spatial resolution on the cortical surface (2 to 3 mm under optimal conditions; Hämäläinen et al., 1993). However, for deeper brain structures with increasing distance to the sensors, the spatial resolution diminishes and is worse as compared to neuroimaging techniques such as fMRI. Nevertheless, in comparison to electrical fields as measured by EEG, magnetic fields are less susceptible to distortion by skull and scalp allowing better spatial resolution (Cohen and Cuffin, 1983; Hämäläinen et al., 1993). Another advantage of MEG as compared to EEG, especially in the context of studies involving patient populations, relates to the preparation of participants (e.g., attachment and placement of electrodes in EEG) before the actual experiment which is usually less time-consuming and tiring for the participants when using MEG.

Concerning the functional relevance of neural oscillations, it has been proposed that oscillatory activity subserves a mechanism of functional integration within neural networks. This assumption arose from intensive research in the last decades which has revealed that a wide range of functions, including motor and cognitive processes, are associated with synchronized oscillatory activity in different frequency bands (reviewed by Varela et al., 2001; Buzsáki and Draguhn, 2004; Schnitzler and Gross, 2005; Uhlhaas and Singer, 2006). The investigation of oscillatory dynamics in the context of motor control has produced evidence that oscillations in the beta frequency band are involved in planning, preparing and executing

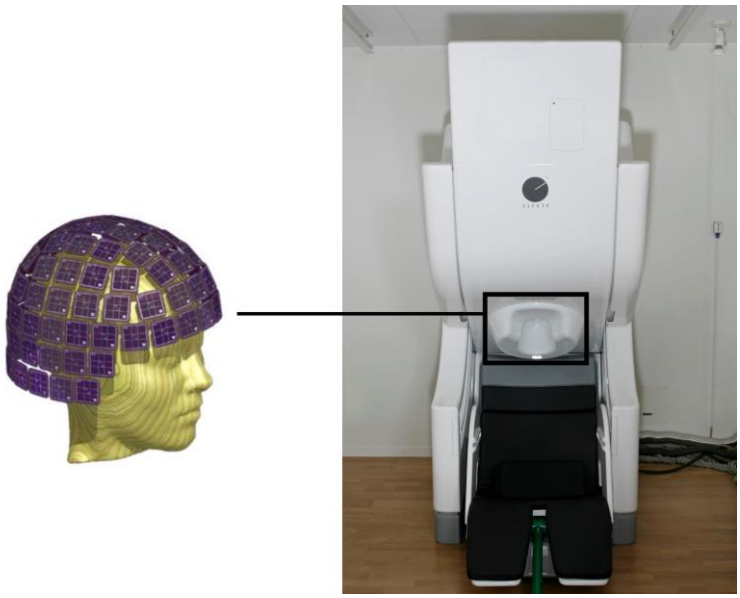

Figure 2: MEG system. Frontal view of the 306-channel whole-head MEG system (Elekta Neuromag, Helsinki, Finland) at the Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine-University Düsseldorf. The insert on the left-hand side adapted and modified from Hari and Kujala (2009) depicts the MEG sensors (so-called SQUIDs) arranged within a helmet-shaped inlay.

movements (Pfurtscheller and Lopes Da Silva, 1999; Kaiser et al., 2001; Engel and Fries, 2010; Heinrichs-Graham and Wilson, 2015). A stable and extensively studied finding relates to the typical pattern of beta and alpha power modulations with a decrease in power before and during execution of voluntary movements followed by its increase exceeding baseline levels (Pfurtscheller and Lopes Da Silva, 1999). The decrease in power is often termed beta power suppression or event-related desynchronization, whereas the increase after movement termination is referred to as beta rebound or event-related synchronization. Due to the prominent occurrence of beta oscillations at rest, they were traditionally thought to reflect an idling or even an inhibited motor cortical state (Pfurtscheller et al., 1996). However, a more recent hypothesis on the functional role of beta oscillations by Engel and Fries (2010) proposes that beta activity might rather be seen as an active process which signals the 'status quo', i.e. the current cognitive or motor state, at the expense of more flexible control strategies. Thus, a decrease in beta power should be observed if a change in motor or cognitive state is about to occur. Based on this assumption, Brown and colleagues suggested that beta power suppression may represent a prospective control mechanism of motor and cognitive readiness (Jenkinson and Brown, 2011; Oswal et al., 2012). In line with these concepts of beta activity, evidence exists that beta oscillations in particular but also alpha oscillations may be critically involved in motor sequence learning in healthy adults (Zhuang et al., 1997; Pollok et al., 2014). More specifically, Pollok and colleagues (2014) reported that

stronger beta power suppression in motor cortical areas might be linked to superior learning on the SRTT. Similarly, transcranial alternating current stimulation (tACS) over M1 was found to stabilize a newly learned motor sequence when applied at beta but not at other frequencies (10 or 35 Hz; Pollok et al., 2015; Krause et al., 2016). Since tACS is hypothesized to interact with oscillations in a frequency-dependent manner (Thut et al., 2012; Helfrich et al., 2014; Herrmann et al., 2016), these findings strengthen the assumption of beta oscillations and their role in motor sequence learning.

1.1.3 Age-related changes in implicit motor sequence learning

Implicit motor sequence learning underlies many everyday activities and is essential for proper functioning in various contexts. It is thus an important aspect across the life span until old age. The literature on age-related changes in this type of learning is not unequivocal. Whereas some studies report intact acquisition in healthy older adults employing the SRTT and related tasks (e.g., Howard and Howard, 1992; Brown et al., 2009; Nemeth and Janacsek, 2011; Verneau et al., 2014), reports of age-related declines are no exception either, especially when more complex tasks involving dual tasking or higher-order sequencing were applied (e.g., Frensch and Miner, 1994; Howard et al., 2004; Nejati et al., 2008).

Despite increasing attention towards the investigation of age-related changes in motor sequence learning, at least two caveats should be taken into consideration. First, most of the research has so far concentrated on adults above the age of 50 as compared to young adults. Thus, much less is known about the development of motor sequence learning across the adult life span. There is first evidence for developmental changes in implicit motor sequence learning provided by two studies investigating different age groups ranging from childhood to adults above the age of 80 (Janacsek et al., 2012; Lukacs and Kemeny, 2015). Results of these studies suggest that learning abilities increase with age, peaking between 35 and 45 years, and are then beginning to decrement. In contrast, another study did not find differences between age groups in SRTT performance indicating similar learning abilities independent of age (Gaillard et al., 2009). Second, the majority of studies on motor sequence learning have focused on age-related changes in acquisition rather than consolidation of motor sequences. A few studies have examined consolidation as reflected by offline improvement on the SRTT and related tasks in older as compared to young adults and report diminished or even absent improvement after a period of at least 12 hours in healthy older adults (Spencer et al., 2007; Brown et al., 2009; Nemeth and Janacsek, 2011). These findings

fuel the assumption that offline improvement is affected by healthy aging. Whether stabilization of skills, the second form of motor consolidation, might also vary with age and how processes related to consolidation develop across the adult life span is yet to be determined.

As outlined in section 1.1, young adults might rely on working memory capacity in motor sequence learning tasks such as the SRTT. Previous studies on working memory in healthy aging provide evidence for the assumption that performance in tasks involving the maintenance or updating of information declines with increasing age (e.g., Park et al., 2002; Bopp and Verhaeghen, 2005; Reuter-Lorenz and Sylvester, 2005; Cappell et al., 2010; Nyberg et al., 2012; Draganski et al., 2013). For example, studies using *n*-back tasks which require participants to decide whether the stimulus presented on the screen was the same as the stimulus presented *n* trials back, report poorer performance in older adults, especially in trials with larger memory load (Mattay et al., 2006; Geerligs et al., 2014). Accordingly, it has been proposed that working memory decrements in the elderly might at least partially explain age-related alterations in motor sequence learning (Seidler et al., 2012). More specifically, previous studies indicate that older adults rely on working memory processes to maximize performance when intentional processing is emphasized (Bo et al., 2009) and provide first evidence for the relation between working memory capacity and learning under implicit conditions (Bo et al., 2012). The majority of studies examining motor sequence learning and its relation to working memory implemented tasks posing strong demands on working memory storage capacity (Unsworth and Engle, 2005; Bo et al., 2011, 2012). Interestingly, a more recent study revealed that training on a visuospatial *n*-back task which requires updating of information enhances retrieval of explicitly learned motor sequences in young and older adults (Chan et al., 2015). Whether performance on these working memory tasks can also be linked to more implicit forms of motor sequence learning is not clear yet.

In parallel to the mixed findings of implicit motor sequence learning in healthy aging at the behavioral level, neuroimaging studies on age-related changes yielded equivocal results. Whereas Daselaar and colleagues (2003) found similar activation patterns in young and older adults during performance on the SRTT, age-related changes in cortico-basal ganglia regions have been reported as well. For example, a study by Aizenstein et al. (2006) revealed decreased activity in the DLPFC and striatum in older compared to younger participants. Furthermore, several studies suggest that increased activity in the medial temporal lobe,

including the hippocampus, might compensate for disrupted functioning in the cortico-basal ganglia system in the elderly (Rieckmann et al., 2010; Dennis and Cabeza, 2011; for a review see King et al., 2013).

The knowledge of age-related changes in oscillatory activity in the context of implicit motor sequence learning is sparse. However, MEG and EEG studies have begun to investigate oscillatory activity during preparation and regulation of simple movements in healthy aging without the relation to learning (Vallesi et al., 2010; Rossiter et al., 2014; Meziane et al., 2015; Heinrichs-Graham and Wilson, 2016; Quandt et al., 2016; Schmiedt-Fehr et al., 2016). These studies demonstrate a more widespread spatial distribution of beta power suppression in healthy aging (e.g., Quandt et al., 2016) and suggest a shift from hemispheric asymmetry in young adults with stronger beta power modulation in sensorimotor regions contralateral to the motor effector, to more symmetrical, bilateral patterns of modulation in the elderly (e.g., Vallesi et al., 2010; Meziane et al., 2015). Besides this spatial expansion, increased modulation of beta power with increasing age has been reported as well (Rossiter et al., 2014; Heinrichs-Graham and Wilson, 2016; Schmiedt-Fehr et al., 2016). These changes have been suggested to represent a compensatory mechanism accounting for alterations in motor control (Quandt et al., 2016; Schmiedt-Fehr et al., 2016).

1.2 Feedback learning

In our daily life, we often need to decide which action or behavior fits best within the framework of the current situation. Successful adaptation to the (constantly changing) environment is often guided by the ability to learn from consequences of chosen actions. Instrumental conditioning, the most basic form of such behavior, allows an organism to learn contingencies between own responses and outcomes and enables individuals to use previous outcomes to modify future actions (Thorndike, 1911; Skinner, 1938; Mackintosh, 1983; Balleine and Dickinson, 1998; Dayan and Balleine, 2002). Whereas actions and decisions followed by positive outcomes (e.g., reward or positive feedback) are usually increased in frequency, actions and decisions followed by negative outcomes (e.g., punishment or negative feedback) are less likely to occur. Such outcomes affecting learning in this manner have been termed ‘reinforcers’ (Hollerman and Schultz, 1998). A well-established assumption implies that the extent of the difference between the expected and the actual outcome, the so-called prediction error, might serve as a signal that teaches us whether to select an alternative action or to repeat the respective action in future similar situations (Sutton and

Barto, 1998). However, an action may lead to different consequences depending on the specific context (e.g., stimuli or situations). Therefore, it has been assumed that prediction errors are used to learn the values of stimuli, stimulus-response pairs or both, which are then used to optimize action selection (Sutton and Barto, 1998; Maia, 2009, 2010). In other words, learning might comprise not only the processing of action-outcome related prediction errors but also action-independent prediction errors reflecting the difference between the received outcome and the subjective value of the stimulus (Kobza and Bellebaum, 2015). In the last decades, a large amount of studies both in animals and humans has investigated such feedback-based learning processes in detail (for a review of neural underpinnings see Haber and Knutson, 2010).

1.2.1 Active and observational feedback learning

Feedback learning involves the incremental acquisition of stimulus-response-outcome associations via response-contingent feedback. Under experimental conditions, several tasks are used to investigate feedback learning processes. Frank and colleagues (2004) introduced a probabilistic selection task requiring participants to learn to select one of two presented stimuli (i.e., Asian symbols). Each selection is followed by positive or negative feedback to indicate whether the participant's selection is correct or incorrect. However, the feedback given is probabilistic in nature, i.e. selected symbols are not always followed by valid (positive or negative) feedback. Other paradigms require two-choice decisions upon the presentation of one stimulus at a time (e.g., press a left or right button; Holroyd and Coles, 2002; Eppinger et al., 2008; Bellebaum and Colosio, 2014). As distinct from the probabilistic selection task in which outcomes are related to the stimulus itself, in such tasks the outcome is associated with a stimulus–response ensemble. Akin to the probabilistic selection task, the validity of feedback is often manipulated, including deterministic (e.g., 100% positive feedback when pressing the correct button in response to a specific stimulus) as well as probabilistic feedback (e.g., 80% or 50% positive feedback when pressing the correct button; Eppinger et al., 2008; Bellebaum and Colosio, 2014). Figure 3 (top row) displays an example of such a feedback learning task as applied in the present thesis. Another established paradigm that requires individuals to modify their behavior in response to trial-by-trial feedback includes probabilistic classification tasks such as the weather prediction task (e.g., Knowlton et al., 1994). Here, participants are asked to predict outcomes based on a complex stimuli pattern as well as on trial-by-trial feedback on the accuracy of their predictions.

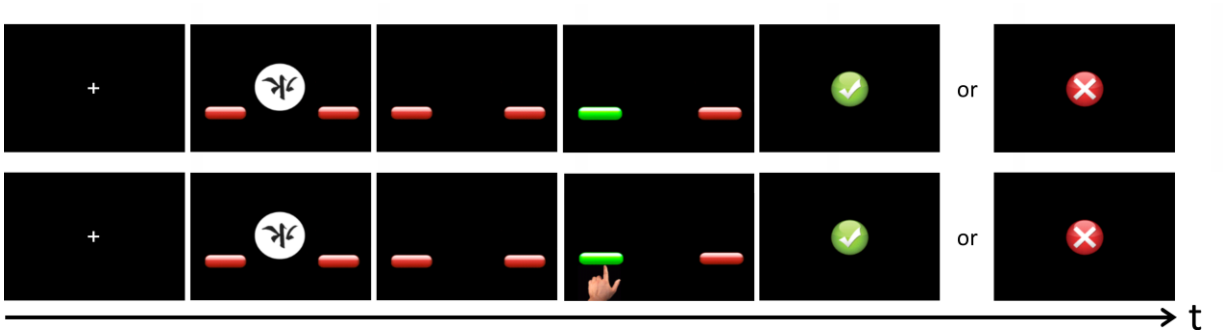

Figure 3: Exemplary feedback learning task. Depiction of one exemplary feedback learning trial on an active (top) and observational task variant (bottom). Participants are asked to press a left or right key in response to the presented stimulus (top) or to observe a response of another person (bottom). Positive or negative feedback is presented after each (observed) response. Adapted and modified from Meissner et al. (2016a).

Feedback given to participants often involves monetary feedback (gains and losses) or other rewards (O'Doherty et al., 2004; Bellebaum et al., 2012; Bellebaum and Colosio, 2014). But, feedback may also be more abstract (e.g., 'cognitive' feedback) and might merely inform participants about their choice/response accuracy or the right response (e.g., Aron et al., 2004; Frank et al., 2004; Bellebaum et al., 2016). Interestingly, more abstract forms of feedback might engage mechanisms generally similar to those in monetary feedback (Aron et al., 2004). With regard to its timing, feedback is usually delivered immediately or shortly after the respective response. However, it is also possible to deliver it with a certain delay (Foerde and Shohamy, 2011; Foerde et al., 2013; Weismüller and Bellebaum, 2016). Interestingly, it has been suggested that task characteristics might influence learning strategies and the underlying neural processes recruited by the task (Foerde and Shohamy, 2011; Wilkinson et al., 2011; Foerde et al., 2013; Bellebaum et al., 2016). For example, tasks being more probabilistic in nature and comprising complex stimulus structures have been suggested to reflect rather non-declarative, implicit learning whereas tasks with less complex structures might also allow the use of more declarative, explicit learning strategies in the sense of explicit if-then rules, at least to some extent (Knowlton et al., 1994; Wilkinson et al., 2011; Bellebaum et al., 2016).

In feedback learning, establishing an association between a particular action and its outcome is the basis for behavioral adaptation. These associations can be learned by linking one's own actions to accompanying feedback. Alternatively, they can also be established by observing another person's behavior and the accompanying feedback that this person receives (Bellebaum et al., 2010; Burke et al., 2010). The ability to learn from observed actions and

outcomes may be crucial, especially in dangerous situations, as one might avoid putting oneself at risk. Although the majority of studies investigate active feedback learning, several research groups have developed observational task variants allowing to examine both types of feedback learning (e.g., Bellebaum et al., 2010; Burke et al., 2010; Cooper et al., 2012; see Figure 3). Interestingly, there is evidence that associations between actions and outcomes may be learned equally well by active responding and observation (Bellebaum et al., 2012; Bellebaum and Colosio, 2014).

A recent study further investigated the strategies underlying observational feedback learning in detail (Bellebaum et al., 2016). Interestingly, participants imitated the observed behavior – especially in early phases of the task. However, the observer also paid attention to the course of the feedback received by the observed participant and used this to adapt behavior.

1.2.2 Neural correlates of feedback learning

Up to date, a wealth of research investigated the neural mechanisms involved in feedback learning revealing that the dopaminergic system and cortico-basal ganglia circuits play an essential role (reviewed by Haber and Knutson, 2010). Single-cell recordings in monkeys showed that dopaminergic neurons code the discrepancy between expected and actual reward (Schultz et al., 1993, 1997; Hollerman and Schultz, 1998; Schultz, 1998). While phasic bursts of activity were associated with unexpected reward in these studies, omission of expected reward was linked to dips in activity. These phasic changes have been suggested to be superimposed on the basal tonic activity of dopaminergic neurons which may signify that things are as expected (Montague et al., 1996, 2004; Schultz and Dickinson, 2000). Microelectrode recordings in PD patients undergoing DBS surgery for treatment have reported similar patterns of activity (Zaghloul et al., 2009) suggesting a link between dopaminergic activity and feedback learning in humans. Interestingly, the fact that DBS of the STN, a part of the basal ganglia, has become a well-established treatment in advanced PD (Limousin et al., 1998; Deuschl et al., 2006) affords the opportunity to examine the role of this nucleus in feedback learning. Animal studies indicate that the STN may play a role in feedback-based learning, as lesions may enhance the incentive salience of stimuli associated with rewards (Uslaner and Robinson, 2006; Uslaner et al., 2008). How DBS of the STN in humans affects feedback learning will be discussed in more detail in section 1.3.6.

At the network level, neuroimaging studies identified the importance of cortico-basal ganglia circuits in feedback learning and could link several brain areas to key aspects of this type of learning, including activations in dopaminergic midbrain regions (e.g., the substantia nigra) as well as dopaminergic projection sites in striatal (dorsal and ventral) and cortical areas (e.g., medial prefrontal cortex including the anterior cingulate cortex (ACC); Aron et al., 2004; O'Doherty et al., 2004; D'Ardenne et al., 2008; Bellebaum et al., 2012; for a review see Haber and Knutson, 2010). The majority of research has concentrated on active feedback learning which requires to establish links between own actions and outcomes. However, several studies have begun to investigate neural mechanisms underlying observational feedback learning and whether these mechanisms differ from those in active feedback learning (e.g., Bellebaum et al., 2010; Burke et al., 2010; Cooper et al., 2012; Kobza and Bellebaum, 2015). Although some of these results suggest that both types of learning are mediated by similar brain structures (Burke et al., 2010; Cooper et al., 2012), there is converging evidence that neural mechanisms might differ at least to some extent (Bellebaum et al., 2010; Burke et al., 2010; Bellebaum et al., 2012; Bellebaum and Colosio, 2014; Kobza and Bellebaum, 2015). For example, Bellebaum and colleagues (2010) observed differences between observational and active learning in the feedback related negativity (FRN), a feedback-related negative event-related potential component generated in the ACC which is typically larger for negative than positive feedback (see Cohen et al., 2011). More specifically, the FRN difference between negative and positive outcomes was less pronounced in observational than in active learners. Furthermore, activations in the basal ganglia, and in the striatum particularly, might also differ between active and observational feedback learning (Bellebaum et al., 2012; Kobza and Bellebaum, 2015). More specifically, parts of the striatum – particularly dorsal striatal areas – have been proposed to be more strongly involved when associations have to be learned between own (as opposed to observed) actions and action outcomes (Bellebaum et al., 2012; Kobza and Bellebaum, 2015; however see Cooper et al., 2012). This fits well to the general assumption that the ventral and dorsal striatum might differ in their relative contribution during feedback learning tasks depending on the active involvement of participants: whereas the ventral striatum seems to be recruited when outcomes do or do not depend on a preceding response, the dorsal striatum only comes into play when outcomes are related to participants' responses (O'Doherty et al., 2004). These data suggest that parts of the (dorsal) striatum are of specific significance in ascribing outcomes to own rather than observed actions (Bellebaum et al., 2012, 2016; Kobza and Bellebaum, 2015).

Feedback learning requires the fast, dynamic interplay of several structures distributed across the brain. As outlined in section 1.1.2, synchronization of neuronal activity may represent a suitable functional mechanism to establish efficient communication between different brain regions. EEG and MEG studies have investigated oscillatory activity during feedback learning and have provided evidence for a prominent role of theta and beta oscillations (e.g., Gehring and Willoughby, 2004; Cohen et al., 2007; Marco-Pallares et al., 2008; van de Vijver et al., 2011; Andreou et al., 2017; for a review see Cohen et al., 2011). These studies suggest that negative feedback may elicit synchronization of theta oscillations, whereas positive feedback might be associated with beta activity. Concerning the neural generators underlying these effects, multimodal approaches combining methods such as EEG and fMRI suggest that theta activity in response to negative feedback may be associated with activations in cortical networks including the ACC; beta activity in response to positive feedback, on the other hand, corresponded to a network comprising cortical and subcortical areas including the striatum and the hippocampus (Mas-Herrero et al., 2015; Andreou et al., 2017). Interestingly, with regard to neurophysiological mechanisms, the above introduced FRN has been proposed to be partly related to the described theta activity or might even be a reflection of such oscillations in the time-domain (reviewed by Cohen et al., 2011).

1.3 Parkinson's disease

PD first described in 1817 by the English physician James Parkinson (Parkinson, 1817) is one of the most common progressive neurodegenerative diseases. The prevalence rises with age from 0.04% in adults between the ages of 40 to 49 years to 1.9% in adults over the age of 80 (Pringsheim et al., 2014). As the average age of our population continues to rise, the proportion of PD patients is expected to increase which places a major social and economic burden on our society.

1.3.1 Clinical characteristics

PD is characterized as a movement disorder and its clinical diagnosis relies on the presence of cardinal motor symptoms such as bradykinesia (slowness of movement), resting tremor, and muscular rigidity (stiffness and resistance to limb movement; reviewed by Lang and Lozano, 1998a, 1998b). The onset of these symptoms is predominantly asymmetric. Although they usually spread to the other side of the body during the course of the disease, the symptoms continue to be worse on the side of the body affected first (Hoehn and Yahr, 1967; Lee et al.,

1995; Djaldetti et al., 2006). Postural instability, a fourth cardinal motor symptom, usually develops in later stages of the disease and leads to increased risk of falls (Lang and Lozano, 1998b). The severity of PD motor symptoms can be assessed by means of the motor part of the *Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale* (MDS-UPDRS III; Goetz et al., 2008) with higher scores relating to more severe motor symptoms. In addition to motor symptom severity, the *Hoehn and Yahr scale* allows the evaluation of disease progression (Hoehn and Yahr, 1967). Increasing progression can be charted from stage 1, representing unilateral motor symptoms, to stage 5, indicating that patients are bound to bed or a wheelchair. In general, the clinical picture of the disease is heterogeneous and, based on the predominant motor signs, mainly two different subtypes have been classified, i.e. akinetic-rigid and tremor-dominant PD. These two subtypes differ with respect to their predominant motor symptoms and have also been linked to a different clinical course and prognosis (Jankovic and Kapadia, 2001; Rajput et al., 2009). As compared to patients with tremor-dominant PD, akinetic-rigid PD patients show a more rapid progress of the disease with relatively worse prognosis. They further exhibit stronger cognitive decline and have an increased risk to develop dementia (Jankovic and Kapadia, 2001; Rajput et al., 2009). Relating to the latter, despite the emphasis on cardinal motor symptoms, non-motor disturbances in PD including cognitive impairment in domains such as executive functions, learning and memory, attention, and visuospatial functions have gained increasing attention as they contribute to disability and impaired quality of life (Dubois and Pillon, 1997; Schrag et al., 2000; Chaudhuri et al., 2006; Svenningsson et al., 2012).

1.3.2 Etiology and Pathophysiology

Although the cause of PD has not been elucidated yet, several risk factors have been identified. Apart from age, which constitutes the greatest risk factor to develop the disease, genetic susceptibility and environmental factors have been identified (reviewed by Kalia and Lang, 2015). More specifically, several environmental exposures including pesticide exposure or head injuries have been revealed (Noyce et al., 2012). Furthermore, a recent meta-analysis identified several potential gene loci associated with increased disease risk including *SNCA*, a gene encoding the protein α-synuclein (Nalls et al., 2014).

One underlying pathological finding in PD is the loss of dopaminergic neurons most pronounced in the substantia nigra pars compacta (SNc), a basal ganglia structure, resulting in dopamine depletion in striatal areas (Kish et al., 1988; Hornykiewicz, 2008). Another

hallmark of PD is the accumulation of Lewy bodies, an aggregation of abnormally folded proteins (reviewed by Goedert et al., 2012). The main component of these Lewy bodies in PD is α-synuclein, which aggregates when in a misfolded state and forms Lewy bodies in different regions of the brain, the spinal cord, and the peripheral nervous system (Polymeropoulos et al., 1997; Spillantini et al., 1997; Braak et al., 2003; Goedert et al., 2012). Braak and colleagues hypothesized that the Lewy body pathology spreads in a specified pattern of six stages in PD, beginning peripherally and then affecting the central nervous system (Braak et al., 2003). This progression seemingly corresponds with the clinical course, including motor and non-motor symptoms.

An influential pathophysiological model developed in the 1980s suggests that dopamine depletion in PD disrupts the functionality of the basal ganglia including its connections to cortical areas (Crossman, 1987; Albin et al., 1989; DeLong, 1990). The basal ganglia consist of a group of interconnected subcortical nuclei, including the striatum (i.e., the caudate nucleus, putamen, nucleus accumbens, and the tuberculum olfactorium), the internal and external segment of the globus pallidus (GPi, GPe), the STN, and the SNc and substantia nigra pars reticulata (SNr). They form parallel, segregated loops with various cortical structures (e.g. with the M1 and SMA) via thalamic nuclei (Alexander et al., 1986; Albin et al., 1989; DeLong, 1990; Obeso et al., 2008). These loops are functionally subdivided into distinct pathways with different cortical projection areas sustaining a variety of motor and non-motor functions including learning (Redgrave et al., 2010). Whereas the striatum is considered to be the main input structure of the basal ganglia receiving major connections from the cortex, the GPi and SNr form output nuclei which send information to cortical areas via the thalamus. The intrinsic connections within the basal ganglia are thought to be organized in form of direct and indirect pathways, thus information is conveyed either directly or indirectly within the basal ganglia via STN and GPe. A simplified but generally accepted model proposes that activity in the direct pathway inhibits the output structures of the basal ganglia, resulting in a net disinhibition or excitation of the thalamus, whereas activity in the indirect pathway disinhibits the output structures resulting in increased inhibition of the thalamus (Albin et al., 1989; DeLong, 1990; Obeso et al., 2008). In the Parkinsonian state, it has been suggested that the activity in the indirect pathway mediated by D2 dopamine receptors is increased, whereas activity in the direct pathway mediated by D1 dopamine receptors is thought to be reduced (Figure 4; Albin et al., 1989; DeLong, 1990).

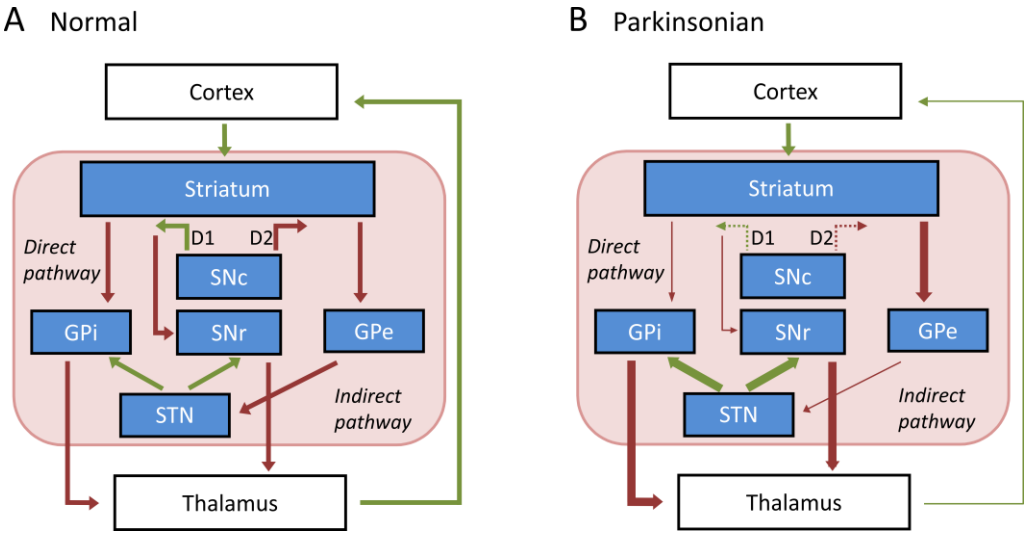

Figure 4: Classical model of basal ganglia (dys-)function. Basal ganglia function in normal (A) and parkinsonian (B) states (Albin et al., 1989; DeLong, 1990). Increased activity of the indirect and reduced activity of the direct pathway results in excessive inhibition of the thalamus, and ultimately reduced feedback to the cortex in PD. Green arrows depict excitatory, red arrows inhibitory projections. Arrow thickness indicates the relative activity, dashed arrows the relative reduction of D1 and D2 dopaminergic projections from the SNc to the striatum. Adapted and modified from Peterson and Horak (2016).

This internal imbalance of the basal ganglia results in excessive inhibition of the thalamo-cortical motor system. Due to its simplicity and hypothesis-generating nature, this classical model has been attractive and has had an important impact on the understanding of basal ganglia functionality and deviations in PD; however, the system might be more complex than assumed by this model (for a review see Obeso et al., 2008; Nelson and Kreitzer, 2014). For example, beyond the direct and indirect pathways, it has been suggested that there is a third direct cortico-STN pathway, the 'hyperdirect' link with projections from motor cortical areas to the STN (Nambu et al., 1996). The strengthening of this pathway might be a prerequisite for some of the pathological alterations in basal ganglia circuits in PD (Holgado et al., 2010). Furthermore, whereas this model suggests that the motor state in PD is predicted solely by the neuronal firing rate in the basal ganglia output, more recent studies provide evidence that changes in neuronal synchronization in cortico-basal ganglia circuits add to the understanding of PD pathophysiology (Schnitzler and Gross, 2005; Hammond et al., 2007; Oswal et al., 2013). Increased oscillatory beta activity in motor areas of the basal ganglia and cortex has received particular attention due to its link to PD motor symptoms such as akinesia and rigidity and its responsiveness to levodopa administration (Kühn et al., 2006, 2009; Jenkinson and Brown, 2011; Pollok et al., 2012; Oswal et al., 2013; Neumann et al., 2016a; Beudel et al., 2017). Despite the prominent role of beta oscillations, evidence

accumulates that pathological alterations of oscillations across multiple frequencies might be of significance in PD pathophysiology (Oswal et al., 2013). As opposed to beta oscillations which have been classically considered as 'anti-kinetic', oscillations in the gamma frequency range have been proposed to be a rather 'pro-kinetic' signal. Gamma power in the STN increases at movement onset, even more so following levodopa administration, and is correlated with (pre-) motor cortical activity (Litvak et al., 2012). Changes in oscillatory activity might also be associated with cognitive impairment observed in PD. For example, altered modulation of beta activity has been suggested to contribute to impairments in domains such as executive functioning (Engel and Fries, 2010; Oswal et al., 2012). Previous MEG studies exploring the power spectrum in non-demented PD patients in cortical areas reported a widespread increase in theta and alpha oscillations relative to healthy adults (Bosboom et al., 2006; Stoffers et al., 2007). In PD patients with dementia, the increase in theta power was even more pronounced suggesting an important association with cognitive processing (Bosboom et al., 2006; Dubbelink et al., 2013). These findings highlight the role of oscillatory activity across multiple frequency bands in motor and non-motor PD impairment.

1.3.3 Treatment

Up to date, there is no treatment available that could cure or reverse the progression of PD. Therefore, treatment aims at the relief of symptoms. Medication and DBS accompanied by physical exercise are widely used therapeutic means for the treatment of PD motor symptoms. Levodopa (a dopamine precursor), dopamine agonists and monoamine oxidase B inhibitors are the main families of drugs used for treatment, especially in early PD. Unfortunately, sustained medical management is often accompanied by adverse effects such as the appearance of levodopa-induced motor complications with unpredictable and rapid changes between akinesia and mobile periods often characterized by hyperkinesia (Goetz et al., 2005). In advanced PD, when motor symptoms may not be adequately controlled with medication, invasive brain stimulation techniques such as DBS are highly effective treatment options (Limousin et al., 1998; Deuschl et al., 2006). DBS electrodes are implanted into a target area in the brain, most commonly the STN and, to a lesser extent, the GPi. The subcutaneous pulse generator generates electrical current pulses that are directed via an extension wire to the electrode where the current pulses are delivered. In PD, the STN is typically stimulated with a frequency of 130 Hz (Benabid et al., 2009). So far, DBS is considered a treatment option in advanced PD. However, previous research has shown that

STN-DBS may be beneficial in relatively early stages of PD before the appearance of severe motor complications (Schuepbach et al., 2013). This finding has led to the conclusion that DBS should be considered a treatment option in earlier stages of PD for carefully selected patients as it may ensure maintenance of quality of life (Deuschl and Agid, 2013).

Although DBS is an established treatment, the exact mechanisms remain elusive. Initial views suggested that its effects on motor symptoms might relate to the inhibition of overactive basal ganglia neurons in the STN/GPi. However, more recent observations suggest that DBS effects not just manifest through local inhibitory but rather multiple mechanisms ranging from immediate neuromodulatory effects and synaptic plasticity to long-term neural reorganization (reviewed by Ashkan et al., 2017). It has been proposed that these mechanisms include, but are not limited to, the amelioration of abnormal oscillatory activity, especially in the beta frequency band, the stimulation of efferent axons imposing a time-locked, regular pattern of discharge on the axons, the inhibition of hormone and neurotransmitter production or release participating in intercellular communication, the change in cerebral blood flow and neurogenesis resulting in enhanced neuroplasticity, and a potential neuroprotection of dopaminergic cells (for reviews see Benabid et al., 2009; Ashkan et al., 2017).

Beyond its remarkable effect on PD motor symptoms, DBS has also been linked to changes in non-motor domains including cognitive functions. However, the literature on effects of DBS on such functions is rather controversial, ranging from improvement or no significant change (e.g., Ardouin et al., 1999; Funkiewiez et al., 2006) to deterioration of specific functions (Parsons et al., 2006; Witt et al., 2008). A recent meta-analysis indicated that PD patients with STN-DBS exhibit mild to moderate deficits in different domains including learning and memory, attention, executive functions or verbal fluency measures (Combs et al., 2015).

1.3.4 Implicit motor sequence learning in patients with Parkinson's disease

Implicit motor sequence learning is assumed to rely on intact functioning of cortico-basal ganglia brain circuits. PD is primarily associated with pathological changes within such networks. Therefore, individuals with PD are expected to show altered sequence learning when compared to healthy individuals. Although the literature on implicit motor sequence learning in PD patients is not as clear-cut as one might assume, numerous studies indeed provide evidence for impaired performance on the SRTT and related tasks in PD patients

(reviewed by Ruitenberg et al., 2015) which is corroborated by a meta-analysis by Clark et al. (2014). Nevertheless, reports of largely preserved learning are no exception either (Smith et al., 2001; Kelly et al., 2004). A recent review on motor sequence learning by means of the SRTT suggests that task as well as patient characteristics such as medication or disease severity might account for some of the contrasting findings (Ruitenberg et al., 2015). Regarding dopaminergic medication, patients ON as well as OFF medication have been reported to show learning impairment (Pascual-Leone et al., 1993; Muslimovic et al., 2007; Seidler et al., 2007; Wilkinson et al., 2009; Stephan et al., 2011). Further, there is growing evidence for the assumption that motor sequence learning might decrease when PD progresses and when symptoms become more severe (Muslimovic et al., 2007; Wilkinson et al., 2009; Stephan et al., 2011). Up to date, most of the implicit motor sequence learning research in PD has focused on initial acquisition of motor sequences. Additional investigations of processes such as susceptibility to interference or offline improvement have attracted less attention in the literature so far.

Neuroimaging studies investigating neural substrates underlying potential learning deficits in PD patients indicated that the disease adversely affects cortico-basal ganglia and/or medial temporal lobe activity involved in implicit as well as explicit motor sequence learning in healthy aging (e.g., Werheid et al., 2003; Schendan et al., 2013 reviewed by Carbon and Eidelberg, 2006; Doyon, 2008).

As outlined in section 1.3.2, there is ample evidence that alterations in beta oscillations in cortico-basal ganglia circuits contribute to PD pathophysiology. Concurrently, recent studies in healthy adults suggest a link between modulation of cortical beta oscillations and successful implicit motor sequence learning (see section 1.1.2). These findings raise the question whether altered modulation of beta oscillations might relate to deficient motor sequence learning in PD. Interestingly, recordings of subthalamic beta oscillations in PD patients who underwent DBS surgery revealed that the variability in performance during *explicit* learning of a motor sequence might be linked to the modulation of beta oscillations (Ruiz et al., 2014). More specifically, Ruiz et al. (2014) found that stronger suppression of beta activity at sequence boundaries (i.e., the first and last element of a sequence) may promote better task performance, whereas suppression of beta activity before within-sequence elements was associated with worse performance. Since recordings of STN activity are invasive, it is not possible to compare oscillatory activity in patients to ‘normal’ activity in

healthy adults. Studies investigating beta oscillations non-invasively in PD patients as compared to healthy controls in the context of simple motor responses using EEG or MEG reported altered modulation of motor cortical beta activity during index finger movements (Heinrichs-Graham et al., 2014) as well as after prolonged practice of reaching movements in PD (Moisello et al., 2015; Nelson et al., 2017). Whether altered modulation of beta oscillations is also associated with implicit motor sequence learning is yet to be determined.

1.3.5 Feedback learning in patients with Parkinson's disease

Data from animals and healthy humans have emphasized the relevance of cortico-basal ganglia circuits and dopamine in particular in learning from consequences of chosen actions (Haber and Knutson, 2010). Owing to the pathophysiology of PD involving dopamine depletion associated with the disruption of the functionality of the basal ganglia and connected areas, another line of feedback learning research has focused on PD patients. Interestingly, several studies indeed revealed diminished learning in feedback-based tasks in PD patients (Knowlton et al., 1996; Shohamy et al., 2004, 2006; Jahanshahi et al., 2010). For example, Shohamy and colleagues (2004) applied a probabilistic classification task which required participants to predict outcomes based on a complex pattern of stimuli. Whereas PD patients exhibited impaired learning on this task when trial-by-trial feedback was involved, they performed similarly to healthy controls in a non-feedback control version of the task (Shohamy et al., 2004). Such results were regarded as evidence for the assumption that intact basal ganglia functioning is essential for feedback learning in particular (Shohamy et al., 2004, 2006). In contrast to the above, reports of largely preserved feedback learning in PD exist as well (Schmitt-Eliassen et al., 2007; Wilkinson et al., 2008; Shiner et al., 2012). These inconsistencies may be partially attributed to varying task characteristics, such as stimulus complexity or feedback timing, because both have been suggested to influence learning strategies and the underlying neural substrates (Foerde and Shohamy, 2011; Foerde et al., 2013; Bellebaum et al., 2016). Additionally, patient characteristics including symptom severity and treatment status may influence feedback learning in PD. A few studies have explored the influence of medication status by systematically investigating the same PD patients ON as compared to OFF dopaminergic medication (Shohamy et al., 2006; Jahanshahi et al., 2010; Coulthard et al., 2012). Surprisingly, some of these studies report a significant impairment of feedback learning in PD patients ON as compared to OFF medication as well as relative to healthy controls (Shohamy et al., 2006; Jahanshahi et al., 2010). The 'over-dose'

hypothesis – stating that levodopa doses necessary to remedy dopamine-depleted circuits and to alleviate associated motor symptoms, might have detrimental effects on less or non-depleted circuits possibly relevant for feedback learning (Gotham et al., 1988; Swainson et al., 2000; Cools et al., 2001; Cools, 2006) – might constitute one explanation for the detrimental effects of dopaminergic medication on feedback learning in PD.

In addition to these findings, several studies have demonstrated differential effects of altered dopamine function on learning from positive and negative feedback (Frank et al., 2004; Frank, 2005; Kobza et al., 2012; Bellebaum et al., 2016). Interestingly, these studies showed that ON medication, PD patients showed a bias to learn more from positive than from negative outcomes (Frank et al., 2004) while OFF medication the reversed pattern with enhanced learning from negative feedback (i.e., a negative learning bias) emerged (Frank et al., 2004; Kobza et al., 2012; Bellebaum et al., 2016). Noteworthy, higher sensitivity for both positive and negative feedback has a negative impact on daily life of PD patients as it might be associated with behavioral disturbances such as pathological gambling or risk aversion (Frank and Kong, 2008; Vilas et al., 2012).

Feedback learning can also occur by observing actions and accompanying outcomes of another person (Bellebaum et al., 2010; Burke et al., 2010; Kobza et al., 2011, 2012). Studies investigating observational as compared to active feedback learning revealed that PD patients OFF medication exhibit similar performance patterns as healthy controls during observational feedback learning which is in contrast to the performance of PD patients on active task variants, in which a negative learning bias has been reported repeatedly (Kobza et al., 2012; Bellebaum et al., 2016). The data support the assumption that the underlying mechanisms involved in active and observational feedback learning might differ (Bellebaum et al., 2010; Bellebaum et al., 2012; Bellebaum and Colosio, 2014) with parts of the (dorsal) striatum being more strongly involved in active as compared to observational learning (Bellebaum et al., 2012; Kobza and Bellebaum, 2015). Since in early PD, dopamine depletion is suggested to especially affect dorsal parts of the striatum (Kish et al., 1988) it is reasonable that less affected PD patients as those investigated by Kobza et al. (2012) and Bellebaum and colleagues (2016) rather exhibit alterations in active than in observational feedback learning.

1.3.6 Effects of STN-DBS on feedback learning in patients with Parkinson's disease

In addition to medically treated PD patients, a few studies investigated effects of STN-DBS on feedback learning yielding mixed results (e.g., Hälbig et al., 2004; Frank et al., 2007; van Wouwe et al., 2011; Wilkinson et al., 2011; Coulthard et al., 2012). One of the first studies conducted in this field failed to find effects of STN-DBS status (ON versus OFF) on overall feedback learning performance in a probabilistic feedback learning task (Frank et al., 2007). In addition to overall learning performance, the study examined RTs in response to pairs of stimuli which were followed by positive (or negative) feedback rather equally often (high-conflict pairs) as compared to more easily discriminable stimuli (low-conflict pairs). Interestingly, patients ON but not OFF STN-DBS sped up their responses under high-conflict situations. This tendency was especially pronounced in error trials leading to the assumption that STN-DBS might induce impulsive behavior in such situations (Frank et al., 2007). On the other hand, there are studies providing first evidence for a facilitating effect of STN-DBS on feedback learning (Hälbig et al., 2004; van Wouwe et al., 2011; Wilkinson et al., 2011). For example, van Wouwe and colleagues (2011) found that overall feedback learning performance was enhanced ON as compared to OFF STN-DBS. Although mechanisms of STN-DBS are still controversial, the authors speculate that the observed effect might be due to a beneficial effect of STN-DBS on the dorsal striatum through influences of the STN on multiple sites of the cortico-basal ganglia network such as improved cortical processing via the hyperdirect pathway (van Wouwe et al., 2011). Another study on STN-DBS effects on feedback learning which included healthy controls failed to find facilitating effects of STN-DBS or significant differences between PD patients and controls on overall learning performance (Wilkinson et al., 2011). However, in a more detailed analysis, the rather complex stimulus structure of the task was taken into account and stimulus combinations which were weakly or strongly associated with particular outcomes were analyzed separately. Noteworthy, learning of weakly associated stimuli was found to be improved by STN-DBS – only PD patients OFF but not ON STN-DBS exhibited poorer learning performance on these trials compared to healthy controls. This result was interpreted as being indicative of a facilitating effect of STN-DBS on implicit learning aspects recruiting basal ganglia networks (Wilkinson et al., 2011).

The outlined studies applied paradigms which required to link own actions and accompanying outcomes. In order to better understand whether and to what extent STN-DBS

affects feedback-based learning processes in PD, it is important to keep in mind that feedback learning may also occur through observation of others. Although previous studies suggest that PD patients OFF medication in earlier stages of the disease exhibit similar performance patterns as healthy controls on such paradigms, effects of STN-DBS on observational feedback learning in more advanced stages of the disease remain to be investigated.

2 Aims of the thesis

Implicit motor sequence learning is essential for proper functioning in various everyday activities. In the light of an aging population, research has begun to focus on age-related alterations. But, knowledge of implicit motor sequence learning across the adult life span necessary to derive concepts for early detection and prevention of possible age-related declines is still sparse. At the neural level, motor sequence learning seems to rely on intact functioning of cortico-basal ganglia circuits and a specific role of motor cortical beta oscillations has been suggested. Since PD is associated with pathological changes in beta oscillations, it is reasonable to assume that alterations of beta oscillations in PD might be associated with impaired motor sequence learning.

Similar to motor sequence learning, feedback learning has been shown to recruit structures distributed across the brain, including areas of cortico-basal ganglia circuits. Studies reporting alterations in PD patients on active feedback learning tasks further support the role of these circuits and the dopaminergic system in this type of learning. Other than active learning, performance patterns during observational feedback learning have been suggested to be similar to those in healthy adults, at least in earlier stages of the disease. Furthermore, there is first evidence that STN-DBS, an established treatment option in advanced PD, may enhance active feedback learning processes. Effects of STN-DBS on observational feedback learning, on the other hand, have not been determined yet. Further disentangling STN-DBS effects on feedback learning is of high relevance for the precise prognosis of cognitive performance and thereby quality of life in patients receiving such treatment.

Considering the above, this thesis aimed to investigate implicit motor sequence and feedback learning in healthy and pathological aging using the example of PD. The investigation of motor sequence learning across the adult life span at the behavioral level (study 1) was extended by recording brain oscillations in healthy and pathological aging during motor sequence learning (study 2). Study 3 examined feedback learning in PD patients and healthy older adults with a main focus on STN-DBS treatment effects.

Study 1 aimed to examine alterations of implicit motor sequence learning across the adult life span. To this end, healthy participants ranging in age from 18 to 71 years were trained on a SRTT. The study particularly focused on age-related differences in acquisition and consolidation of a motor sequence. Consolidation as reflected by stabilization (i.e., reduced

susceptibility to interference) and offline improvement was assessed after a 1 hour offline period. It was further explored whether working memory is related to motor sequence learning.

Study 2 investigated implicit motor sequence learning in PD as compared to healthy aging. In addition to behavioral alterations, it aimed to characterize oscillatory dynamics underlying motor sequence learning. To this end, PD patients and healthy older adults were trained on a SRTT. To assess motor sequence acquisition and susceptibility to interference immediately after training, the SRTT comprised interfering randomly varying trials. Neuromagnetic brain activity was recorded using MEG. A special emphasis was put on beta oscillations because of their suggested relevance in motor sequence learning and PD pathophysiology. Theta, alpha, and gamma frequencies were also investigated to identify oscillatory signatures related to motor sequence learning in PD as compared to healthy aging.

Study 3 concentrated on feedback learning known to involve cortico-basal ganglia networks and the dopaminergic system. The main focus of the study was the investigation of STN-DBS effects on feedback learning in PD. As feedback learning may occur by linking either own or observed actions to accompanying outcomes, PD patients treated with STN-DBS and healthy control participants completed active and observational feedback learning tasks. To assess effects of STN-DBS, PD patients performed both tasks ON as well as OFF STN-DBS.

This thesis aimed at extending the knowledge about learning abilities in healthy as well as pathological aging. In the light of our aging society and its associated diseases, a better understanding of (normal or pathological) alterations including their neurophysiological correlates takes on increasing significance. Moreover, investigating influences of treatment methods such as DBS on cognitive functions including learning is relevant for the precise prognosis of therapy-related consequences – particularly for younger, still working patients – and thereby quality of life.

3 STUDY 1: Implicit Motor Sequence Learning and Working Memory Performance Changes across the Adult Life Span

Study 1 **(Appendix 1)** examined effects of healthy aging on implicit motor sequence learning. A second aim was to investigate whether working memory processes are related to this type of learning. In the light of an aging population, a better understanding of age-related changes in implicit motor sequence learning and mediating cognitive processes is of increasing social and economic significance. The investigation across the adult life span brings the advantage of being able to pinpoint when alterations in learning are starting to emerge. In the long run, such an approach may lay the foundation for successful approaches to improve learning performance in different phases of life as well as to derive concepts for an early detection and prevention of possible declines in advanced age.

3.1 Introduction

The acquisition of motor sequences occurs during practice and is usually followed by motor consolidation (Karni et al., 1998; Robertson et al., 2004b, 2005) which refers to stabilization (i.e., reduced susceptibility to interference) as well as offline improvement between sessions without further training (Robertson et al., 2004b, 2005). These processes are rather well-studied in young healthy adults. However, the literature on effects of healthy aging on motor sequence learning is controversial, with results ranging from intact (Howard and Howard, 1992; Brown et al., 2009; Nemeth and Janacsek, 2011) to diminished learning abilities (Frensch and Miner, 1994; Howard et al., 2004) in the elderly as compared to young adults. Furthermore, the concept of consolidation and its age-related changes are still rarely examined. Although a few studies report reduced or even lacking offline improvement in older as compared to young adults (Spencer et al., 2007; Brown et al., 2009; Nemeth and Janacsek, 2011), the investigating of stabilization of motor sequences as reflected by reduced susceptibility to interference has attracted less attention so far.

Relating to cognitive processes involved in motor sequence learning, it has been suggested that working memory might contribute to this type of learning, at least in young healthy adults (Unsworth and Engle, 2005; Bo and Seidler, 2009; Bo et al., 2011). Furthermore, another study provided first evidence for the hypothesis that age-related declines in working memory might contribute to alterations in motor sequence learning in older adults (Bo et al.,

2012). The present study was conducted to gain a better understanding of alterations in motor sequence learning and its association with working memory across the adult life span.

3.2 Methods

Twenty young (18-29 years), 20 middle-aged (30-50 years), and 20 older adults (51-71 years) participated in the study. To investigate effects of aging on implicit motor sequence learning and to examine whether working memory is linked to this type of learning, all participants completed verbal and visuospatial *n*-back tasks and were trained on a SRTT on the same day. Task order was counterbalanced across participants within each group. The SRTT was introduced as a measure of RT and participants were not informed about the 8-item sequence of button presses (ring-index-thumb-middle-ring-middle-thumb-index) embedded in the task. Sequence and random trials at the beginning of the task served as RT baseline. To enable acquisition of the motor sequence, it was presented 15 times during training with the last two sequences referred to as *end of acquisition (EoA).* Two sequences of eight randomly varying trials followed which served as control and interference. Subsequently, the investigation of early susceptibility to interference was enabled by another repeating presentation of the learned sequence. As the study further concentrated on consolidation (i.e., stabilization as indicated by reduced susceptibility to interference by a random pattern and offline improvement), the task comprised a second run which followed after a break of 1 hour. In run 2, two sequences of eight randomly varying trials were followed by two presentations of the sequence to assess unspecific and sequence-specific offline improvement as well as stabilization (Figure 5).

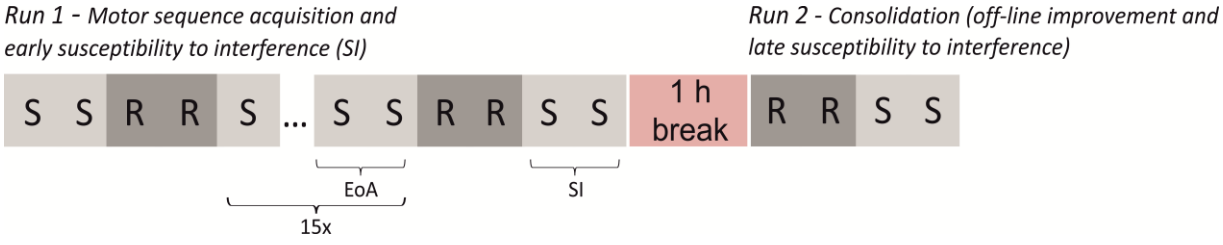

Figure 5: SRTT procedure. Two presentations of the 8-item sequence and randomly varying trials served as baseline. To enable acquisition, the sequence was presented 15 times with the last two sequences referred to as *EoA*. Subsequent randomly varying trials served as control and interference. Then, the sequence was presented twice to assess susceptibility to interference immediately after acquisition (SI). Run 2 after an offline period of 1 hour consisted of both random trials and two presentation of the sequence to assess unspecific as well as sequence-specific offline improvement and susceptibility to interference. 'S' indicates sequence trials, 'R' indicates random trials. Adapted and modified from Meissner et al. (2016b).

To assess explicit sequence knowledge, participants were asked (I) whether they had noticed anything unusual about the task and (II) to recall the sequence if they were aware of a repeating pattern after finishing the task.

Working memory tasks were derived from the classical *n*-back task (Cohen et al., 1994). For both the verbal and visuospatial subtype of the task, three different working memory loads (0-, 1-, and 2-back) were used. During the task, participants were presented with a sequence of stimuli and were asked to press a response key whenever the presented stimulus was identical to the one presented *n* trials back. For the verbal subtype, letters were used as stimuli, whereas for the visuospatial subtype, white circles at different locations on the screen were used.

Statistical analyses on RTs focused on differences between groups in acquisition, susceptibility to interference immediately after training on the SRTT as well as on group differences in consolidation (i.e., offline improvement and reduced susceptibility to interference). Working memory performance (i.e., percentage of hits) was compared between groups and possible links to motor sequence learning were investigated by means of correlational analyses.

3.3 Results and Discussion

As one of the main results, study 1 revealed that both young and older adults were able to acquire the motor sequence embedded in the task. Interestingly enough, the gain in RT in older adults was even larger than the one in young adults suggesting that sequence learning is well preserved in the healthy elderly. But, it is important to note that older adults also showed significantly slower baseline RTs than the younger adults. The present data fit with the results of several studies reporting intact or even better motor sequence acquisition in healthy older as compared to young adults (Howard and Howard, 1992; Brown et al., 2009; Janacsek and Nemeth, 2012). Although findings of age-related deficits in motor sequence learning have been reported as well, it is important to note, that such deficits were particularly observed in tasks involving complex sequences or dual-tasking, thus, when task demands were high (Frensch and Miner, 1994; Howard et al., 2004).

In contrast to the results in young and older adults, middle-aged adults did not exhibit acquisition of the motor sequence in the present study. Notably, middle-aged adults were significantly faster than the oldest age group at the beginning of the task. However, the

elderly were able to bridge the gap and both groups yielded comparable RTs after training. Similarly, a previous study by Janacsek and colleagues (2012) found comparable declines in motor sequence acquisition above the age of 44. However, unlike the present data, this decline was also observable in older adults (Janacsek et al., 2012). Interestingly enough, in the present study, nine older adults exhibited evidence of sequence awareness acquired over the course of the task. In contrast, only one young and one middle-aged adult perceived a sequential pattern. On the basis of this data, one might hypothesize that healthy older adults refer to (compensatory) explicit rather than implicit learning strategies presumably used by younger adults and middle-aged adults. Although speculative, older participants may have adopted the explicit learning strategy to compensate for deficient implicit learning. This assumption was supported by additional analyses revealing that older adults who showed evidence of sequence awareness tended to be faster in sequence than in randomly varying control trials, whereas RTs did not differ significantly in older adults without sequence awareness. Further indirect support comes from a study by Dennis and Cabeza (2011) which found greater activity in the medial temporal lobe – known to be involved in explicit learning (Cohen et al., 1985, 1999) — during the SRTT in older as compared to young adults. Taken together with the present findings in middle-aged adults, one might speculate that, implicit learning may become less effective in middle-aged adults, while the transition to a successful adoption of compensatory strategies might still pend.

As one might expect in the case of lacking sequence acquisition, middle-aged adults were not susceptible to interference immediately after training on the SRTT. In contrast to that, both young and older adults exhibited susceptibility to interference by the random pattern immediately after training on the SRTT which was found to be reduced in both groups after an offline period of 1 hour. In accordance with a hypothesis stated by Brown and colleagues (2009), the data provide first evidence for the assumption that the stabilization of skills, one form of motor consolidation, might be well preserved in older adults. With regard to the second component of consolidation, offline improvement, only young and middle-aged adults exhibited (further) gains in RT between the two runs. However, offline improvement was not specific for sequence trials but rather represented more general, unspecific RT facilitation. This contradicts previous assumptions of the presence of sequence-specific improvement between sessions on similar implicit versions of the SRTT (Robertson et al., 2004a; Brown et al., 2009). Discrepancies between results might be due to longer offline

periods of 12 to 24 hours in those studies as compared to the 1 hour break implemented in the present study suggesting that an offline period of 1 hour may have been too short to induce enhancement of sequence-specific skills. In older adults, there was no further RT improvement observable over the offline period which is in line with previous results and supportive of the hypothesis that offline improvement between learning sessions is affected by healthy aging (Brown et al., 2009; Nemeth and Janacsek, 2011). Although beyond the scope of the study, one might speculate that alterations in neuroplastic processes induced by motor training might account for the lack of further RT improvement in older adults in the present study (Sawaki et al., 2003; Rogasch et al., 2009; Fathi et al., 2010). Taken together, these data give rise to the hypothesis, that offline improvement and stabilization represent discrete aspects of consolidation which might be distinctly affected by aging.

Replicating previous findings on working memory performance in healthy aging (e.g., Mattay et al., 2006; Geerligs et al., 2014), older as compared to young participants exhibited a decline in verbal and visuospatial working memory when memory load was high as in the *2*-back tasks. Although working memory processes have been suggested to contribute to motor sequence learning (Bo et al., 2011, 2012) the present study failed to find evidence for a significant relation between working memory and implicit motor sequence learning. When interpreting the present data, it is important to note that former studies investigated the influence of working memory on motor sequence learning by implementing tasks that pose strong demands on storage capacity (Luck and Vogel, 1997; Fukuda et al., 2010). However, *n*-back tasks used in the present study especially involve manipulating (e.g., updating) of information (Braver et al., 1997; Rottschy et al., 2012). Discrepancies in study results might thus relate to different mental processes required for successful task performance. Despite the lack of significant associations between acquisition and consolidation of a motor sequence and working memory, RTs on the SRTT during baseline measurement were inversely related to working memory performance when memory load was high. A conceivable interpretation of this result might be that although working memory was not significantly linked to motor sequence learning, poorer working memory might still be partly responsible for generally slower RTs as particularly observed in older participants.

3.4 Conclusion

Study 1 revealed that implicit motor sequence learning changes across the adult life span. More specifically, both young and older but not middle-aged adults were able to acquire the

embedded motor sequence. Interestingly, the oldest age group exhibited the greatest gains in RT and possibly relied on explicit rather than implicit learning strategies. These findings might lead to the speculation that in middle-aged adults, implicit learning may become less effective while a strategy change is still lacking. Further, stabilization of skills after the offline period and the lack of offline improvement in older adults give rise to hypothesize, that different processes may underlie these two forms of consolidation which might be distinctly affected by aging. Replicating previous results, older participants showed diminished working memory performance when memory load was high. However, working memory as assessed by *n*-back tasks was not linearly linked to implicit motor sequence learning across the adult life span.

4 STUDY 2: The significance of brain oscillations in motor sequence learning: Insights from Parkinson's disease

Study 1 investigated implicit motor sequence learning in healthy aging and revealed that motor sequence acquisition is observable even in the elderly. To complement these findings, study 2 **(Appendix 2)** aimed at the investigation of implicit motor sequence learning and its underlying oscillatory dynamics in healthy older adults and PD patients as a prominent example of pathological aging. Particular emphasis was placed on a possible relation between alterations in beta oscillations and motor learning in PD.

4.1 Introduction

In young adults, there is evidence that a suppression of brain oscillations at beta frequencies might contribute to successful motor sequence learning on the SRTT (Pollok et al., 2014). At the same time, there is abundant evidence that oscillatory activity, especially in the beta frequency range, is altered in PD (Schnitzler and Gross, 2005; Hammond et al., 2007; Oswal et al., 2013; Nelson and Kreitzer, 2014). Furthermore, implicit motor sequence learning is diminished in PD patients when compared to healthy participants (for a review see Ruitenberg et al., 2015). To shed light on the possible relation between pathological alterations of beta power and motor learning abilities in PD patients, neuromagnetic activity was recorded in PD patients as well as in healthy older adults while performing the SRTT. According to previous findings, it was hypothesized that PD patients exhibit less beta power suppression when compared to healthy adults and, concomitant with this alteration, diminished motor sequence learning. Although the study focused particularly on beta oscillations, activity in the theta, alpha and gamma frequency bands was also examined since cognitive and motor impairment in PD has been proposed to relate to alterations across these frequencies as well (Oswal et al., 2013).

4.2 Methods

Twenty PD patients and 20 age- and sex-matched healthy adults were included in the study. In PD patients, motor impairment was assessed by means of the MDS-UPDRS III (Goetz et al., 2008). All participants performed a version of the SRTT similar to that in study 1 (Nissen and Bullemer, 1987; Figure 6). PD patients completed the task on their regular dopaminergic medication.

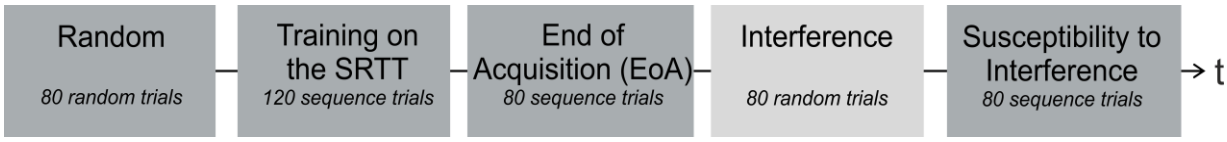

Figure 6: Study design. RTs during *Random* served as baseline measurement. To enable motor sequence acquisition, an 8-item sequence was presented 15 times (*Training on the task*). *EoA* comprised ten repetitions of the sequence. For the assessment of *Susceptibility to Interference*, ten sequences of eight randomly varying trials were presented (*Interference*) and followed by ten repetitions of the introduced sequence. Adapted and modified from Meissner et al. (*submitted*).

Prior to training on the SRTT, randomly varying trials served as baseline (*Random)*. These trials were followed by the repeated presentation of the embedded motor sequence *(Training on the SRTT)* which was the same 8-item sequence as introduced in study 1. To assess whether participants were able to learn the sequence, it was presented again at *EoA* immediately after training on the task. The further investigation of susceptibility to interference was realized by presenting interfering random trials *(Interference)* followed by another block of sequence trials *(Susceptibility to Interference)*. Explicit sequence knowledge was assessed as in study 1. Three PD patients and three healthy older adults were able to recall at least half of the sequence correctly.

Neuromagnetic brain activity was recorded throughout the task using a whole-head MEG system (Elekta Neuromag, Helsinki, Finland). Behavioral analyses on RTs were focused on possible group differences in motor sequence acquisition and susceptibility to interference. Correlational analyses were performed to investigate whether sequence acquisition was related to susceptibility to interference. Further, in patients, clinical characteristics (i.e., motor impairment, antiparkinsonian medication dose) were correlated with RTs and differences in RTs between blocks. For MEG data analyses, data were processed for time-frequency analysis. To investigate whether oscillatory activity differed already between groups during *Random*, i.e. prior to learning, theta, alpha, beta, and gamma power was compared between groups including all sensors by means of cluster-based permutation tests with Monte Carlo randomization to control for multiple comparisons. Cortical sources of oscillatory activity during *Random* were identified using *Dynamic Imaging of Coherent Sources* (DICS). The change in oscillatory activity in the introduced frequency bands over the course of the task (contrasts of interest: *EoA* vs. *Random*; *Susceptibility to Interference* vs. *Random*) was further compared between groups including all sensors as well as in a selection of sensors covering right and left sensorimotor cortices using the same statistical approach as

for *Random*. In a last step, brain-behavior correlations were calculated between time-frequency data and clinical characteristics as well as SRTT performance.

4.3 Results and Discussion

Statistical analyses comparing oscillatory activity between groups *prior* to learning revealed significant differences at alpha and beta frequencies. PD patients exhibited stronger beta modulation as compared to healthy adults which was most pronounced during button press when beta suppression prevailed. As additionally suggested by source reconstruction, beta modulation appeared to be more widespread in PD, proposing that a larger network might be recruited for successful task performance. Although these findings contradict results of a previous MEG study showing *reduced* beta modulation during such basic movements in PD patients as compared to healthy older adults (Heinrichs-Graham et al., 2014), it is important to note, that PD patients in that study were investigated OFF and not ON medication as in the present study. As beta modulation seems to be reduced when dopamine is deficient but promoted by antiparkinsonian medication (Doyle et al., 2005; Litvak et al., 2012; Oswal et al., 2012, 2013), the observed differences might stem from different levodopa levels. Importantly, stronger modulation of beta power was found to be related to slower RTs in the present study. Taken together with the observed differences between groups at beta frequencies as well as with the results by Heinrichs-Graham and colleagues (2014), this finding might provide indirect support for the assumption that lower and higher levels of beta activity – i.e., deviation from 'optimal' activity – might contribute to alterations in motor performance as observed in PD (Brittain et al., 2014). In addition to alterations at beta frequencies, PD patients exhibited a stronger alpha power modulation. Alpha oscillations have been suggested to contribute to automatic motor control processes and to subserve attentional demands (Klostermann et al., 2007; Pollok et al., 2009; Klimesch, 2012). Differences in alpha power modulation may thus reflect enhanced control mechanisms and attentional resources necessary for task execution in PD. Although there was no significant group difference during the execution of simple motor responses at theta or gamma frequencies, less theta power was found to be significantly associated with greater motor impairment suggesting that these oscillations might relate to motor characteristics in PD.

As assumed, PD patients exhibited diminished but basically preserved acquisition of the motor sequence when compared to healthy adults. This finding is in line with previous studies reporting a decline in implicit motor sequence learning in PD (for a review see

Ruitenberg et al., 2015). Furthermore, PD patients showed more pronounced susceptibility to interfering random trials than healthy adults. This finding extends existing literature on SRTT performance in PD, as susceptibility to interference has rarely been studied but needs to be taken into account to understand the various processes involved in motor sequence learning (Doyon, 2008; Marinelli et al., 2017). Surprisingly, better sequence acquisition was related to reduced susceptibility to interference only in healthy adults. These results suggest that while reduced susceptibility to interference relies on successful motor sequence acquisition in healthy aging, these two processes may be distinct in PD.

When relating clinical characteristics of patients to SRTT performance, no significant associations were found. This is in contrast to reports of increasing motor sequence learning deficits with increasing motor impairment (e.g., Muslimovic et al., 2007) but reveals that severity of motor symptoms may not significantly modulate SRTT motor performance per se.

Impaired motor sequence acquisition in PD as compared to healthy adults was paralleled by less motor cortical beta power suppression at *EoA* relative to *Random*. This finding supports the assumption that beta power suppression is relevant for motor sequence learning as it may represent a neurophysiological marker of early reorganization associated with motor learning (Pollok et al., 2014). It is further in line with the hypothesis that beta activity promotes the maintenance of the current motor and cognitive state at the expense of flexible control (Engel and Fries, 2010). Notably, group differences were most pronounced in sensorimotor areas *ipsilateral* to the moving hand. Although cluster-based permutation tests do not provide information about the exact spatial extent of the effect, this finding fits well to results of Meziane et al. (2015) revealing symmetrical, bilateral beta power suppression in motor areas during a reaching task in older adults but not in PD patients. Thus, loss of hemispheric lateralization may be one compensatory mechanism of a healthy but aging motor system (Vallesi et al., 2010) which may be deficient in PD. Increased beta power has been related to decreases in cortical excitability (Noh et al., 2012; McAllister et al., 2013). Thus, one might assume that beta power suppression reflects an increase in cortical excitability promoting changes in practice-related networks which contribute to the enhancement of motor skills. These processes may be impaired in PD.

Group level analyses suggested that less beta power suppression over the course of learning in patients as compared to healthy adults was paralleled by diminished acquisition. But, brain-behavior correlations revealed that in PD, stronger beta power suppression at *EoA* as

compared to random trials prior to learning was associated with *worse* motor sequence acquisition. In contrast to this, stronger beta power suppression in sequence trials after interference as compared to trials prior to learning was found to be linked to *reduced* susceptibility to interference, i.e. *better* performance in PD patients. Although the results seem contradictory at first, it is possible that, in contrast to our hypothesis, beta power suppression might promote reduced susceptibility to interference but not necessarily acquisition per se, at least in PD. Furthermore, the present findings fit well to the assumption that in PD, motor sequence acquisition and susceptibility to interference might represent distinct processes relying on distinct neurophysiological correlates. In the context of motor sequence acquisition, it has been shown before that beta suppression may not always be beneficial in PD. More specifically, a study on explicit sequence learning revealed that beta suppression in the STN was linked to better performance only when occuring at a specific phase of the sequence (Ruiz et al., 2014) which supports the hypothesis that the significance of beta suppression in PD may vary depending on its relation to task phase.

In contrast to previous results (Pollok et al., 2014), there was no significant linear correlation between beta power and SRTT performance in healthy adults. As Pollok and colleagues (2014) investigated young adults, one may speculate that discrepancies relate to age-specific changes in motor sequence learning and underlying neural correlates.

Beyond beta oscillations, significant differences between groups during motor sequence learning emerged in theta power. More specifically, healthy adults showed a significantly stronger increase in theta power in motor cortical areas from *Random* to sequence trials after *Interference* than PD patients most pronounced during button press. This finding suggests that peri-movement theta power may contribute to reduced susceptibility to interference after training on the SRTT. This process appears to be impaired in PD. Correlative evidence linking stronger increase in theta power over the course of the task to less susceptibility to interference in healthy adults further emphasizes the role of theta oscillations for this process. The present results are generally in line with a recent neurofeedback study proposing a link between increases in theta power after learning and better consolidation of an *explicitly* learned motor sequence (Rozengurt et al., 2016). Furthermore, theta oscillations have been suggested to be involved in learning when sensorimotor integration is needed (Bland, 1986; Bland and Oddie, 2001; Caplan et al., 2003; Cruikshank et al., 2012) as well as in the induction of synaptic plasticity which indicate a

mnemonic function of these oscillations (Pavlides et al., 1988; Larson and Lynch, 1989; Orr et al., 2001).

4.4 Conclusion

Study 2 revealed diminished but basically preserved motor sequence acquisition as well as higher susceptibility to interference in PD patients as compared to healthy adults. These differences were paralleled by less beta power suppression in PD patients supporting the hypothesis that the modulation of beta oscillations is of significance in this type of learning. Whereas susceptibility to interference directly after training was found to rely on successful acquisition in healthy controls, these processes appeared to be distinct in PD. Further, stronger beta power suppression may specifically promote reduced susceptibility to interference but might not be beneficial for sequence acquisition in PD. In addition to the relevance of beta oscillations, the data give rise to the assumption that theta power might contribute to reduced susceptibility to interference, at least in an aging but healthy motor system.

5 STUDY 3: Facilitating effects of deep brain stimulation on feedback learning in Parkinson's disease

Whereas study 1 and 2 concentrated on implicit motor sequence learning and the underlying neurophysiological correlates in healthy and pathological aging, study 3 **(Appendix 3)** examined feedback learning known to involve cortico-basal ganglia circuits and the dopaminergic system in particular. The main focus was to investigate *whether* and *how* feedback learning is affected by STN-DBS used for the treatment of PD motor symptoms. Healthy older adults served as control group. The assessment of STN-DBS effects on feedback learning is of particular interest as it may help to gain a better understanding of cognitive alterations associated with STN-DBS in PD. Such knowledge is of high relevance for the prognosis of therapy outcome, particularly for younger patients still pursuing a profession.

5.1 Introduction

Optimal adaptation of behavior in daily life requires, inter alia, learning from consequences of chosen actions. The learning processes which link events, actions and accompanying outcomes (e.g., positive/negative feedback) have been shown to draw on dopaminergic midbrain structures and their projection sites in striatal and cortical areas (Haber and Knutson, 2010). Considering this in the light of the loss of dopaminergic neurons in PD, it might not be surprising that research concentrating on PD patients indeed reported impaired feedback learning in those patients (Knowlton et al., 1996; Shohamy et al., 2004). Interestingly, learning deficits were often reported ON but not OFF dopaminergic medication (e.g., Shohamy et al., 2006; Jahanshahi et al., 2010). Furthermore, several studies have investigated effects of STN-DBS status (ON versus OFF) on feedback learning in PD patients (e.g., Frank et al., 2007; van Wouwe et al., 2011; Wilkinson et al., 2011). They report inconsistent results ranging from no significant effects on overall learning (Frank et al., 2007) to facilitating effects possibly due to a beneficial effect of STN-DBS on the dorsal striatum (van Wouwe et al., 2011). Notably, these studies employed paradigms in which participants were required to link their own actions to respective outcomes. But, feedback learning can also occur by observing actions of another person and linking these actions to accompanying outcomes (Bellebaum et al., 2010). As indicated by neuroimaging studies (Burke et al., 2010; Bellebaum et al., 2012), observational feedback learning as compared to active task variants might involve parts of (dorsal) striatal structures to a lesser extent. Further support for this

assumption is provided by investigations of PD patients in earlier stages of the disease (Kobza et al., 2012) in which dopamine depletion might primarily affect the dorsal striatum (Kish et al., 1988). Here, similar performance patterns in PD patients and healthy adults were reported for observational but not for active feedback learning (Kobza et al., 2012).

In the light of the inconsistencies regarding STN-DBS and its effects on active feedback learning and the lack of comparison to observational task variants, the present study investigated PD patients ON and OFF STN-DBS during active and observational feedback learning and compared their performance to those of healthy older adults. Based on previous results, it was hypothesized that STN-DBS might improve feedback learning in PD patients, especially during the active task variant.

5.2 Methods

Nineteen PD patients treated with bilateral STN-DBS and 18 age- and sex-matched healthy controls participated in the study. Due to severe motor symptoms, one patient was not able to complete the study and had to be excluded leaving a total of 18 PD patients for final analyses. All participants performed active as well as observational task variants twice. PD patients performed both tasks ON and OFF STN-DBS while remaining on their regular dopaminergic medication (Figure 7). The order of tasks (active vs. observational) and STN-DBS status (ON vs. OFF) in patients was counterbalanced across participants.

Each feedback learning task comprised three learning phases. Each of these learning phases was followed by a test phase. Both learning and test phases contained 60 trials each. During active learning phases, one of six abstract Asian symbols was presented and participants had to respond to the presented symbol with a right or left button press. Each response was followed by either positive or negative feedback. For two symbols, feedback was deterministic with valid feedback in 100% of the trials. For the remaining symbols, feedback was probabilistic (80% (two symbols) or 60% (two symbols) of the responses were followed by valid feedback). The observational task variant involved the same stimuli and feedback conditions as the active task. It differed only with regard to the responses given: During observational learning, participants did not select the responses themselves but observed responses and accompanying outcomes of another participant on a computer screen. In order to receive the corresponding negative or positive feedback, participants were required to confirm the observed response by pressing the respective right or left button.

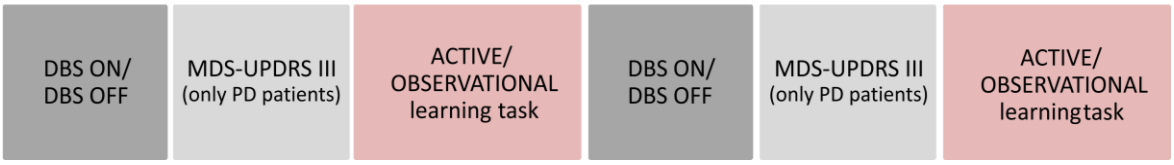

Figure 7: Experimental procedure. Motor symptoms (MDS-UPDRS III) as well as active and observational feedback learning were assessed ON and OFF STN-DBS in PD patients. Healthy controls performed active and observational feedback learning tasks twice as well. Order of task (and DBS status) was counterbalanced across participants in each group. Adapted and modified from Meissner et al. (2016a).

In both task variants, participants had to acquire stimulus-response-outcome associations by trial and error. Active and observational test phases served to assess stimulus-response-outcome associations acquired during learning phases. These test phases involved the same symbols as during learning but no feedback to selected responses. In addition to feedback learning, motor impairment in PD patients ON and OFF STN-DBS was assessed by means of the MDS-UPDRS III.

Statistical analyses were performed separately for active learning, active and observational test phases and focused on group differences and effects of STN-DBS on task performance (i.e., percentage of correct responses). Separate analyses of active learning phases were included to examine whether the ability to learn and to apply what has been learned is differently affected by STN-DBS. Further, it was investigated whether symptom severity (MDS-UPDRS III scores) somehow influences effects of STN-DBS on feedback learning. Additional control analyses where conducted to examine whether effects of STN-DBS on motor impairment and basic motor performance (RTs and missed responses recorded during feedback learning tasks) might contribute to performance on feedback learning tasks in patients with PD.

5.3 Results and Discussion

In line with the hypothesis, STN-DBS was found to significantly improve active feedback learning in PD patients. The data not only replicate results reported by a previous study (van Wouwe et al., 2011) but also extend those by additionally showing that PD patients OFF but not ON STN-DBS exhibited poorer active feedback learning than healthy adults. Thus, the present data support the hypothesis that, at least for the purpose of feedback-based learning, STN-DBS helps to reach a rather ‘healthy’ level of (dorsal) striatal functioning. Although another study by Wilkinson and colleagues (2011) did not find a beneficial effect of

STN-DBS on overall feedback learning in PD patients, it is important to note that the stimulus structure used in their study was more complex and is thus not directly comparable to the present data.

Surprisingly, in active test phases without feedback, there was no beneficial effect of STN-DBS. This result gives rise to the assumption that STN-DBS differently modulates the ability to learn and to apply what has been learned. Previous reports of partially distinct roles of striatal structures and dopamine for feedback learning per se and the application of what has been learned are in line with this assumption and might provide one possible explanation of the present pattern of results (Shiner et al., 2012; Smittenaar et al., 2012). Additional analyses taking symptom severity of PD patients into account further helped to disentangle these distinct effects of STN-DBS. These analyses revealed that PD patients with more severe motor symptoms benefited from STN-DBS and showed improved task performance ON as compared to OFF STN-DBS, whereas there was no facilitating effect of STN-DBS on active test performance in patients with less severe symptoms. Furthermore, differences in active test performance between STN-DBS ON and OFF states tended to be correlated with symptom severity: with increasing symptom severity task performance improved ON relative to OFF STN-DBS and vice versa. Although these findings can be taken as evidence that symptom severity might modulate the effect of STN-DBS on the application of learned associations, a systematic investigation of larger cohorts of PD patients at different disease stages is necessary to disentangle modulatory influences and underlying mechanisms of STN-DBS effects.

For the observational task variant, STN-DBS tended to modulate performance assessed during test phases. Similar to active learning trials, PD patients ON STN-DBS reached a performance level similar to healthy adults, whereas OFF STN-DBS they performed significantly worse than healthy adults. The present data give rise to the hypothesis that STN-DBS might not only facilitate active but also observational learning from feedback. At a more general level, it has been suggested that STN-DBS is beneficial for cognitive functions relying on ventral striatal structures and connected areas (Funkiewiez et al., 2006). As such structures are suggested to contribute to observational learning from feedback (Burke et al., 2010; Bellebaum et al., 2012), the present findings support this assumption. Interestingly, a previous study investigated PD patients during observational feedback learning and reported no significant differences in performance patterns between PD patients and healthy

participants (Kobza et al., 2012). Noteworthy, the study of Kobza et al. (2012) included PD patients in rather early stages of the disease, whereas in the present study, PD patients in more advanced stages participated. It has been suggested that the level of dopamine depletion in ventral striatal structures is rather small in early PD but becomes more pronounced in advanced PD (Kish et al., 1988). Thus, different levels of dopamine depletion might be one explanation for the difference in results.

STN-DBS has been shown to be effective in improving PD motor symptoms (Deuschl et al., 2006). In the present study, it is not possible to completely rule out that such an improvement contributed to STN-DBS effects on feedback learning. However, additional control analyses on RTs and number of missed responses did not reveal significant modulations of these variables by STN-DBS. Further, motor improvement due to STN-DBS as determined by the change in MDS-UPDRS III scores (STN-DBS OFF - STN-DBS ON) was not significantly related to differences between STN-DBS ON and OFF states in active or observational feedback learning. Considering this, one might conclude that beneficial effects of STN-DBS on feedback learning as observed in the present study are independent of motor improvement due to STN-DBS, at least to some extent.

5.4 Conclusion

Study 3 revealed that STN-DBS which is known to be an effective treatment of PD motor symptoms also possess beneficial effects on cognitive functions such as learning from feedback. More specifically, the finding that PD patients OFF but not ON STN-DBS showed worse active feedback learning than healthy adults supports the hypothesis that STN-DBS exerts a facilitating effect on learning which requires to link own actions to accompanying outcomes. Interestingly, when it comes to the application of what has been learned, only more severely impaired patients might benefit from STN-DBS. In addition to active feedback learning, the study provided first evidence that STN-DBS might be beneficial for observational feedback learning, thus when outcomes are required to be linked to actions of another person.

6 General Discussion

The current thesis aimed at contributing to the understanding of implicit motor sequence learning and feedback learning in healthy and pathological aging using the prominent example of PD. In addition to the investigation of motor sequence learning across the adult life span with a focus on healthy aging (study 1), the thesis concentrated on oscillatory dynamics underlying this type of learning in PD as compared to healthy aging (study 2). In a second line of research, feedback learning was investigated in PD patients and healthy older adults with a main focus on effects of DBS treatment on this type of learning (study 3).

The investigation of implicit motor sequence learning in study 1 and 2 revealed that healthy older adults are still able to acquire motor sequences without being instructed to do so, whereas this ability seems to be diminished but basically prevailed in PD patients. The fact that study 1 included not only participants of 'extreme' groups (i.e., older and young adults) but also middle-aged adults bridging the gap, allowed the investigation of learning across the adult life span. Surprisingly, in contrast to older and young participants, middle-aged adults did not exhibit acquisition of a motor sequence. As almost half of the older participants showed evidence of sequence awareness (as compared to one young/one middle-aged adult), one of the conclusions drawn from study 1 was that the observed difference in the acquisition of the motor sequence, especially between middle-aged and older adults, might be attributable to compensatory explicit strategies applied by older adults. Although this explanation might contradict reports of impeded motor sequence learning in older adults by providing *explicit* information and declines in explicit learning with advanced age (Verneau et al., 2014; see also King et al., 2013), it is important to keep in mind that in this thesis, participants were neither informed about a repeating pattern of button presses in the task nor explicitly instructed to acquire a given sequence. Explicit strategies were thus not prompted by the instruction or task itself. Therefore, one might speculate that healthy participants at higher age might incidentally apply explicit learning strategies to compensate for possibly deficient implicit learning. In contrast, in middle-aged participants, implicit learning may already be impaired but the adoption of explicit strategies is less efficient resulting in impaired sequence learning. Noteworthy, sequence awareness did not differ between healthy adults and PD patients in study 2 and was also observed to a lesser extent as in study 1. It has been suggested that the length of the response-to-stimulus interval might influence the feasibility of explicit strategies (Frensch and Miner, 1994). Therefore, the

difference between study 1 and 2 regarding the length of this interval might be one possible explanation for the difference in results.

In addition to motor sequence acquisition, the thesis concentrated on stabilization of a newly acquired sequence reflected by reduced susceptibility to interference both immediately after training (study 1 and 2) and after an offline period of 1 hour (study 1) as well as on offline improvement (study 1). Surprisingly, PD patients but not healthy older adults were found to be susceptible to interference right after training on the SRTT in study 2, whereas study 1 revealed susceptibility to interference in healthy older and young adults. Both studies applied similar versions of the SRTT. However, they differed in the number of sequence repetitions, owing to the investigation of neural oscillations in study 2. Our findings may thus suggest that enhanced training of the sequence (as in study 2) leads to a more stabilized pattern of movement in healthy adults which may be affected by PD. This observation highlights the ability of the aging but healthy brain for neuroplastic reorganization. Whether the ability for such reorganization is generally impaired in PD or whether these patients just need more extensive training on the task cannot be answered by the present data. In line with the interpretation of neuroplasticity in the aging brain, study 1 further revealed that although healthy older adults were susceptible to interference immediately after sequence acquisition, they showed stabilization of the newly learned sequence after the offline period similar to young adults. For offline improvement, a different pattern of results emerged. Only young and middle-aged but not older adults showed faster RTs after the 1 hour break. Interestingly, the improvement in young and middle-aged adults was not specific for sequence trials but rather represented unspecific RT facilitation. A previous study comparing young and older adults on the SRTT found a similar lack of offline improvement in older adults (Brown et al., 2009). But, in that study, young adults showed sequence-specific improvement over an offline period of 24 hours. A plausible explanation for these differences might lie in the length of the offline period. Furthermore, in the study of Brown and colleagues (2009), the offline period included both wake and sleep, whereas participants stayed awake during the break in the present study 1. Although offline improvement of implicit skills has been suggested to be time rather than sleep dependent (Robertson et al., 2004a; for a review see King et al., 2013), sleep-specific processes have been suggested to be involved in long-term synaptic plasticity (Fogel and Smith, 2011). Therefore, the enhancement of skills might not only be influenced by the length of the offline period but

may also depend on whether this period includes an interval of sleep or not. Taken together, the present results provide evidence for the speculation, that although motor skills might not be enhanced over the offline period in older adults, consolidation may be expressed in stabilization of skills rather than being completely affected by aging (Brown et al., 2009). Furthermore, the data lead to the hypothesis that offline improvement and stabilization represent discrete aspects of consolidation which are distinctly affected by aging processes.

In contrast to former studies by Bo and colleagues (2011, 2012) which suggest a link between working memory and SRTT performance in young and older adults, study 1 revealed no significant correlation between working memory and acquisition or consolidation independent of age. These previous studies implemented working memory tasks that pose strong demands on storage capacity (Luck and Vogel, 1997; Fukuda et al., 2010), while *n*-back tasks as used in study 1 mainly involve updating of information (Braver et al., 1997; Rottschy et al., 2012). Thus, discrepancies in study results might relate to different mental processes and their neurophysiological correlates required for successful task performance.

The significance of motor cortical beta oscillations in implicit motor sequence learning was revealed in study 2. More specifically, PD patients exhibited less beta power suppression than healthy adults paralleling diminished acquisition of the motor sequence at the behavioral level. This finding is in line with the assumption that beta power suppression is relevant for motor sequence learning and may represent a neurophysiological marker of early reorganization associated with this type of learning derived from results in young adults (Pollok et al., 2014). Thus, although study 2 did not involve testing of young adults, one may conclude that motor sequence learning might be linked to a suppression of beta oscillations in healthy adults, irrespective of age. Reduced beta power suppression, as observed in PD, might go along with deficits in motor sequence learning in pathological aging. This is especially interesting in the light of the fact that increased synchronization in the beta band displays one hallmark of PD (reviewed by Oswal et al., 2013). Despite the proposed role of beta oscillations in motor sequence learning, it is important to keep in mind that unlike in young adults (Pollok et al., 2014), beta oscillations were not linearly linked to motor sequence learning in healthy older adults which might relate to age-specific changes. A different picture emerged in PD, thus in a pathological form of aging: Although beta suppression promoted reduced susceptibility to interference, it was not beneficial for motor sequence acquisition indicating that these processes may relate to distinct

neurophysiological correlates in PD. This assumption was further indirectly supported by the behavioral finding that acquisition and susceptibility to interference were related in healthy adults but not in PD. Beyond beta oscillations, study 2 provided first evidence for the relevance of motor cortical theta activity for processes related to susceptibility to interference in healthy older participants. More specifically, healthy adults did not only show stronger increases in theta power over the course of the task than PD patients, but this increase was also correlated with less susceptibility to interference. Unfortunately, on the basis of these results, it is not possible to determine whether theta oscillations are related to reduced susceptibility to interference per se or rather reflect a compensatory mechanism in a healthy but aging motor system which might be impaired in pathological aging such as in PD. Further studies are needed to answer this question more profoundly. In sum, the findings of study 2 support the significance of beta oscillations for initial learning of a motor sequence and propose a role for theta oscillations in stabilization of a newly acquired motor sequence in healthy adults. These processes appear to be altered in PD.

Study 3 of the thesis examined feedback learning with a main focus on the influence of STN-DBS treatment on this type of learning in PD. At a general level, the effects of treatment in PD on cognitive functions such as feedback learning are of high relevance for optimizing treatment strategies and thereby quality of life of those patients (Schrag et al., 2000; Chaudhuri et al., 2006). In contrast to its remarkable effects on PD motor symptoms, previous studies have linked DBS to changes in cognitive function ranging from improvement or no significant change (e.g., Ardouin et al., 1999; Funkiewiez et al., 2006) to a deterioration of specific functions (Parsons et al., 2006; Witt et al., 2008). Therefore, investigations as in study 3 which disentangle the effects of DBS on specific cognitive functions are needed and must be further integrated to capture the complete picture of PD and the effects of its treatment options. This is particularly relevant for PD patients at younger age, since detrimental effects of DBS on cognitive functions may have considerable implications for their occupational capacity and quality of life. Study 3 revealed a facilitating effect of STN-DBS on active feedback learning which replicates former results of van Wouwe and colleagues (2011). Importantly, the data also showed that PD patients OFF but not ON STN-DBS performed worse than healthy older adults suggesting that STN-DBS may improve deficient feedback learning in PD patients and might help to reach a rather ‘normal’ level of functioning in this context. Interestingly, in contrast to active learning itself, the application

of what has been learned may only be facilitated by STN-DBS in more severely impaired patients. Although this finding points towards a modulating influence of disease severity on the effects of STN-DBS, further investigations of larger cohorts of PD patients treated with STN-DBS at different disease stages are necessary to systematically disentangle modulatory influences of such characteristics as well as their underlying mechanisms.

To the best of knowledge, study 3 was the first study to investigate observational feedback learning in PD patients treated with STN-DBS and provided evidence for the assumption that STN-DBS might promote observational feedback learning in these patients. More specifically, whereas PD patients OFF STN-DBS performed worse than healthy controls, ON STN-DBS these patients reached a performance level similar to that in controls. Thus, STN-DBS might ameliorate deficient feedback learning in PD not only in the context of active feedback learning but also when associations between actions and outcomes were learned by observing another person. Previous studies on observational feedback learning in PD patients reported similar performance patterns in PD patients as in healthy participants (Kobza et al., 2012; Bellebaum et al., 2016). When comparing these findings to the present result of deficient learning in PD patients OFF STN-DBS, it is important to note that those studies included PD patients in rather early stages of the disease. In contrast, in the present study 3, patients with more advanced PD participated. One might thus speculate that although observational feedback learning may be well preserved in early PD, it seems to be altered when the disease progresses. This assumption goes well with the finding that the level of dopamine depletion in ventral striatal structures presumably involved in observational feedback learning (e.g., Burke et al., 2010) is rather small in early PD but becomes more pronounced in advanced PD (Kish et al., 1988). Furthermore, in study 3, PD patients remained on their regular dopaminergic medication, whereas Kobza and colleagues (2012) and Bellebaum et al. (2016) tested PD patients OFF medication. Although it cannot be completely ruled out that this difference might have further influenced the varying results, a previous study revealed that cognitive functions relying on the ventral striatum do not vary depending on dopaminergic medication status in advanced PD (MacDonald et al., 2013) suggesting medication-related effects to be less likely.

With regard to the underlying mechanisms of the observed facilitating effect of STN-DBS on feedback learning, previous studies suggest that this facilitation might be due to a beneficial effect of STN-DBS on the dorsal striatum through influences of the STN on multiple sites of

the cortico-basal ganglia network (van Wouwe et al., 2011). Interestingly, in study 3, active feedback learning did not differ significantly between PD patients ON STN-DBS and healthy control subjects. Relating this result to the assumption of van Wouwe and colleagues (2011), one may speculate that for the purpose of active feedback learning, STN-DBS helps to reach a rather 'normal' level of dorsal striatum functioning. In contrast to active feedback learning, parts of the dorsal (as opposed to the ventral) striatum have been proposed to be less strongly involved in observational feedback learning (Burke et al., 2010; Bellebaum et al., 2012, 2016; Kobza et al., 2012). Thus, the facilitating effect of STN-DBS in tasks requiring to link observed actions and outcomes may be mediated by a different mechanism which may relate to the 'normalization' of ventral striatal functioning. Interestingly, a previous study reported that STN-DBS-induced blood flow changes in the ACC, an area connected to the ventral striatum, was related to the variability in STN-DBS effects on cognitive performance (Campbell et al., 2008). Although the data of the present study 3 does not allow drawing conclusions about underlying mechanisms, one might speculate that changes in blood flow might represent one conceivable mechanism underlying STN-DBS effects on active as well as observational feedback learning. Furthermore, DBS has been proposed to achieve some of its effects by disrupting pathological oscillatory activity and might thereby allow the restoration of 'functionality' of the cortico-basal ganglia circuits (reviewed by Benabid et al., 2009; Wichmann and DeLong, 2016; Ashkan et al., 2017). Noteworthy, previous studies have provided evidence for a prominent role of oscillatory activity in (active) feedback-based learning in healthy adults (Cohen et al., 2011). Whether a 'normalization' of pathological oscillatory activity by STN-DBS constitutes a mechanism for the facilitating effect on feedback learning remains to be determined. Regarding the interpretation of results at the neurophysiological level, it is important to keep in mind that it remains purely speculative, since the exact mechanisms of actions of DBS as well as some of the mechanisms underlying feedback learning – observational variants in particular – are still debated. Future studies recording brain activity in PD patients treated with DBS during cognitive tasks are needed to gain a better understanding of DBS effects on cognitive functions.

An issue which warrants a comment in this discussion relates to the fact that all tasks used in this thesis involved motor responses. PD is generally characterized as a movement disorder and its clinical diagnosis relies on motor symptoms. Therefore, when discussing the results of the thesis including learning deficits in PD patients as compared to healthy adults (study 2

and 3) and their amelioration by STN-DBS (study 3), the question arises whether motor impairment and its improvement by STN-DBS might have contributed to these findings. Although a potential influence of motor impairment on task performance cannot be completely ruled out, several control analyses indicated that RTs per se were not significantly associated with motor impairment or significantly modulated by STN-DBS. Furthermore, learning improvement due to STN-DBS in study 3 was not linked to improvement of motor symptoms. Thus, it appears to be reasonable to assume that the observed differences in learning might be independent of motor impairment.

In summary, this thesis contributes to the understanding of learning in healthy aging as well as in PD constituting a prominent example of pathological aging. Novel findings regarding implicit motor sequence learning across the adult life span with a possible compensatory change in learning strategy as well as the occurrence of consolidation manifesting as stabilization of skills in healthy older adults were revealed (study 1). It was further demonstrated that motor sequence learning is affected by pathological aging such as PD. Reduced modulation of beta and theta oscillations may underlie these deficits implying their significance in this type of learning (study 2). Moreover, a beneficial effect of STN-DBS on feedback learning was found. Noteworthy, it was revealed that STN-DBS may enhance not only learning from own but also from observed actions and outcomes in PD patients to a level similar to that in healthy adults (study 3). Such knowledge about physiological and pathological changes as well as treatment effects is an essential prerequisite for the preservation of functionality in healthy aging as well as for precise prognosis and optimization of treatment outcome in disease.

7 Outlook

This thesis contributed to the understanding of implicit motor sequence and feedback learning in healthy and pathological aging and provides several avenues for future research.

Study 1 and 2 provide evidence for alterations in implicit motor sequence learning across the adult life span as well as in PD. Interestingly, initial acquisition and consolidation of a motor sequence have been shown to be modulated by non-invasive brain stimulation such as tDCS (Savic and Meier, 2016). Moreover, such techniques may have the potential to enhance performance which might be diminished due to aging or disease (Gutchess, 2014). A recent study provided evidence that tDCS applied over M1 has the potential to promote offline improvement of an explicitly known motor sequence in healthy older adults (Rumpf et al., 2017). Thus, tDCS might constitute a useful tool to reduce deficits such as lacking offline improvement in healthy aging or diminished acquisition in PD as observed in this thesis.

Study 2 supports the significance of beta oscillations in motor sequence learning and suggests that oscillatory theta activity might be involved in processes related to susceptibility to interference. But, on the basis of study 2, it is not possible to determine whether theta oscillations are associated with such processes per se or rather reflect a mechanism of compensation in an aging motor system. Future studies concentrating on theta oscillations and their possible role in motor sequence learning across the adult life span are needed to shed further light on this question. Moreover, although study 2 provides neurophysiological correlates of motor sequence learning, it does not allow drawing causal conclusions regarding the contribution of beta and theta oscillations to motor sequence learning. Interestingly, tACS, another non-invasive brain stimulation technique, has been suggested to modulate brain oscillations in a frequency-dependent manner (Thut et al., 2012; Helfrich et al., 2014). Thus, by selectively and directly modulating brain oscillations at distinct frequencies, this method might allow the investigation of the causal role of cortical beta and theta activity in motor sequence learning. For beta oscillations, previous studies using such an approach in young healthy adults provided evidence that beta oscillations might play a role in stabilizing newly acquired motor sequences (Pollok et al., 2015; Krause et al., 2016). By extending such an approach to other frequency bands as well as to cohorts other than young healthy adults, a broader understanding of oscillatory activity and its significance in motor sequence learning might be gained.

As set out, motor symptoms in PD usually begin on one side of the body. With disease progression, symptoms also spread to the other side of the body (Hoehn and Yahr, 1967; Lee et al., 1995; Djaldetti et al., 2006). Systematically investigating motor sequence learning abilities in the (yet) unaffected side might provide insight into the temporal progression of learning deficits relative to pure motor symptoms. Applying such an approach, a recent study suggests that diminished consolidation of explicitly learned motor sequences might be evident even before the onset of classical motor symptoms (Dan et al., 2015). By further investigating the neural processes underlying learning with the (yet) unaffected versus affected side or learning in early and advanced disease stages by means of MEG may permit an assertion about changes in oscillatory dynamics over the course of the disease. This constitutes another important step towards the goal of capturing the complete picture of PD and its underlying dynamics.

Study 3 revealed a facilitating effect of STN-DBS on feedback learning in PD patients. A major step towards a better understanding of STN-DBS effects on cognitive functions such as feedback learning may be achieved by determining the neural mechanisms underlying such effects. Patients undergoing DBS afford a unique opportunity to record brain activity directly from the human basal ganglia. However, such recordings are only attainable during or immediately after the therapeutic implantation of DBS electrodes, when patients may still be weakened by surgery. Solving this problem, new technologies provide the opportunity to record neural signals from an implanted sensing stimulator via wireless data transfer (Medtronic Activa PC+S; Quinn et al., 2015; Neumann et al., 2016b; Trager et al., 2016). With such a device, it is possible to acquire data months after DBS surgery and to study underlying neurophysiological correlates of STN-DBS effects on more complex cognitive functions. Apart from basal ganglia activity, the development of new artefact rejection methods allows the recording of cortical brain activity via non-invasive techniques such as MEG both ON and OFF DBS (Abbasi et al., 2016). A huge advantage of non-invasive recordings is that they allow the assessment of cortical brain activity in healthy humans and thereby provide the opportunity to compare brain activity ON and OFF DBS in patients to ‘healthy’, physiological activity.

These future projects will further broaden the understanding of learning abilities and how these abilities might change due to aging or disease. Such an understanding is indispensable, not only for the development of strategies to preserve functionality as best as possible in healthy aging but also to improve therapeutic options in disease and thereby quality of life.

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9 Erklärung

Ich versichere an Eides Statt, dass die Dissertation von mir selbständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität Düsseldorf“ erstellt worden ist. Die Dissertation wurde in der vorliegenden oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den

Sarah Nadine Meißner

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11 Appendix

This work is based on:

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Implicit Motor Sequence Learning and Working Memory Performance Changes Across the Adult Life Span

Sarah Nadine Meissner[1], Ariane Keitel[1], Martin Südmeyer[1,2] and Bettina Pollok[1]*

[1] Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany, [2] Department of Neurology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany

Although implicit motor sequence learning is rather well understood in young adults, effects of aging on this kind of learning are controversial. There is first evidence that working memory (WM) might play a role in implicit motor sequence learning in young adults as well as in adults above the age of 65. However, the knowledge about the development of these processes across the adult life span is rather limited. As the average age of our population continues to rise, a better understanding of age-related changes in motor sequence learning and potentially mediating cognitive processes takes on increasing significance. Therefore, we investigated aging effects on implicit motor sequence learning and WM. Sixty adults (18–71 years) completed verbal and visuospatial *n*-back tasks and were trained on a serial reaction time task (SRTT). Randomly varying trials served as control condition. To further assess consolidation indicated by off-line improvement and reduced susceptibility to interference, reaction times (RTs) were determined 1 h after initial learning. Young and older but not middle-aged adults showed motor sequence learning. Nine out of 20 older adults (compared to one young/one middle-aged) exhibited some evidence of sequence awareness. After 1 h, young and middle-aged adults showed off-line improvement. However, RT facilitation was not specific to sequence trials. Importantly, susceptibility to interference was reduced in young and older adults indicating the occurrence of consolidation. Although WM performance declined in older participants when load was high, it was not significantly related to sequence learning. The data reveal a decline in motor sequence learning in middle-aged but not in older adults. The use of explicit learning strategies in older adults might account for the latter result.

Keywords: aging, SRTT, implicit motor sequence learning, consolidation, working memory, *n*-back

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Lutz Jäncke,
University of Zurich, Switzerland

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Rachael D. Seidler,
University of Michigan, USA
Lakshmi Rajagopal,
Northwestern University, USA

****Correspondence:***
Sarah Nadine Meissner
sarah.meissner@med.uni-duesseldorf.de

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INTRODUCTION

Implicit motor sequence learning refers to the ability to incidentally acquire knowledge of sequences of events and actions. The acquisition of such skills occurs "on-line" during practice but skills can stabilize—manifesting as reduced susceptibility to interference—or even improve "off-line" without further training (Robertson et al., 2004a, 2005). Reduced interference as well as off-line improvement constitute two components of the concept of consolidation (Robertson et al., 2004a). Previous studies suggest that consolidation requires

an interval of at least 1 h after acquisition (Robertson et al., 2005; Janacsek and Nemeth, 2012). However, Pollok et al. (2014) who utilized the serial reaction time task (SRTT), a common paradigm to assess implicit motor sequence learning (Nissen and Bullemer, 1987), observed off-line changes after a break of only 10 min. Findings of how motor sequence learning changes with advancing age are controversial. Whereas some studies found intact acquisition in older adults (Howard and Howard, 1992; Brown et al., 2009; Nemeth and Janacsek, 2011), others suggest age-related declines in implicit motor sequence learning (Frensch and Miner, 1994; Howard et al., 2004). Two studies investigating sequence learning abilities not only in young and older adults but across the adult life span reported differing results. Gaillard et al. (2009) found no significant differences in motor sequence learning between young, middle-aged, and older adults, whereas Janacsek et al. (2012) reported a decrement in sequence learning abilities around the age of 45. Interestingly, changes of cortico-spinal interaction reflecting the integrity of the pyramidal's system occur at this age as well (Kamp et al., 2013). Concerning consolidation of implicitly learned motor sequences in the elderly, studies are rare. There are a few studies reporting reduced or even lacking off-line improvement in healthy older adults when compared to younger ones (Spencer et al., 2007; Brown et al., 2009; Nemeth and Janacsek, 2011). To the best of our knowledge, age-related differences in susceptibility to interference, the second component of consolidation, have not been investigated directly so far.

Implicit motor sequence learning involves the striatum, the cerebellum as well as supplementary motor, primary motor, premotor and dorsolateral prefrontal cortices (DLPFC; Grafton et al., 1995; Destrebecqz et al., 2005; Doyon et al., 2009). Findings of whether these neural correlates change with advancing age are mixed. Daselaar et al. (2003), for example, found similar activations in young and older adults during implicit sequence learning, whereas others reported age-related changes in task-related activity with decreased activation in the DLPFC and striatum in older subjects (Aizenstein et al., 2006). Increased medial temporal lobe (MTL) activity might compensate for such changes in striatal structure and function with advancing age (Dennis and Cabeza, 2011).

Cognitive processes such as working memory (WM) seem to play an important role in motor sequence learning (Unsworth and Engle, 2005; Bo and Seidler, 2009). Regarding WM, which refers to the active storage and manipulation of information (Baddeley, 1992), evidence exists that performance declines with increasing age (Reuter-Lorenz et al., 2000; Park et al., 2002; for meta-analysis see Bopp and Verhaeghen, 2005). Studies using *n*-back paradigms in which participants were asked to indicate when the currently presented stimulus was the same as the one presented *n* trials back, reported poorer performance in the elderly than in younger subjects, especially when WM load was high (Mattay et al., 2006; Geerligs et al., 2014). Furthermore, it has been proposed that age-related declines in WM performance may contribute to age-related changes in motor sequence learning. This assumption has been supported by a study showing that older adults relied on WM processes to maximize learning performance (Bo et al., 2009). However, the authors used explicit motor learning tasks. Recently, Bo et al. (2011) provided the first evidence that in young adults, not only explicit but also implicit motor sequence learning is related to both verbal and visuospatial WM capacity, whereas in older adults verbal rather than visuospatial WM is suggested to be of importance to perform well in implicit motor sequence learning tasks (Bo et al., 2012). As is the case for motor sequence learning in general, the literature on potentially mediating cognitive processes is dominated by the comparison between young and older adults. Thus the understanding of changes across the adult life span is still sparse. At the neural level, a possible association between WM and motor sequence learning has at least partially been attributed to the suggested role of the DLPFC—a structure involved in WM processes (e.g., Jonides et al., 1993; D'Esposito et al., 1998; Curtis and D'Esposito, 2003)—in motor sequence learning (Bo et al., 2011). For example, disrupting normal functioning of the DLPFC by means of transcranial magnetic stimulation (TMS) impairs motor sequence learning in young adults (Pascual-Leone et al., 1996; Robertson et al., 2001).

As the average age of our population continues to rise, a better understanding of age-related changes in motor sequence learning and potentially mediating cognitive processes across the adult life span takes on increasing significance. In the present study, we aimed at investigating whether implicit motor sequence learning and consolidation as well as verbal and visuospatial WM changes across the adult life span and whether these processes are interrelated.

MATERIALS AND METHODS

Participants

Twenty young (10 males, mean age: 23.65 ± 0.61 years [standard error of the mean; SEM], range: 18–29 years), 20 middle-aged (11 males, mean age: 36.25 ± 1.38 years, range: 30–50 years) and 20 older adults (10 males, mean age: 60.20 ± 1.50 years, range: 51–71 years) participated in the study. Exclusion criteria were: dementia (Mattis Dementia Rating Scale (MDRS) score ≤130; Mattis, 1988), history of neurological or psychiatric disorders, and medication affecting the central nervous system (CNS). Groups did not differ significantly with respect to mean years of education, visuospatial (Block-Tapping-Test; Schellis, 1997) or verbal short-term memory (Digit span; Von Aster et al., 2006; all $p > 0.10$). Although older adults scored significantly worse on the MDRS (median score 142.00) than young (median score 143.00; $U = 1.93$; $p = 0.05$) and middle-aged adults (median score 143.50; $U = 2.06$; $p < 0.05$), all participants scored within the normal range (score >130). All participants were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971) and had normal or corrected-to-normal vision. The study was approved by the local ethics committee (study no. 4792) and was conducted according to the Declaration of Helsinki. All subjects participated voluntarily and provided written informed consent prior to the study.

Testing Procedure and Tasks

To investigate visuospatial and verbal WM, motor sequence learning and potential links between these processes, all participants completed computerized verbal and visuospatial *n*-back tasks as well as the SRTT on the same day. Stimulus presentation and response recording were controlled by Eprime® Software version 2 (Psychology Software Tools, Sharpsburg, PA, USA) installed on a standard windows computer. The order of task (SRTT vs. *n*-back) and task subtype (verbal vs. visuospatial *n*-back) was counterbalanced and randomly determined among participants within each group. Prior to performing the tasks, participants filled out handedness (Oldfield, 1971), biographical and health screening questionnaires and completed the MDRS (Mattis, 1988). Verbal and visuospatial short-term memory were assessed by means of the Block-Tapping-Test (Schellis, 1997) and the subtest "Digit Span" of the German version of the Wechsler Memory Scale Revised (Von Aster et al., 2006). Testing took approximately 2 h (1 h break included). For an overview of the experimental procedure, see **Figure 1A**.

Implicit Motor Sequence Learning: SRTT

The SRTT was introduced to the participants as a test of reaction time (RT). A custom-made response box with four response keys anatomically aligned to the right hand was used. Each response key corresponded to one of four horizontally aligned bars presented on a 19″ computer screen (1024 × 768 mm resolution; 75 Hz refresh rate). Participants were instructed to rest their thumb, index, middle and ring finger of their right hand on the response buttons and to press as quickly as possible the corresponding button as soon as one of the four bars on the computer screen changed from dark blue to light blue. RT was defined as the interval between the change in color and the button press onset. If participants responded correctly, the next bar was presented after a time interval of 1 s. In case of incorrect responses, the bar remained light blue until participants pressed the correct button.

Before starting the experimental phase, a practice block of 12 randomly presented bars was administered to familiarize participants with the response box. To assess motor sequence learning as well as consolidation, the task comprised two runs which were separated by a break of 1 h in which the subjects remained in the testing room without any specific task. The first two sequences of eight bar positions (*ring-index-thumb-middle-ring-middle-thumb-index*) were introduced and served as sequence baseline condition. The sequence used was a second-order conditional sequence that requires knowledge of the previous two positions to predict the next position, as the immediately preceding position alone provides insufficient information. Subjects were not informed of the existence of the sequence. Sixteen randomly presented bars serving as random baseline condition followed. To enable motor sequence learning, the same sequence as during sequence baseline was then repeated 15 times with the last two sequences referred to as end of acquisition (EoA_S). Subsequently, 16 interfering randomly presented bars (EoA_R) followed. To further examine whether the presentation of randomly presented bars interfered with the learned sequence immediately after learning (early interference), the sequence was again presented twice (SInterference). After a 1 h break, 16 randomly located bars followed by two repetitions of the previously learned sequence were presented in order to determine whether consolidation had occurred. Although implicit motor sequence learning is often investigated by sequences that consist of 10 or even 12 items we decided to use a sequence with only 8 bar positions. This decision

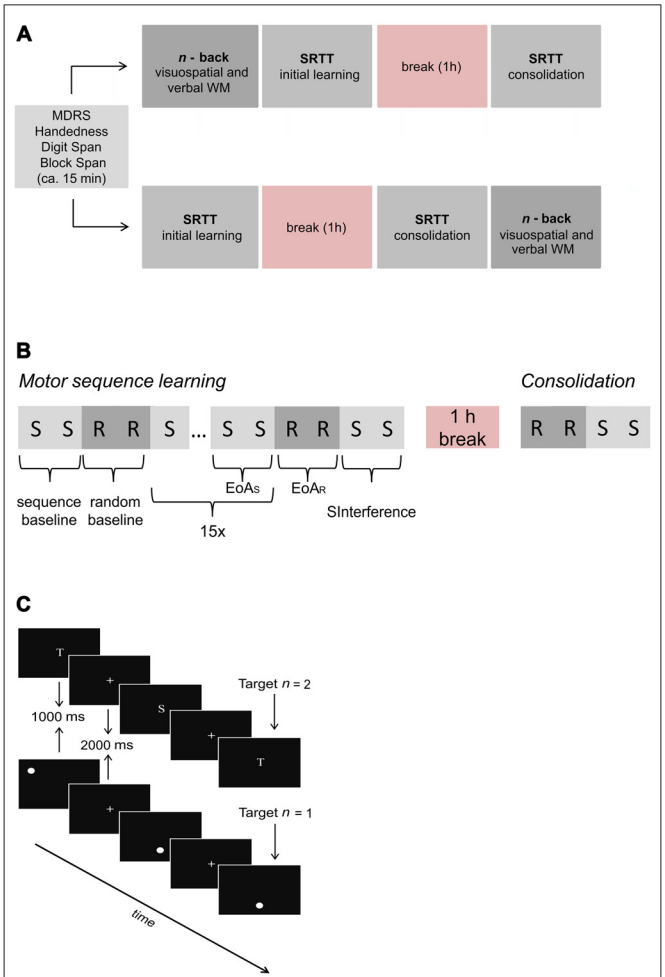

FIGURE 1 | Overview of the experimental procedure. (A) Prior to serial reaction time task (SRTT) and *n*-back tasks, screening measures were assessed. Task order (SRTT vs. *n*-back) and task subtype (visuospatial vs. verbal *n*-back) were counterbalanced across subjects. **(B)** SRTT procedure. First, the sequence was introduced and presented twice (sequence baseline). After 16 randomly presented bars (random baseline), the sequence was presented 15 times with the last two sequences referred to as end of acquisition (EoA_S). For the assessment of early interference, 16 randomly presented bars referred to as end of acquisition random (EoA_R) were followed by two presentations of the sequence (SInterference). Run 2 (consolidation) consisted of 16 randomly presented bars which were followed by the presentation of the sequence (2 times). Note that "S" indicates sequence trials whereas "R" indicates random trials. **(C)** Sequence of events in three exemplary verbal 2-back (upper part) and visuospatial 1-back trials (lower part), respectively. Participants were asked to respond via button press whenever a stimulus occurred which was identical to the one presented "*n*" trials back.

was based on previous studies providing evidence that implicit motor sequence learning can be investigated by using an 8-item sequence, especially when the number of sequence presentations is rather low (Pollok et al., 2014, 2015; Krause et al., 2016). **Figure 1B** depicts the procedure of the SRTT.

Immediately after finishing the SRTT, participants were asked whether they had noticed anything significant or unusual about the task. If they were aware of the repeating pattern of the task, they were asked to recall the sequence.

WM: Verbal and Visuospatial *n*-back Tasks

The WM tasks were derived from the classical *n*-back task (Cohen et al., 1994) and required subjects to temporarily store and update information. Two subtypes (verbal vs. visuospatial), each with three WM loads (0- vs. 1- vs. 2-back) were used. Subjects were presented with a sequence of stimuli and were required to press a key whenever a presented stimulus was identical to the one presented *n* trials back. The 0-back tasks did not involve WM and were used as attentional control tasks (Cohen et al., 1994). In each task, participants were asked to respond as accurately and quickly as possible.

In the verbal 1-, and 2-back tasks, stimuli consisted of six white capital letters (N, I, R, S, T, A; see **Figure 1C**) which appeared serially and pseudorandomly on a black background in the center of the computer screen. The letters were selected from the lexical database dlexDB © (dlex project, DWDS Project, University of Potsdam, Germany) and matched with respect to frequency of occurrence. Each letter was presented for 1 s and was followed by a white central fixation cross presented for 2 s. Participants were asked to press the right arrow button on a conventional computer keyboard every time the currently presented letter matched the letter presented one (1-back) or two trials (2-back) back. Responses occurring after 3 s were coded as "miss". In case of a non-match, subjects did not need to press any button. In the 0-back task, the letter "X" was presented in addition to the six other letters and participants were required to press the right arrow button every time an "X" appeared on the screen.

In the visuospatial 1-, and 2-back tasks, stimuli consisted of identical white circles with a diameter of 1.75 cm which appeared serially and pseudorandomly for 1 s in one of six possible locations on the black screen. They were followed by the presentation of a white central fixation cross for 2 s (see **Figure 1C**). The six locations corresponded to the center of the cells of a 2 × 3 grid with the size of 12.75 cm by 13.50 cm. During the experiment, grid lines were not presented. Participants were asked to press the right arrow button on the computer keyboard every time the circle appeared in the same location as the circle one (1-back) or two trials (2-back) back. In case of a non-match, subjects did not need to press any button. In the 0-back task, participants were required to press the right arrow button every time the circle appeared in the center of the screen, a location engaged in this condition only.

A brief practice sequence of 10 trials was given prior to each task which consisted of five matching letters or locations with 17, 18 and 19 stimuli presented in the 0-, 1-, and 2-back tasks, respectively. While subtype order (verbal vs. visuospatial) was counterbalanced across participants, order of WM load was fixed and increased from low to high (0-, 1-, 2-back).

Data Analyses

SRTT

Mean RTs for baseline, EoA, and consolidation trials for sequence and random trials separately as well as a mean RT for early interference sequence trials were calculated. RTs two standard deviations below or above the respective individual mean as well as the group mean were excluded from further analyses. Furthermore, the percentage of errors was calculated for each participant.

WM Tasks

Performance in each *n*-back task was quantified as percentage of hits (correct responses and correct non-responses) in individual data for each task subtype and load. One older adult was excluded from further analyses as she did not understand task instructions, leaving a final sample of $n = 19$ for the older group.

Statistical Analyses

Statistical analyses were performed using IBM SPSS 22 (IBM Corporation, Armonk, NY, USA). All tests for statistical significance were two-sided. For the SRTT, Kolmogorov-Smirnov tests did not show evidence that the data significantly deviate from Gaussian distribution. Therefore, mixed-design analysis of variance (ANOVA) on mean RT with *time* (baseline vs. EoA) and *condition* (sequence vs. random) as within-subjects factors and *group* (young vs. middle-aged vs. older adults) as between-subjects factor was conducted to assess motor sequence learning. In order to compare learning effects more directly and to control for possible baseline RT differences between groups, we investigated percentage RT improvements. Each participant's gain in RT during sequence trials (sequence baseline—EoA_S) was divided by the respective sequence baseline RT and multiplied by 100. The same score was calculated for gain in RT during random trials ((random baseline—EoA_R)/random baseline × 100). Participants with percentage RT improvements two standard deviations below or above the respective group mean were excluded from further analyses. The scores were subjected to a mixed-design ANOVA with *condition* (sequence vs. random) and *group* as factors. To assess early susceptibility to interference immediately after learning, mixed-design ANOVA on mean RT with the factors *time* (EoA_S vs. SInterference) and *group* was conducted. The investigation of consolidation was realized with two mixed-design ANOVAs on mean RT. For susceptibility to interference, we performed an ANOVA with the factors *group* and *time* (SInterference vs. sequence consolidation). To estimate off-line improvement, an ANOVA with *time* (EoA vs. consolidation), *condition* (random vs. sequence) and *group* was conducted. Potential differences in mean percentage of errors between the three age groups were investigated by a one-way ANOVA. To resolve interactions, *post hoc* tests were calculated by means of two-tailed *t*-tests and ANOVAs.

For WM data, Kolmogorov-Smirnov tests revealed deviations from normal distribution requiring nonparametric tests. We examined whether verbal and visuospatial 0-, 1-, and 2-back WM performance differed in any of the age groups using Wilcoxon signed-rank tests. As none of the tests revealed significant differences between the two subtypes in any of the groups (all $p > 0.25$), percentage of hits for verbal and visuospatial subtypes were pooled for 0-, 1-, and 2-back tasks, respectively. Kruskal-Wallis tests were applied to determine WM differences between age groups in the 0-, 1-, and 2-back tasks, respectively.

Spearman correlations were calculated to examine whether and to what extent motor sequence learning and consolidation is related to WM performance. To this end, we calculated a sequence learning (sequence baseline—EoA_S) as well as a random control score (random baseline—EoA_R), an early interference (EoA_S—SInterference) and consolidation scores (SInterference—sequence consolidation; EoA_S—sequence consolidation) for each individual. Each of these scores was correlated with the pooled percentage of hits for verbal and visuospatial subtypes in 1- and 2-back tasks, respectively. To further investigate whether WM is related to RTs in general, percentage of hits in 1- and 2-back tasks respectively was also correlated with baseline RTs. All correlations were calculated for different age groups separately as well as for the entire group. Bonferroni corrections for multiple testing were applied.

RESULTS

Due to RTs two standard deviations below or above the respective individual mean, max 6.02% of trials in young and 6.48% of trials in middle-aged and older adults respectively were excluded from further SRTT analyses. At the group level, two participants of each age group showed RTs that were more than two standard deviations below or above the respective group mean in baseline, EoA and interference trials and were thus excluded from motor sequence learning and susceptibility to interference analyses. For similar reasons, two young and two older as well as three middle-aged adults were excluded from off-line improvement analysis. Concerning percentage RT improvement, one young, three middle-aged and two older adults were excluded from analysis due to gains in RT that were more than two standard deviations below or above the respective group mean.

Motor Sequence Learning

Since we were interested in the effect of age on motor sequence learning, only main effects or interactions involving the factor *group* are reported here. Mixed-design ANOVA with *time* (baseline vs. EoA), *condition* (sequence vs. random) and *group* (young vs. middle-aged vs. older adults) as factors revealed a significant main effect of *group* [$F_{(2,5)} = 7.78$; $p = 0.001$; $\eta_p^2 = 0.23$] with *post hoc t*-tests indicating slower RTs in older than in young [$t_{(34)} = 3.46$; $p = 0.001$] and middle-aged adults [$t_{(34)} = 2.47$; $p = 0.02$] regardless of condition and time. Importantly, a significant *group* by *time* [$F_{(2,51)} = 4.33$; $p = 0.02$; $\eta_p^2 = 0.15$] and *group* by *condition* by *time* interaction emerged [$F_{(2,51)} = 10.19$; $p < 0.001$; $\eta_p^2 = 0.29$; see **Figures 2A,B**].

To resolve the three-way interaction, *post hoc* ANOVAs were conducted. Separate ANOVAs for the factor *group* revealed a significant interaction between *condition* and *time* for young and older [young: $F_{(1,17)} = 36.59$; $p < 0.001$; $\eta_p^2 = 0.68$; older: $F_{(1,17)} = 33.04$; $p < 0.001$; $\eta_p^2 = 0.66$] but not for middle-aged

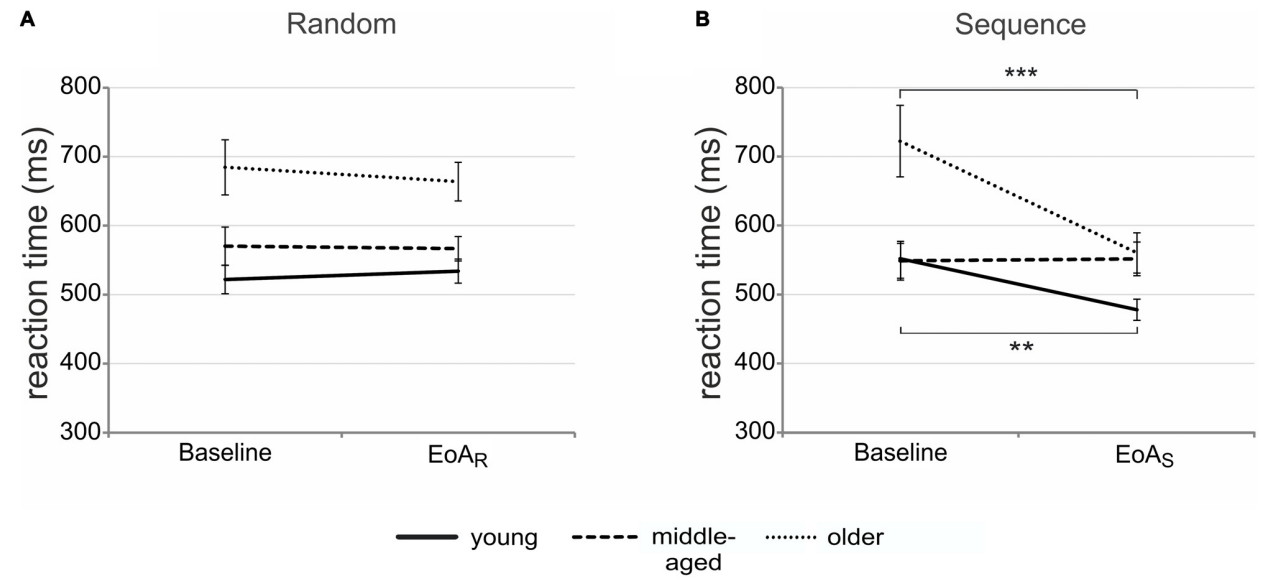

FIGURE 2 | Motor sequence learning. Mean reaction times (RTs) for randomly **(A)** and sequentially **(B)** presented bars at baseline and end of acquisition in the three age groups. Error bars indicate standard error of the mean (SEM); $^{**}p < 0.01$; $^{***}p < 0.001$; end of acquisition random (EoA_R); end of acquisition sequence (EoA_S).

adults [$F_{(1,17)}$ = 0.05; p = 0.83; η_p^2 = 0.003]. In the random condition, RTs between baseline and EoA_R trials did not differ significantly, neither in older nor in young adults (all $p > 0.36$). When the sequence was presented, however, both young and older adults were significantly faster at EoA_S as compared to baseline [young: $t_{(17)}$ = 3.58; p = 0.002; older: $t_{(17)}$ = 5.43; $p < 0.001$]. The data suggest that motor sequence learning occurred in young and older but not in middle-aged participants. *Post hoc t*-tests for independent samples revealed that at sequence baseline, older adults were significantly slower than young [$t_{(34)}$ = 2.93; p = 0.006] and middle-aged adults [$t_{(34)}$ = 2.98; p = 0.005]. However, at EoA_S, both middle-aged [$t_{(34)}$ = 2.55; p = 0.02] and older adults [$t_{(34)}$ = 2.22; p = 0.03] were significantly slower than young ones. To further exclude the possibility that middle-aged adults showed motor sequence learning in earlier phases of the task, we calculated the mean RT for each sequence during learning and selected the sequence with the fastest RT (sequence 12, see learning curves presented in **Figure 3**). However, the comparison with sequence baseline RT did not result in significant differences (p = 0.50), ruling out the possibility that middle-aged adults showed motor sequence learning earlier in the course of the SRTT.

Mixed-design ANOVA with *condition* (sequence vs. random) and *group* (young vs. middle-aged vs. older adults) as factors which was conducted to investigate percentage gains in SRTT performance revealed a significant main effect of *group* [$F_{(2,51)}$ = 5.94; p = 0.005; η_p^2 = 0.19] with *post hoc t*-tests indicating higher RT gains in older than in young [$t_{(35)}$ = 2.56; p = 0.04] and middle-aged adults [$t_{(33)}$ = 3.48; p = 0.006]. A significant *group* by *condition* interaction [$F_{(2,51)}$ = 12.65; $p < 0.001$; η_p^2 = 0.33] revealed significantly greater gains in RT in sequence than in random trials in young and older [young: sequence mean = 10.63 ± 12.45 [SD]; random mean = −3.46 ± 12.55; $t_{(18)}$ = 5.50; $p < 0.001$; older: sequence mean = 21.87 ± 11.14; random mean = 2.41 ± 12.03; $t_{(17)}$ = 5.57; $p < 0.001$] but not in middle-aged adults (sequence mean = −2.06 ± 14.83; random mean = 3.63 ± 13.91; $t_{(16)}$ = −1.18; p = 0.26). Interestingly, for sequence trials, *post hoc t*-tests for independent samples revealed not only lower percentage RT improvements in middle-aged adults when compared to young [$t_{(34)}$ = −2.79; p = 0.009] and older ones [$t_{(33)}$ = 5.42; $p < 0.001$] but also lower percentage RT improvements in young than in older adults [$t_{(35)}$ = 2.89; p = 0.007]. There was no significant difference between groups when random scores were compared (all $p > 0.12$).

Susceptibility to Interference and Off-Line Improvement

To examine potential differences between age groups in susceptibility to interference immediately after learning, we conducted mixed-design ANOVA with *time* (EoA_S vs. SInterference) and *group* (young vs. middle-aged vs. older adults) as factors. The main effect of *group* tended to be significant [$F_{(2,51)}$ = 3.16; p = 0.05; η_p^2 = 0.11] with faster RTs in young than in older adults [$t_{(34)}$ = 2.46; p = 0.04]. Young and middle-aged [$t_{(34)}$ = 1.46; p = 0.15) as well as middle-aged and older adults [$t_{(34)}$ = 1.15; p = 0.26] did not differ significantly. In addition, a significant *time* by *group* interaction emerged [$F_{(2,51)}$ = 3.42; p = 0.04; η_p^2 = 0.12; see **Figure 4A**]. *Post hoc t*-tests revealed that in young and older adults, RTs were significantly faster at EoA_S than at SInterference (young: $t_{(17)}$ = 2.88; p = 0.01; older: $t_{(17)}$ = 3.33; p = 0.004) indicating susceptibility to interference in both groups. In middle-aged participants, no significant difference emerged [$t_{(17)}$ = 0.16; $p > 0.87$].

The analysis of potential differences between age groups in susceptibility to interference 1 h after initial learning revealed a significant main effect of *group* [$F_{(2,51)}$ = 6.93; p = 0.002; η_p^2 = 0.21] with faster RTs in young and middle-aged than in older adults [young vs. older adults: $t_{(34)}$ = 3.26; p = 0.003; middle-aged vs. older adults: $t_{(34)}$ = 2.53; p = 0.02] while no significant difference between young and middle-aged adults emerged [$t_{(34)}$ = 0.87; p = 0.39]. The significant main effect of *time* [$F_{(1,51)}$ = 42.37; $p < 0.001$; η_p^2 = 0.45; see **Figure 4B**] suggests faster RTs in consolidation than in early interference trials. The *time* by *group* interaction failed to reach significance [$F_{(2,51)}$ = 0.55; p = 0.58; η_p^2 = 0.02].

The ANOVA conducted to investigate off-line improvement revealed a significant main effect of *group* [$F_{(2,50)}$ = 12.66; $p < 0.001$; η_p^2 = 0.33] with faster RTs in young and middle-aged

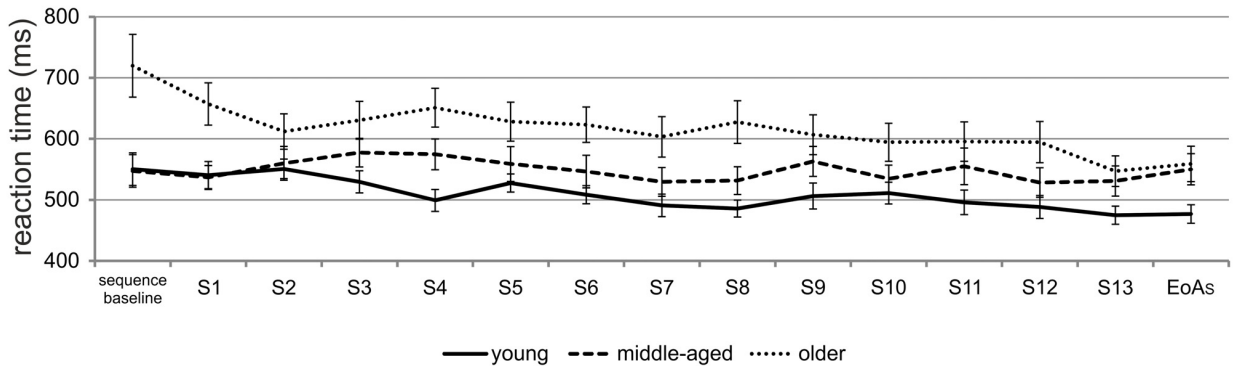

FIGURE 3 | Learning curves for all age groups. Mean RTs during training on the SRTT in young, middle-aged and older adults; end of acquisition sequence (EoA_S); S = sequence (e.g., S1 = sequence 1).

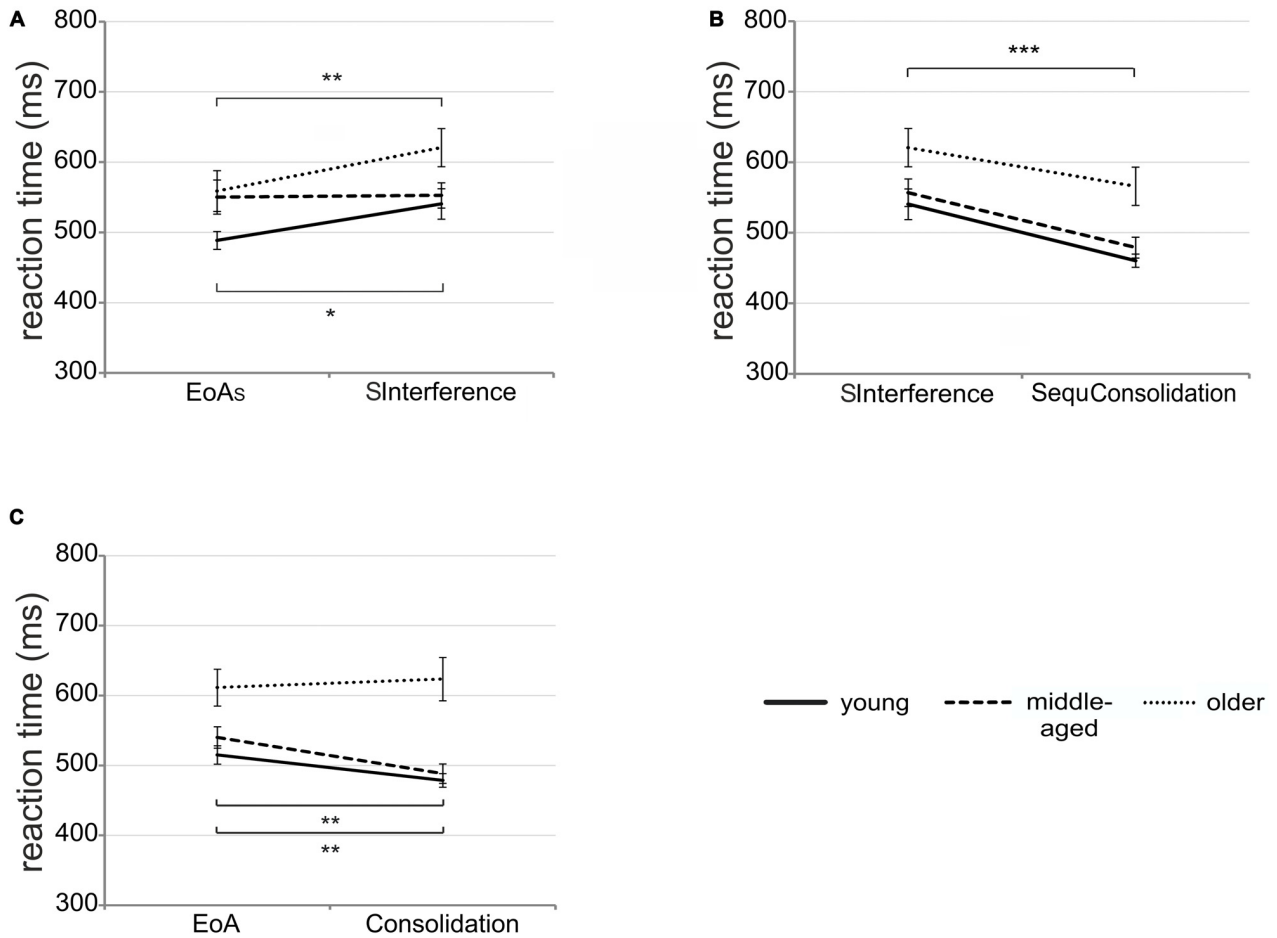

FIGURE 4 | Early interference and off-line changes. (A) Mean RTs in the three age groups on sequence trials (SInterference) after 16 interfering randomly presented bars as compared to sequence trials at end of acquisition (EoA_S). **(B)** Mean RTs in the three age groups on sequence trials after 1 h break (SequConsolidation) as compared to sequence interference trials (SInterference). **(C)** Significant *time* by *group* interaction showing mean RTs in the three age groups on consolidation trials after 1 h break as compared to trials at EoA. Note that consolidation and EoA trials refer to pooled sequence and random trials. Error bars represent SEM; $^*p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$.

than in older adults [young vs. older adults: $t_{(34)} = 4.16$; $p < 0.001$; middle-aged vs. older adults: $t_{(33)} = 3.39$; $p = 0.001$] but no significant difference between young and middle-aged adults [$t_{(33)} = 1.01$; $p = 0.32$]. Furthermore, we found a significant *condition* by *group* interaction [$F_{(2,50)} = 10.34$; $p < 0.001$; $\eta_p^2 = 0.29$]. *Post hoc t*-tests revealed significantly faster RTs in sequence than in random trials in young and older [young: $t_{(17)} = 6.25$; $p < 0.001$; older: $t_{(17)} = 6.53$; $p < 0.001$] but not in middle-aged adults [$t_{(16)} = 2.04$; $p = 0.06$]. Moreover, the *time* by *group* interaction reached significance [$F_{(2,50)} = 4.89$; $p = 0.01$; $\eta_p^2 = 0.16$; see **Figure 4C**]. *Post hoc t*-tests revealed significantly faster RTs in consolidation trials than at EoA for both young [$t_{(17)} = 3.50$; $p = 0.003$] and middle-aged adults [$t_{(16)} = 3.64$; $p = 0.002$]. In older participants, RTs at EoA and consolidation did not differ significantly [$t_{(17)} = -0.66$; $p = 0.52$] suggesting no off-line improvement in this group. As the *time* by *condition* by *group* interaction did not reach significance ($p = 0.53$) the findings indicate unspecific RT facilitation over the off-line period.

SRTT Error Rates

As expected for a SRTT, mean percentages of errors were low (overall mean: 2.71 ± 2.61 [SD]; young: 2.50 ± 2.20; middle-aged: 2.89 ± 2.95; older: 2.73 ± 2.72) and did not differ between age groups ($p = 0.89$).

Awareness of Sequence Pattern

One young and one middle-aged adult recognized a repeating pattern and both were able to repeat half of the sequence correctly. In the older adults group, one participant was able to correctly repeat the whole sequence and four participants were able to correctly repeat half of the sequence. Four older participants reported the impression of a pattern but could not repeat the sequence. Although we realize that verbal reports can fail to reveal explicit knowledge, especially when

knowledge is held with low confidence, we decided to further investigate whether potential sequence awareness of these nine older participants may have affected performance on the SRTT, at least on an exploratory basis. Therefore, the group of older adults was divided into two subgroups (awareness vs. no awareness). For motor sequence learning, a mixed-design ANOVA with *sequence awareness* (awareness vs. no awareness), *time* (baseline vs. EoA) and *condition* (sequence vs. random) was conducted and the *condition* by *sequence awareness* interaction tended to be significant [$F_{(1,16)} = 3.34$; $p = 0.08$; $\eta_p^2 = 0.17$]. While RTs in sequence and random trials in older adults with no sequence awareness did not differ significantly from each other (sequence mean = 658.01 ± 55.33 [SD]; random mean = 670.44 ± 48.56; $p = 0.52$), older adults with sequence awareness were significantly faster in sequence than in random trials (sequence mean = 609.92 ± 53.26; random mean = 679.95 ± 39.55; $t_{(6)} = 2.63$; $p = 0.04$). No other effects involving the factor *sequence awareness* were significant (all $p > 0.43$). Due to small subgroup sample sizes, we performed additional nonparametric Wilcoxon signed-rank tests comparing sequence and random trials in subgroups with sequence awareness and no sequence awareness. These analyses revealed similar results as parametric analyses.

Regarding early susceptibility to interference and consolidation, mixed-design ANOVAs with *time* (early interference: EoA_S vs. SInterference; consolidation: SInterference vs. sequence consolidation; EoA_S vs. sequence consolidation) and *sequence awareness* as factors did not yield significant effects involving the factor *sequence awareness* (all $p > 0.11$).

WM Performance

Kruskal-Wallis tests revealed no significant performance differences between groups for 0- and 1-back tasks (all $p > 0.65$). However, we found significant differences between groups for the 2-back task ($\chi^2 = 7.55$; $df = 2$; $p = 0.02$; **Figure 5**). *Post hoc* comparisons based upon *critical mean rank differences* (Schaich and Hamerle, 1984) revealed that older adults performed significantly worse than young adults ($p < 0.05$), while no significant difference between young and middle-aged or middle-aged and older adults emerged (all $p > 0.05$).

Relationship Between SRTT and WM Performance

To assess a possible relationship between motor sequence learning and WM performance, learning-related difference scores were correlated with percentages of hits in 1- and 2-back tasks (pooled for verbal and visuospatial subtypes) in each age group as well as in the entire group. No significant correlation emerged (all $p > 0.08$). However, baseline RTs on the SRTT and percentage of hits in 2-back tasks were negatively correlated when all participants were included in the analysis ($\rho = -0.47$; $p < 0.001$) indicating that faster baseline RTs were associated with better WM performance.

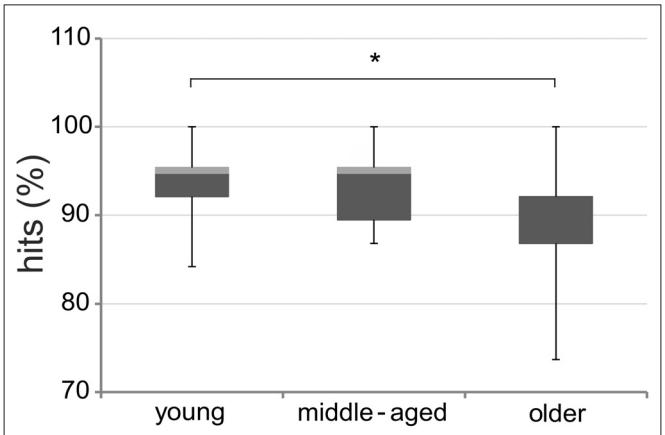

FIGURE 5 | Performance on 2-back tasks. Percentage of hits on the 2-back tasks in young, middle-aged, and older adults. Boxplots indicate medians (horizontal line between dark gray and light gray box) and the 75th (top of box) and 25th (bottom of box) percentile ranges; the whiskers indicate full ranges. Note that visuospatial and verbal data were pooled. *$p < 0.05$.

DISCUSSION

The present study aimed at investigating whether implicit motor sequence learning changes across the adult life span and whether age-related differences might vary with WM performance. Sixty volunteers aged between 18 and 71 years completed the SRTT as well as verbal and visuospatial *n*-back tasks. As a main result, we found motor sequence learning in young and older but not in middle-aged adults. The largest gain in RT was found in the elderly, but their baseline RT was significantly slower as compared to the younger groups. Interestingly, in older adults, training on the SRTT yielded RTs comparable to that of middle-aged adults. Young and older adults showed interference of the newly learned motor sequence. After 1 h, this susceptibility to interference was reduced indicating motor sequence consolidation even in older participants. Off-line improvement was observed only in young and middle-aged adults. Importantly, this improvement was not specific to sequence trials indicating unspecific RT facilitation. Although motor sequence learning was not significantly related to WM performance regardless of age, the data indicate reduced WM abilities in older as compared to younger adults when WM load was high. Moreover, baseline RTs were found to significantly vary with WM across age groups.

Implicit Motor Sequence Learning Across the Adult Life Span

The present data suggest that implicit motor sequence learning changes across the adult life span. Although young adults showed faster RTs than older ones during baseline already, both age groups significantly improved RTs after training on the SRTT. As RTs decreased for sequentially but not for randomly presented bars, this gain reflects the acquisition of sequence-specific knowledge rather than general, unspecific RT facilitation. Furthermore, older adults showed greater RT improvement than

young ones. Immediately after learning, both young and older adults were susceptible to interference. Even though findings of age-related changes in motor sequence learning are by far not consistent, the present data are in line with numerous studies reporting no decline (Howard and Howard, 1992; Janacsek and Nemeth, 2012) or even better motor sequence learning in the elderly when compared to younger adults (Brown et al., 2009). Furthermore, age-related deficits in motor sequence learning are often only observed when task demands are high like learning of complex sequences or dual-tasking (Frensch and Miner, 1994; Howard et al., 2004). Also, when compared to subjects of studies reporting age-related motor sequence learning deficits (mean age of around 70; Frensch and Miner, 1994; Howard et al., 2004), our group of older adults (mean age of 60.20 ± 1.50) was relatively young.

Surprisingly, middle-aged adults between the age of 30 and 50 failed to show motor sequence learning. The literature of age-related changes in motor sequence learning has focused on the comparison between young and older adults. Two studies investigated implicit motor sequence learning across the adult life span (Gaillard et al., 2009; Janacsek et al., 2012). Gaillard et al. (2009) examined groups with an age range similar to the one in the present study on the SRTT, but they failed to find significant differences when comparing middle-aged to young and older adults, respectively. In contrast, Janacsek et al. (2012) reported a decline in sequence learning in participants above the age of 44. Although this is in accordance with the present data, the authors also found learning deficits in older adults (Janacsek et al., 2012). Interestingly, when asking participants about potential sequence awareness in the present study, only one middle-aged and one young adult were aware of the repeating pattern of the task, whereas nine older participants perceived a sequential pattern or were even able to repeat at least parts of the sequence. Although the assessment of sequence awareness in the present study was not optimal, results nevertheless might led to the speculation that the elderly may adopt explicit rather than implicit learning strategies. This interpretation is supported by the observation that older adults with potential sequence awareness tended to be faster in sequence than in random trials. It is thus conceivable that the lack of motor sequence learning in middle-aged but not in older adults in the present study might be at least partly attributable to a stronger involvement of a compensatory explicit strategy in the elderly. In line with this, a neuroimaging study reported greater activity in MTL areas (Dennis and Cabeza, 2011)—which have been related to explicit learning (Cohen et al., 1985, 1999)—during the SRTT in adults above the age of 60 as compared to younger ones. Moreover, results of the middle-aged participants led to the speculation that at this age a transition may occur in which implicit learning may become less effective while compensatory strategies have not been successfully adopted, yet.

Consolidation and Unspecific RT Facilitation Across the Adult Life Span

To our knowledge, this is the first study investigating both susceptibility to interference and off-line improvement as two components of consolidation across the adult life span. As outlined above, young and older adults showed susceptibility to interference immediately after learning which was reduced over the off-line period indicating motor sequence consolidation in these age groups. These findings support the hypothesis of the occurrence of consolidation manifesting as stabilization of skill between sessions in older adults (Brown et al., 2009). In terms of sequence-specific off-line improvement, the second component of motor sequence consolidation, a different pattern of results emerged. Both young and middle-aged adults exhibited gains in RT over the off-line period possibly subserved by neuroplastic changes induced by the motor training (for review, see Dayan and Cohen, 2011). However, as indicated by the non-significant three-way interaction between *time, condition* and *group*, the observed RT facilitation was not specific to sequence trials. Although this finding is in line with a general RT facilitation but lacking sequence-specific improvement over off-line periods on the related alternating serial reaction task (ASRT) reported by Nemeth and Janacsek (2011), it contradicts previous results of sequence-specific off-line improvement on the SRTT (Robertson et al., 2004b; Brown et al., 2009). However, it is important to keep in mind that these authors implemented off-line periods of 12–24 h. Thus, the break of 1 h in the present study might have been too short to allow sequence-specific RT improvements.

In contrast to young and middle-aged adults, older adults failed to exhibit further gains in RT over the off-line period which replicates previous results (Brown et al., 2009; Nemeth and Janacsek, 2011) and suggests that off-line RT facilitation is affected by aging. Previous studies revealed a decrease in motor cortical plasticity in older adults when compared to younger ones (Sawaki et al., 2003; Rogasch et al., 2009; Fathi et al., 2010). Thus, one might speculate that such changes might at least partly account for lacking off-line gains in older adults in the present study. Interestingly, reduced susceptibility to interference even in the elderly reveals evidence for the assumption that different processes may underlie off-line improvement and reduced interference, although both are assumed to reflect consolidation. But, we realize that the present data do not allow any conclusions regarding brain processes underlying the observed behavioral effects.

WM Performance and Its Relation to Motor Sequence Learning

We found age-related differences in WM independent of task subtype as assessed by the *n*-back tasks. Older participants were impaired when WM load was high replicating the results of former studies (Mattay et al., 2006; Geerligs et al., 2014). Mattay et al. (2006) showed that this age-related decline was associated with reduced DLPFC activation in older as compared to young adults.

The present data did not provide evidence for a significant association between implicit motor sequence learning and WM performance in any of the examined groups. Results of a previous study suggest that WM might be stronger related to explicit than implicit learning (Unsworth and Engle, 2005). Yet, recent studies provided first evidence for an association between implicit motor sequence learning and WM capacity in young as well as in older

adults (Bo et al., 2011, 2012). It should be stressed, however, that they used a change detection task in which participants were required to detect changes between sample and test displays. This type of WM task rather taps into storage capacity of WM ability (Luck and Vogel, 1997; Fukuda et al., 2010) whereas *n*-back tasks involve a strong updating component (Braver et al., 1997; Rottschy et al., 2012). Thus, conflicting results might be at least partly due to differences in mental processes required to perform the respective tasks.

Although there was no significant relationship between learning scores and WM performance, baseline RT on the SRTT was inversely correlated with WM performance when task difficulty was high (i.e., high WM load). It is thus conceivable that although WM is not significantly associated with motor sequence learning, poorer WM performance might account for considerably slower baseline RTs, e.g., as observed in older participants.

Limitations

A major limitation of the present study refers to the assessment of sequence awareness. We realize that computerized tasks such as the process dissociation procedure (Destrebecqz and Cleeremans, 2001) or recognition tasks (Shanks and Johnstone, 1999) constitute more sensitive tests of explicit knowledge. Thus, the present investigation of sequence awareness has to be considered as rather exploratory. Nevertheless, we think that the observation that almost half of the older participants perceived (or were even able to repeat) a sequential pattern might be a hint that with advancing age, different strategies might come into play to accomplish motor sequence learning. In future studies, these processes should be assessed and differentiated more specifically. Moreover, the sample size—especially with regard to sequence awareness subgroup analysis—was small. Thus, the results have to be interpreted with caution, even though it is conceivable that some of the older adults in the present study learned the sequence by compensatory explicit strategies. Furthermore, although we did not assess motivation before, during or after the experiment, higher motivation in older subjects may account for the observed behavioral effects as well.

Finally, to keep verbal and visuospatial *n*-back tasks as comparable as possible, we used only capital letters during verbal *n*-back tasks. Although this is common practice, we are not able to completely rule out the possibility that participants used the shape of the stimuli rather than verbal encoding.

CONCLUSION

The present data indicate changes in implicit motor sequence learning across the adult life span. Middle-aged adults failed to show motor sequence learning while older adults exhibited gains that were even greater than that of young adults, possibly by adopting explicit rather than implicit learning. The observation of reduced susceptibility to interference 1 h after initial training in young and older adults suggests that consolidation also occurs in the elderly. However, older adults—in contrast to young and middle-aged adults—did not show further (unspecific) off-line gains. As previously shown, older participants showed poorer WM performance than young adults when WM load was high; but, WM processes assessed by *n*-back tasks seem to be unrelated to motor sequence learning independent of age.

AUTHOR CONTRIBUTIONS

SNM: conception and design of the experiment, data collection and analysis, interpretation of the data, drafting the article; AK: interpretation of the data, critical revision of the article; MS: interpretation of the data, critical revision of the article; BP: conception and design of the experiment, interpretation of the data, critical revision of the article.

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The significance of brain oscillations in motor sequence learning: Insights from Parkinson's disease

Sarah Nadine Meissner[1]*, Vanessa Krause[1], Martin Südmeyer[2], Christian Johannes Hartmann[3], Bettina Pollok[1]

[1]Institute of Clinical Neuroscience and Medical Psychology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany

[2]Department of Neurology, Ernst von Bergmann Klinikum, Potsdam, Germany

[3]Department of Neurology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany

* Address for correspondence: Sarah Nadine Meissner, Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine-University, Universitaetsstr. 1, 40225 Duesseldorf, Germany; Phone: +49-211-81-13014; Email: sarah.meissner@med.uni-duesseldorf.de

Running Title: Brain oscillations in motor learning

Abstract

Motor sequence learning plays a pivotal role in various everyday activities. Motor cortical oscillations, especially in the beta band, are suggested to be involved in this type of learning. In Parkinson's disease there is evidence that oscillatory activity within cortico-basal ganglia circuits is altered. Pathologically increased beta oscillations have received particular attention as they have been suggested to be associated with motor symptoms like akinesia. In the present magnetoencephalography study, we investigated Parkinson's disease patients and healthy controls during implicit motor sequence learning with the aim to shed light on the relation between changes of cortical brain oscillations and motor learning in Parkinson's disease with a particular focus on beta power. To this end, 20 Parkinson's disease patients and 20 age- and sex-matched healthy controls were trained on a serial reaction time task while neuromagnetic activity was recorded. Patients exhibited diminished acquisition of the motor sequence and were more susceptible to interference by random trials after training than healthy controls. These results were paralleled by changes at the neurophysiological level. Although patients exhibited a stronger modulation of alpha and beta power in random trials prior to learning, they showed less training-related beta power suppression in motor cortical areas than healthy controls supporting the hypothesis that beta power suppression is relevant for motor sequence learning. Interestingly, in healthy controls, better sequence acquisition was linked to reduced susceptibility to interference while no significant correlation was observed in patients suggesting that these processes might be distinct in Parkinson's disease. Further indirect support for this assumption was provided by the finding that stronger beta power suppression over the course of the task was linked to reduced sequence acquisition but to less susceptibility to interference in patients. Additionally, healthy controls showed a stronger training-related theta power increase in motor cortical areas than patients. This increase was found to be associated with less susceptibility to interference in healthy controls indicating the significance of theta oscillations for reduced susceptibility to interference in healthy older adults.

Keywords: implicit motor learning, oscillatory beta activity, SRTT, interference, magnetoencephalography (MEG)

Abbreviations

BDI = Beck Depression Inventory; DICS = dynamic imaging of coherent sources; HC = healthy controls; HPI = head position indicator; LED = mean daily levodopa equivalent dose; MDRS = Mattis Dementia Rating Scale; MDS-UPDRS III = motor part of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MEG = magnetoencephalography; RT = reaction time; SRTT = serial reaction time task; tACS = transcranial alternating current stimulation

Introduction

Motor sequence learning plays a crucial role in various everyday activities. The acquisition of skills during practice is characterized by performance improvement followed by motor consolidation (Karni *et al.*, 1998; Robertson *et al.*, 2005). Consolidation refers to stabilization of skills, i.e. reduced susceptibility to interfering stimuli, and 'off-line' improvement without further practice (Robertson *et al.*, 2004). An established measure of motor sequence learning is the *serial reaction time task* (SRTT) which involves a repeated sequence of button presses (Nissen and Bullemer, 1987). Learning is reflected in a reaction time (RT) decrease over the course of the task. Since participants are usually not aware of the sequence, this task allows the induction of implicit learning.

Neuroimaging studies suggest that brain networks including primary motor, premotor, dorsolateral prefrontal cortices, the basal ganglia and the cerebellum are involved in motor sequence learning (Grafton *et al.*, 1995; Destrebecqz *et al.*, 2005; Doyon *et al.*, 2009; Hardwick *et al.*, 2013). As Parkinson's disease is characterized by loss of dopaminergic neurons in the substantia nigra leading to dopamine depletion in the basal ganglia (Kish *et al.*, 1988; Buddhala *et al.*, 2015) it is not surprising that a considerable set of studies reports impaired motor sequence learning in Parkinson's disease patients compared to healthy controls (HC; Muslimovic *et al.*, 2007; Wilkinson *et al.*, 2009; Stephan *et al.*, 2011) which is corroborated by a recent meta-analysis (Clark *et al.*, 2014). But, largely preserved learning in Parkinson's disease is no exception either (Smith *et al.*, 2001; Kelly *et al.*, 2004).

Motor and cognitive functions are accompanied by synchronized oscillatory activity in different frequency bands proposing a mechanism of functional integration within brain networks (Varela *et al.*, 2001; Buzsáki and Draguhn, 2004; Schnitzler and Gross, 2005). In motor sequence

learning, oscillations in the beta (13-30 Hz) and alpha band (8-12 Hz) are suggested to be of importance in young adults (Zhuang *et al.*, 1997; Pollok *et al.*, 2014). This fits nicely to the assumption that beta oscillations are functionally relevant for motor control in general and movement planning, selection and preparation in particular (Pfurtscheller and Lopes Da Silva, 1999; Engel and Fries, 2010; Tzagarakis *et al.*, 2010; Heinrichs-Graham and Wilson, 2015). Movement execution is associated with a typical pattern of beta power modulation with power suppression (i.e., decrease in power) prior to and during movement execution followed by a rebound (i.e., increase in power) after movement termination exceeding baseline levels (Pfurtscheller and Lopes Da Silva, 1999). Interestingly, Pollok and colleagues (2014) found stronger beta power suppression in motor cortical areas to be associated with superior implicit motor learning in young adults. Similarly, transcranial alternating current stimulation (tACS), assumed to interact with oscillations in a frequency dependent manner (Thut *et al.*, 2012; Helfrich *et al.*, 2014), was found to stabilize newly acquired motor sequences when applied over the primary motor cortex at 20 Hz but not at 10 (Krause *et al.*, 2016) or 35 Hz (Pollok *et al.*, 2015). These findings additionally strengthen the role of beta oscillations in motor sequence learning.

In Parkinson's disease, abnormalities in oscillatory activity in the cortico-basal ganglia loop may add to the understanding of the pathophysiology (Schnitzler and Gross, 2005; Hammond *et al.*, 2007; Oswal *et al.*, 2013). Especially altered beta activity could be linked to symptoms such as akinesia and rigidity (Kühn *et al.*, 2006, 2009; Jenkinson and Brown, 2011; Pollok *et al.*, 2012; Oswal *et al.*, 2013). A magnetoencephalography (MEG) study further demonstrated pathologically reduced beta modulation in brain areas associated with motor processing during transient movements in such patients (Heinrichs-Graham *et al.*, 2014).

Taken together, beta oscillations are altered in Parkinson's disease and a link between suppression of motor cortical beta oscillations and successful motor sequence learning has been suggested. Therefore, in the present MEG study, we investigated Parkinson's disease patients and HC while performing a SRTT with the aim to shed light on the possible relation between changes of beta power and motor learning abilities in Parkinson's disease patients. We hypothesized that patients exhibit less beta power suppression during the SRTT than HC and, concomitant with that, diminished motor sequence learning. Although we were particularly interested in beta oscillations, we also investigated theta (4-7 Hz), alpha and gamma oscillations (30-90 Hz) since

alterations across these frequency bands have been suggested to relate to alterations of cognitive and motor functions in Parkinson's disease as well (Oswal *et al.*, 2013).

Material and methods

Participants

Twenty patients with idiopathic Parkinson's disease (9 male; age: 52.85 ± 6.88 years; mean ± SD), and 20 HC (9 male; age: 54.05 ± 7.71 years) participated in the study. Patients were recruited and tested at the *Movement Disorder Center* of the University Hospital Duesseldorf and their diagnosis was based upon the UK Parkinson's Disease Society Brain Bank Criteria (Hughes *et al.*, 1992). Exclusionary criteria involved tremor-dominant Parkinson's disease, dementia (*Mattis Dementia Rating Scale* (MDRS) score ≤ 130; Mattis, 1988), clinically relevant depressive symptoms (*Beck Depression Inventory* (BDI-II; Hautzinger *et al.*, 2006) score ≥ 18) or other psychiatric and neurological disorders besides Parkinson's disease. One patient was additionally diagnosed with ataxia several months after testing. Since SRTT performance scores and oscillatory power values were within two standard deviations of the group mean, we did not exclude these data to keep statistical power as high as possible. All patients were treated with antiparkinsonian medication with a mean daily levodopa equivalent dose (LED; Tomlinson *et al.*, 2010) of 550.81 ± 265.03 mg. Patients remained on their medication during study participation to minimize general motor impairment. Motor impairment was characterized by the motor part of the *Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale* (MDS-UPDRS III; Goetz *et al.*, 2008). *Digit span* (von Aster *et al.*, 2006) and *Block-Tapping-Test* (Schellis, 1997) were used to assess verbal and visuospatial short-term memory.

For each patient, a sex- and age-matched HC was tested. All participants were right handed (Edinburgh Handedness Inventory; Oldfield, 1971) and had normal or corrected-to-normal vision. There were no significant group differences in mean years of education (p = .16), MDRS score (p = .14), or verbal short-term memory (p = .93). Patients tended to exhibit better visuospatial short-term memory (p = .07) and scored significantly higher on the BDI-II (median = 6.50) than HC (median = 2.00; U = 73; z = -3.46; p = .001). But, none of the participants exhibited clinically relevant depressive symptoms (score ≥ 18). The study was approved by the local ethics committee (study no. 4792) and was conducted according to the Declaration of Helsinki. All participants provided written informed consent prior to the study and received monetary compensation. Characteristics of patients and HC are shown in Table 1.

Insert Table 1 about here

Experimental paradigm: SRTT

The SRTT was introduced as a measure of RT and participants were not informed of the 8-item sequence embedded in the task. A nonmagnetic custom-made response box with four response keys anatomically aligned to the right hand was used. Each key corresponded to one of four horizontally aligned bars presented on a back projection screen. Participants were instructed to rest the fingers of their right hand on the response buttons and to press as quickly as possible the corresponding button as soon as one of the four bars changed from dark to light blue. RT was defined as the interval between onset of color change and button press. The next bar was presented with a 2 s delay after the correct response. In case of incorrect responses, the bar remained light blue until participants responded correctly.

Prior to SRTT, a practice block of 12 randomly varying bars was administered. The experimental phase comprised five blocks. The first block served as baseline (*Random*) and consisted of ten sequences of eight randomly varying bars. To enable learning, the 8-item sequence (ring-index-thumb-middle-ring-middle-thumb-index) was repeated 15 times. Then, ten repetitions of the sequence served as an estimation of RT at *end of acquisition* (*EoA*). To examine whether the presentation of randomly presented bars interfered with the sequence after *EoA*, ten repetitions of a random pattern (*Interference*) were followed by ten repetitions of the sequence (*SIn*). Stimuli timing and response recording was controlled by E-Prime® software version 2 (Psychology Software Tools, Sharpsburg, PA, USA). For an overview of the task design, see Fig. 1.

Insert Fig. 1 about here

To assess whether explicit learning had occurred, participants were asked at the task's end whether they had noticed anything significant. If they reported to be aware of a sequential pattern, they were asked to recall it. Four HC as well as four patients recognized a repeating pattern. However, only three participants in each group recalled at least half of the sequence correctly.

Statistical analyses of behavioral data

Statistical analyses of behavioral data were performed using IBM SPSS 24 (IBM Corporation, Armonk, NY, USA). For each block of interest (*Random*, *EoA*, *Interference*, *SIn*), we calculated individual mean RTs. RTs exceeding two standard deviations from the respective mean were excluded (patients: 4.9 ± 2.1% of all trials; HC: 4.0 ± 0.9% of all trials). Kolmogorov-Smirnov tests revealed no significant deviation from Gaussian distribution (all $p > .05$). Analyses of variance (ANOVA) on mean RT with *block* (*Random* vs. *EoA* vs. *Interference* vs. *SIn*) as within- and *group* (HC vs. patients) as between-subjects factor were conducted. *Post-hoc* tests were calculated by means of two-tailed *t*-tests. In case of violation of sphericity assumptions, Greenhouse-Geisser correction was applied.

To control for group differences during *Random*, we computed percentage RT gains. The scores for motor sequence acquisition ((*Random* – *EoA)*/*Random* x 100) and susceptibility to interference ((*Interference* – *SIn*)/*Interference* x 100) were compared between groups using independent-samples *t*-tests.

To investigate whether SRTT performance was related to clinical characteristics, parametric (Pearson's *r*; for correlations involving LED) as well as non-parametric (Spearman's ρ; for correlations involving MDS-UPDRS III scores because of deviation from Gaussian distribution) correlations were calculated for all patients. To further examine the relationship between acquisition and susceptibility to interference, Pearson's correlation coefficients were calculated in each group. Bonferroni corrections for multiple testing were applied.

MEG data acquisition

Neuromagnetic brain activity was recorded during task execution by means of a 306-channel whole-head MEG system with 204 gradiometers and 102 magnetometers (Elekta Neuromag, Helsinki, Finland). The data was sampled at 1 kHz with a bandwidth of 0.1-330 Hz.

Four head position indicator (HPI) coils were fixed to the scalp of each participant and vertical electrooculogram was recorded during the SRTT. Prior to data acquisition, anatomical landmarks (nasion, left and right preauricular points) and HPI positions were digitized (Polhemus Isotrak, Colchester, Vermont, USA). Structural MRIs were acquired using a 3 T Siemens-Magnetom (Siemens, Erlangen, Germany) after the MEG session. MRIs were aligned with the MEG coordinate system using HPI coils and the position of the anatomical landmarks.

MEG data preprocessing

The data from the 204 planar gradiometers were analyzed with the Matlab-based FieldTrip toolbox (Oostenveld *et al.*, 2011) using Matlab R2015a (Mathworks, Natick, MA, USA). The data were segmented into epochs of 1.5 s pre to 2 s post button press (t = -1.5 to 2 s). For preprocessing, a 200 Hz low-pass and a 1 Hz high-pass filter was applied. Line noise was removed using band-stop filter for 50 Hz and its harmonic at 100 Hz and data was demeaned. By visual inspection, trials containing sensor jumps or muscle artifacts were rejected from further analyses. A nearest-neighbors approach was used to interpolate the data of broken channels by the mean signal of their neighboring channels. A principal component analysis was applied to correct for further artifacts. Components whose topographies and time-courses represented eye blinks or cardiac signals were removed. Groups did not differ in the number of trials subjected to analyses (mixed-design ANOVA: all $p \geq .18$).

Statistical analyses of MEG data

We computed time–frequency representations of power using a fast Fourier transformation. For frequencies of interest between 2 and 30 Hz we used an adaptive sliding time window with a width of five full cycles of the respective frequency f ($\Delta t = 5/f$) multiplied by a Hanning taper. The time window moved in steps of 50 ms and the frequency resolution was $1/\Delta t$. For frequencies between 30 and 90 Hz, we used a multi-taper approach (sliding time window of 500 ms length) with four orthogonal Slepian tapers resulting in a frequency smoothening of ± 5 Hz. Spectral power was calculated for the vertical and horizontal planar gradiometers separately and was then combined. Due to strong muscle artefacts, we had to exclude one participant of each group for the analysis of higher frequencies. Power changes were defined as relative change with respect to the mean of the complete time window according to previous studies (Pollok *et al.*, 2014; te Woerd *et al.*, 2014, 2015).

First, we investigated whether oscillatory activity in the different frequency bands differed between groups during *Random*. We averaged the power across the respective frequencies (theta, alpha, beta, and gamma) and computed cluster-based, independent-samples *t*-tests with Monte Carlo randomization controlling for multiple comparisons (Maris and Oostenveld, 2007) to compare power between groups in all channels in a time interval between t = -0.75 to 1.5 s. Source reconstruction was conducted at alpha and beta frequencies. Cortical sources were identified using the frequency based beamformer algorithm *Dynamic Imaging of Coherent*

Sources (DICS; Gross *et al.*, 2001). For beta activity, we contrasted two time windows of 500 ms centered on the time points of maximal beta power suppression and rebound, respectively. 20 Hz was chosen as center frequency (spectral smoothening of ± 5 Hz) which resulted in 10 full cycles per time window. We created a realistic, single-shell brain model (Nolte, 2003) based on the individual anatomical MRI or on a MNI template brain (n = 10). Forward solution for each participant was estimated using a regular 3D grid with 1 cm resolution in MNI space which was warped onto individual anatomy. A lead-field matrix was computed for each grid point according to the head position in the MEG and the forward model. Using the cross-spectral density and lead-field matrices, a common spatial filter was constructed on both time windows (suppression and rebound) for each individual grid point. The spatial filter was then applied to beta power suppression and rebound epochs and contrasted. For each group, source reconstructed oscillatory power was grand-averaged across participants and visualized on the cortical surface of the MNI template brain. The same steps were applied for alpha activity, using a center frequency of 10 Hz (spectral smoothening of ± 2 Hz) resulting in five full cycles per time window.

To examine differences in oscillatory activity during acquisition as well as after interference between groups, we used cluster-based permutation tests as described above. We calculated the difference in oscillatory power between *EoA* and *Random* as well as between *SIn* and *Random*, and compared these contrasts of interest between groups by means of cluster-based independent-samples *t*-tests with Monte Carlo randomization. Since motor cortical areas are suggested to play a pivotal role in motor sequence learning, statistical analyses were performed in a selection of channels covering left and right primary sensorimotor cortices (S1/M1; Pollok *et al.*, 2014; see Fig. 3). Additionally, we performed explorative analyses including all sensors. The resulting clusters with *p*-values below an alpha level of 0.05 were considered significant.

Correlations between MEG and behavioral/clinical data

Brain-behavior relationships were examined using cluster-based permutation tests implemented in Fieldtrip. First, we correlated time-frequency data during *Random* with *Random* RTs in both groups and with clinical variables (MDS-UPDRS III, LED) in patients. We further correlated the time-frequency data of contrasts of interest (*EoA* vs. *Random*, *SIn* vs. *Random*) with the respective RT gains (*Random* to *EoA*; *Interference* to *SIn*). Correlational analyses were performed for frequency bands showing significant differences between groups (*Random:* alpha,

beta; contrasts of interest: theta, beta) and separately for patients and HC for the S1/M1 channel selection.

Results

Behavioral data

The ANOVA revealed significant main effects of *block* ($F(2.5, 94.8) = 8.69$; $p < .001$) and *group* ($F(1, 38) = 10.43$; $p = .003$) with generally slower RTs in patients than in HC. Importantly, a significant *group* by *block* interaction emerged ($F(2.5, 94.8) = 4.21$; $p = .01$). *Post-hoc t*-tests revealed that HC were significantly faster during *EoA* than *Random* ($t(19) = -6.68$; $p < .001$) and *Interference* ($t(19) = -3.25$; $p = .004$) indicating sequence acquisition. Additionally, HC were significantly faster during *Interference* than *Random* ($t(19) = -3.39$; $p = .003$) suggesting unspecific RT improvement. In patients, we found a trend towards faster RTs during *EoA* than *Random* ($t(19) = -2.00$; $p = .06$) and *Interference* ($t(19) = -2.00$; $p = .06$) suggesting reduced but preserved sequence acquisition in patients. *Random* and *Interference* RTs did not differ significantly in patients ($p = .71$). Furthermore, HC were significantly faster during *SIn* than *Interference* ($t(19) = -5.22$; $p < .001$) indicating that they were not susceptible to an interfering condition. In patients, no significant differences emerged ($p = .93$) suggesting an interfering effect (Fig. 2A).

To account for faster RTs in HC during *Random*, percentage RT gains were compared between groups by independent-samples *t*-tests. Significantly less RT gain from *Random* to *EoA* in patients ($t(38) = -2.39$; $p = .02$; Fig. 2B) indicated diminished motor sequence acquisition. When comparing RT changes from *Interference* to *SIn*, significantly smaller gains in patients ($t(38) = 2.30$; $p = .03$; Fig. 2C) indicated higher susceptibility to interference.

Correlational analyses relating sequence acquisition to (reduced) susceptibility to interference revealed a significant association in HC ($r = .57$; $p = .01$; Fig. 2E) but not in patients ($r = .28$; $p = .23$; Fig. 2D), suggesting that these processes might be related only in HC. Correlational analyses linking clinical characteristics of patients to SRTT performance revealed no significant associations (all $p \geq .16$).

Insert Fig. 2 about here

MEG data

Group differences during Random

Oscillatory power in frequencies up to 30 Hz is shown in Fig. 3A and 3B. Expected (alpha and) beta power suppression before and during button press followed by a rebound was present in both groups. In addition, we observed a theta power increase relative to baseline, especially in HC. It started approximately 500 ms prior to button press and lasted for several hundred milliseconds. Cortical sources of beta and alpha power modulation are illustrated in Fig. 3C and 3D. In general, beta power modulations were most pronounced in bilateral pericentral regions, while alpha power modulations were less focal.

Insert Fig. 3 about here

Significant group differences at beta frequencies were most pronounced in a time window between 0.1 and 0.5 s, indicating stronger beta power suppression in patients than in HC (p = .02; Fig. 4A). For alpha frequencies, differences were most pronounced in time windows between -0.35 and 0.55 s (p = .003) and between 1.1 and 1.5 s (p = .04), indicating stronger alpha modulation in patients (Fig. 4B). For other frequencies, no significant group differences were found.

Insert Fig. 4 about here

Group differences over the course of the SRTT

Fig. 5A and 5C show differences in oscillatory power between blocks for frequencies up to 30 Hz. For *EoA* as compared to *Random*, the statistical analyses between groups including all sensors revealed a difference for beta frequencies most pronounced between t = -0.45 and -0.25 s which tended to be significant (p = .06). Cluster statistics for the S1/M1 channel selection resulted in a significant difference in the beta band (p = .048; Fig. 5B) most pronounced between t = -0.45 and -0.35 s. Noteworthy, this difference was most pronounced in motor areas ipsilateral to the moving hand. These results suggest less beta power suppression during *EoA* relative to *Random* in patients. In other frequency bands, no significant differences emerged.

Insert Fig. 5 about here

For *SIn* as compared to *Random*, the statistical analyses between groups for S1/M1 channels revealed a significant difference in the theta band (p = .02; Fig. 5D) most pronounced between t = -0.05 and 0.15 s contralateral to the moving hand. This indicates less theta power increase from *Random* to *SIn* in patients. In all other frequency bands, no significant differences were found. Cluster statistics including all sensors revealed no significant results either.

Oscillatory activity and its relation to behavioral data and clinical characteristics

Correlational analyses between time-frequency data during *Random* and clinical characteristics in patients revealed a significant negative correlation between theta power (t = -0.2 to 0.3 s) and MDS-UPDRS III scores (p = .004; Fig. 6A) suggesting that lower theta power was related to higher symptom severity. For beta power, we found no significant correlation with MDS-UPDRS III scores (p = .09). There were also no significant correlations involving LED.

When correlating time-frequency data during *Random* with *Random* RTs, a significant negative correlation in a time window between t = -0.6 to 0.55 s (p = .003) as well as a significant positive correlation in a time window between t = 1 to 1.5 s (p = .01) between beta power and RTs in patients emerged, indicating that stronger beta power modulation was associated with slower RTs (Fig. 6B). A similar negative correlation was found for alpha frequencies (t = -0.6 to 0.6 s; p = .02). In HC, we found no significant correlations (p > .10).

Insert Fig. 6 about here

In patients, less beta power suppression during *EoA* compared to *Random* (t = -0.5 to -0.35 s) was associated with greater RT improvement from *Random* to *EoA* (p = .02; Fig. 7A). Further, stronger beta power suppression from *Random* to *SIn* (t = -0.5 and -0.25 s) was associated with greater RT gain from *Interference* to *SIn* thus with less susceptibility to interference (p = .04; Fig. 7B). Again, these effects were most pronounced ipsilateral to the moving hand. For the theta band, no significant correlation was obtained in patients. In HC, less susceptibility to interference was significantly correlated with a stronger increase in theta power from *Random* to *EoA* most pronounced between t = 0.05 to 0.25 s (p = .04; Fig. 7C). All other correlations including correlations with beta power failed to yield significance in HC (all p > .07).

Insert Fig. 7 about here

Discussion

The present MEG study investigated Parkinson's disease patients and HC during implicit motor sequence learning with the aim to elucidate the relation between beta oscillations and motor learning in Parkinson's disease. We found reduced but preserved motor sequence acquisition and higher susceptibility to interference in patients. This was paralleled by less training-related beta power suppression in motor cortical areas in patients supporting the relevance of beta power suppression for motor sequence learning. Superior motor sequence acquisition was significantly associated with reduced susceptibility to interference in HC but not in patients suggesting distinct processes in Parkinson's disease. Further indirect support for this assumption was provided by the finding that beta power suppression might be beneficial for reduced susceptibility to interference but not for motor sequence acquisition in patients. Beyond beta oscillations, we found a stronger training-related increase in theta power in HC as compared to patients. As this increase was associated with reduced susceptibility to interference, the data provide first evidence for the hypothesis that theta oscillations might specifically contribute to reduced susceptibility to interference, at least in healthy older adults.

Oscillatory activity prior to learning and its relation to clinical and behavioral data

During *Random*, we found the established pattern of alpha and beta power suppression before and during button press and a subsequent rebound in sensors covering sensorimotor areas. Statistical analyses revealed significantly stronger alpha and beta power modulation in patients. As shown by sensor level analyses and source reconstruction, beta modulation was more widespread in patients, possibly suggesting recruitment of a larger brain network for task execution. At first glance, this finding is rather surprising in view of a previous MEG study evaluating oscillatory activity during basic movements in Parkinson's disease as compared to HC (Heinrichs-Graham *et al.*, 2014). In contrast to our results, those patients exhibited *diminished* beta suppression prior to and during movement. It is important to note, that that study examined oscillations in patients OFF medication. Since the modulation of beta oscillations is impaired when dopamine is deficient but promoted by dopaminergic medication (Doyle *et al.*, 2005; Litvak *et al.*, 2012; Oswal *et al.*, 2012, 2013), findings are likely related to different levels of levodopa. The data by Heinrichs-Graham et al. (2014) suggest that deficient beta power suppression contributes to diminished movement capacities in Parkinson's disease. The present data, including the correlative evidence linking stronger beta modulation to slower RTs in patients, supports the

hypothesis of Brittain and colleagues (2014) that not only higher but also lower levels of beta activity (i.e., deviation from task- and context-related "optimal" activity) might be associated with alterations in motor performance.

At alpha frequencies, patients showed a stronger modulation in sensors covering, but not limited to, sensorimotor areas. Alpha oscillations may subserve less specific functions in motor processing, such as attentional demands and automatic motor control (Klostermann *et al.*, 2007; Pollok *et al.*, 2009; Klimesch, 2012). Thus, stronger modulation in patients may reflect the need for greater attentional resources and control mechanisms in Parkinson's disease.

Theta and gamma power did not differ significantly between groups during *Random*. Previous MEG studies reported a widespread increase in theta power in Parkinson's disease patients relative to HC during rest (Bosboom *et al.*, 2006; Stoffers *et al.*, 2007). Although we did not find significant group differences during task execution, correlational analyses suggest lower theta power to be associated with more severe motor symptoms supporting the assumption that theta power might indeed relate to motor impairment in Parkinson's disease.

In Parkinson's disease, alterations in gamma oscillations have also been described. More specifically, cortical resting-state power was reduced in comparison to HC (Bosboom *et al.*, 2006; Stoffers *et al.*, 2007). In patients undergoing surgery for deep brain stimulation, several studies reported diminished movement-related gamma activity in the basal ganglia OFF medication which was promoted by levodopa (Androulidakis *et al.*, 2007; Litvak *et al.*, 2012; Oswal *et al.*, 2013). Thus, it is conceivable that the lack of group differences at gamma frequencies was due to dopaminergic therapy restoring a rather physiological pattern also at (motor) cortical levels.

Motor sequence acquisition and susceptibility to interference in patients and HC

The present data indicate altered motor sequence learning in Parkinson's disease. Whereas patients showed only a trend for improved RTs after training on the SRTT, HC exhibited significant improvement. Although the data suggest that patients are able to acquire motor sequences to some extent, this ability appears to be diminished. This assumption is supported by percentage analyses revealing less RT improvement from *Random* to *EoA* in patients than in HC. The present data are in line with several studies reporting diminished motor sequence acquisition (reviewed by Ruitenberg *et al.*, 2015). HC but not patients showed additional unspecific RT improvement from *Random* to *Interference*. Since RTs during *SIn* and *EoA* were significantly

faster than during *Interference*, sequence-specific improvement was more pronounced than unspecific gain. Apart from motor sequence acquisition, we examined susceptibility to interfering trials. This was of particular interest, as it has rarely been studied in Parkinson's disease but needs to be taken into account to understand the different processes involved in motor sequence learning (Doyon, 2008; Marinelli *et al.*, 2017). Reflected in significantly less RT gain from *Interference* to *SIn*, the present data suggest higher susceptibility to interference in patients than in HC. Interestingly, correlational analyses between acquisition and susceptibility to interference revealed that whereas in HC reduced susceptibility to interference was significantly linked to better acquisition, no significant association was found in patients. This indicates that these two processes might be related to each other in HC, while they are rather distinct in Parkinson's disease.

In contrast to previous data (Muslimovic *et al.*, 2007) we found no significant link between symptom severity and RTs or motor sequence learning in patients.

Oscillatory activity and its functional significance in motor sequence learning

Beta oscillations

To our knowledge, this is the first study investigating oscillatory dynamics of motor sequence acquisition as well as susceptibility to interference in Parkinson's disease. During *EoA* as compared to *Random*, we observed significantly less beta power suppression in patients which was most pronounced prior to button press in sensors covering motor cortical areas. This finding parallels diminished sequence acquisition in patients and fits nicely with the hypotheses (i) that beta activity promotes the current motor and cognitive state at the account of flexible control strategies (Engel and Fries, 2010; Brittain and Brown, 2014) and (ii) that its modulation – particularly suppression – represents a learning-related marker of reorganization of neural activity (Pollok *et al.*, 2014). Interestingly, group differences in beta power suppression were most pronounced in sensorimotor regions *ipsilateral* to the responding hand. We are aware that results of cluster-based permutation tests do not provide information on the exact spatial extent of the effect. Nevertheless, differences between Parkinson's disease patients and HC in beta oscillations ipsilateral to the effector have been reported before. Meziane et al. (2015) found symmetrical beta power suppression in motor areas during a reaching task in older adults (but not in patients) which is in line with the assumption of loss of hemispheric lateralization as one characteristic of an aging motor system (Vallesi *et al.*, 2010). Older adults may need more extensive recruitment

of (bilateral) sensorimotor areas than young adults to achieve optimal performance levels (Meziane *et al.*, 2015). This compensatory mechanism may be deficient in Parkinson's disease.

Interestingly, although our group analyses suggested that less beta power suppression in patients as compared to HC was paralleled by diminished SRTT performance, correlational analyses yielded seemingly inconsistent results. In patients, stronger beta power suppression at *EoA* than *Random* was associated with *worse* acquisition while stronger beta power suppression during *SIn* than *Random* was associated with *less* susceptibility to interference, thus *better* performance. Consistent with the reported group differences in learning-related beta power suppression, these effects were most pronounced in motor areas ipsilateral to the moving hand. Thus, in contrast to our hypothesis, in Parkinson's disease beta power suppression appears to be beneficial for reduced susceptibility to interference but not for sequence acquisition itself. Furthermore, the data indirectly supports the assumption that motor sequence acquisition and susceptibility to interference might be distinct processes with distinct neurophysiological correlates in Parkinson's disease. Interestingly, in the context of explicit sequence learning, recordings of subthalamic beta oscillations in Parkinson's disease patients revealed that beta suppression only promoted sequence acquisition when it was observed at sequence boundaries, whereas suppression before within-sequence elements was related to worse performance (Ruiz *et al.*, 2014). This finding supports the assumption that in Parkinson's disease, the significance of beta suppression might vary depending on its occurrence in relation to task phase. Surprisingly, we found no significant correlation between beta oscillations and behavioral performance in HC. The applied statistical tests only capture linear relations between variables. As (correlative) associations between variables can also be nonlinear in nature, the limitation of the analysis might be one explanation for the present null finding in HC. Nevertheless, previous results suggest a linear relationship between beta power suppression and motor learning in young adults (Pollok *et al.*, 2014). These differences in findings might relate to age-specific changes of brain oscillations and their association with motor sequence learning.

There is evidence for a link between increased beta oscillations and decreased cortical excitability (Noh *et al.*, 2012; McAllister *et al.*, 2013). It is tempting to speculate that beta power suppression reflects an increase in cortical excitability which might promote plastic changes in training-related neural networks. This interpretation is supported by impaired (motor) cortical plasticity already apparent in early stages of Parkinson's disease (reviewed by Koch, 2013).

Surprisingly, in our study, patients exhibited stronger beta power suppression during *Random* prior to learning but less increase in beta power suppression over the course of learning than HC. Thus, it is reasonable to assume that practice-dependent changes in beta power suppression subserving motor learning are independent of the depth of beta power modulation prior to learning during the execution of a simple motor response.

Theta oscillations

Beyond group differences in beta activity, we found a significantly smaller motor cortical theta power increase from *Random* to *SIn* in patients. This result provides new evidence that theta oscillations might contribute to susceptibility to interference, at least in healthy older adults. In general, theta oscillations have been linked to executive processes and declarative memory functions (Klimesch *et al.*, 1997, 2001; Sauseng *et al.*, 2005; Brier *et al.*, 2010; Burke *et al.*, 2014). Furthermore, the implication of theta oscillations in the induction of synaptic plasticity indicates their mnemonic function (Pavlides *et al.*, 1988; Larson and Lynch, 1989; Orr *et al.*, 2001) and militates for a functional mechanism of these oscillations in sequence learning which might be impaired in Parkinson's disease. Based on animal studies but also applied to humans, theta rhythms are further suggested to be involved in learning, especially when sensorimotor integration is necessary (Bland, 1986; Bland and Oddie, 2001; Caplan *et al.*, 2003; Bland *et al.*, 2007; Cruikshank *et al.*, 2012). Caplan et al. (2003) hypothesized that cortical theta synchronization might represent one mechanism coordinating sensory and motor brain activity to facilitate learning. A recent study trying to enhance early consolidation of explicitly acquired motor sequences by means of post-training modulation of oscillations by neurofeedback, found beneficial effects of theta power increases (Rozengurt *et al.*, 2016). These findings are indicative of the involvement of theta oscillations in early consolidation, at least when participants are explicitly instructed to learn a sequence. Additionally, perimovement theta power modulation in motor cortical areas has been linked to different parameters such as timing of responses, force measures of grip, and movement acceleration (Anzak *et al.*, 2012; Zavala *et al.*, 2013; Ofori *et al.*, 2015). Since we observed significant differences between groups in theta power over the course of the task but not prior to learning, our findings suggest a specific significance of theta oscillations in susceptibility to interference following implicit motor learning. This assumption is supported by the correlative evidence linking stronger increases in theta power at *EoA* as compared to *Random* to less susceptibility to interference in HC. This at the same time further

fuels the idea that in HC susceptibility to inference after training relies on neurophysiological changes occurring during acquisition already.

Caveats

At least three caveats should be acknowledged. First, we investigated patients ON medication. Therefore, we cannot separate medication from disease-related effects. However, as we were interested in oscillatory dynamics underlying motor sequence learning, recordings were made in patients' best motor state. Since patients were slower than HC during *Random* we cannot exclude that general motor impairment has somehow influenced motor sequence learning though. But, symptom severity was not significantly associated with general RT performance on the SRTT. We therefore assume that impairment observed in the present study relates to sequence learning rather than motor performance per se. Second, we cannot exclude that patients might have reached similar performance levels as HC with more extensive training. This issue has to be addressed in future studies using more sequence repetitions. Third, studies suggest that Parkinson's disease patients may have difficulties in exploring optimal task solutions and maintaining appropriate mental effort and motivation, especially in complex tasks (Schneider, 2007; Vakil *et al.*, 2014). We did not assess motivational aspects during participation, which makes it difficult to rule out such influences on our results. However, patients tended to perform better on a visuospatial short-term memory task than HC suggesting that motivational factors seem to play a minor role.

Conclusion

Both motor sequence acquisition and susceptibility to interference seem to be altered in Parkinson's disease. In healthy adults, reduced susceptibility to interference relies on successful acquisition of a motor sequence. Furthermore, the MEG data (indirectly) supports the significance of beta oscillations for sequence acquisition and theta oscillations for susceptibility to interference in healthy aging. In contrast, in Parkinson's disease, acquisition and susceptibility to interference seem to be distinct processes. This was further supported by the finding that beta power suppression may be beneficial for reduced susceptibility to interference rather than acquisition of a motor sequence.

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758

759 Figure legends

760 **Fig. 1: Overview of the task design. (A)** Sequence of events in two exemplary SRTT trials. The
761 response keys of the response box were spatially mapped to four bars presented on the back
762 projection screen. Subjects were instructed to press the corresponding button as soon as one of
763 the bars changed from dark to light blue. The interval between the correct response and the next
764 trial was set to 2 s. **(B)** SRTT procedure. Neuromagnetic brain activity was recorded during the
765 entire task. During *Random*, ten sequences of eight randomly varying trials were presented. To
766 enable acquisition of a motor sequence, an 8-item sequence was presented 15 times (training on

767 the task). The end of acquisition (*EoA*) comprised ten repetitions of the sequence. For the
768 assessment of susceptibility to interference, ten sequences of eight randomly varying trials were
769 presented (*Interference*) and followed by ten repetitions of the introduced sequence (*SIn*).

770 **Fig. 2: Behavioral results. (A)** Mean RTs of the blocks of interest in patients and HC.
771 Percentage RT gains in HC and patients from **(B)** *Random* to *EoA* reflecting sequence acquisition
772 and from **(C)** *Interference* to *SIn* reflecting susceptibility to interference. Note that greater RT
773 improvement from *Interference* to *SIn* reflects *less* susceptibility to interference. Correlation
774 between percentage gains in RT from *Random* to *EoA* and percentage gains in RT from
775 *Interference* to *SIn* in **(D)** patients and **(E)** HC. The data indicate that these two measures are
776 significantly associated in HC but not in patients. Error bars indicate standard error of the mean
777 (SEM); *** $p < .001$; ** $p < .01$ * $p < .05$; (*) $p = .06$; ns = not significant; End of Acquisition
778 (EoA); Interference (Int); sequence trials after interference (SIn).

779 **Fig. 3: Oscillatory activity in the lower frequency bands during *Random*.** Sensor plot of 102
780 combined planar gradiometers showing time-frequency representations of power (4-30 Hz);
781 expressed as relative change to baseline averaged across **(A)** HC and **(B)** patients during *Random*.
782 The inserts indicate the spectral power averaged across the channel selection covering S1/M1 in
783 HC and patients. Warm colors indicate an increase, cold colors a decrease in power. Button press
784 was at 0 s. Color bar placed at the far left applies to all plots. Source reconstruction of the **(C)**
785 beta and **(D)** alpha power modulation, measured from maximal rebound to maximal suppression
786 averaged over each group (left panel: HC, right panel: patients) projected onto the MNI template
787 brain.

788 **Fig. 4: Results of statistical group comparisons during *Random*.** Results of the cluster-based
789 permutation tests (HC vs. patients) comparing oscillatory activity averaged across the **(A)** beta
790 and **(B)** alpha frequency bands during *Random*. Clusters that show a difference between groups
791 ($p < .05$) are indicated by white circles. Warm colors indicate stronger decrease, cold colors
792 stronger increase in power in patients than in HC. Color bars placed at the far right apply to all
793 cluster plots.

794 **Fig. 5: Oscillatory activity over the course of the SRTT.** Time-frequency representations of
795 power for the contrasts of interest **(A)** *EoA* vs. *Random* and **(C)** *SIn* vs. *Random* averaged across
796 the S1/M1 channel selection in HC (left) and patients (right). Cold colors indicate stronger

decrease in power during *EoA/SIn* than *Random*. Warm colors indicate stronger increase in power during *EoA/SIn* than *Random*. Button press was at 0 s. Color bar placed at the right applies to HC and patients. Results of the statistical analyses (HC vs. patients) for the contrasts of interest **(B)** *EoA* vs. *Random* averaged across the beta band (13-30 Hz) including all channels (top) and the S1/M1 channel selection (bottom) and for **(D)** *SIn* vs. *Random* averaged across the theta band (4-7 Hz) for the S1/M1 channel selection. Clusters that show a difference between groups ($p < .05$) are indicated by white circles. White Xs indicate clusters with $p = .06$. Cold colors indicate less decrease (in B) and warm colors less increase in power (in D) from *Random* to *EoA* or *SIn* in the respective frequency bands in patients than in HC. Color bars placed at the far right apply to all cluster plots. Please note that the cluster in (B) for all channels was most pronounced between t = -0.45 to -0.25 s. For illustrative reasons, we kept the displayed time window equal for the top and bottom row.

Fig. 6: Correlations between oscillatory activity during *Random* and behavioral/clinical data. (A) Theta power during *Random* is significantly correlated with symptom severity (MDS-UPDRS III scores) in patients. **(B)** Correlation between *Random* RTs and beta power in patients. Please note that we found similar results for alpha as for beta frequencies in patients. However, only results for the beta band are shown here. Warm colors indicate a positive correlation, cold colors a negative correlation. Clusters that show a correlation ($p < .05$) are indicated by white circles. The color bar placed at the far right applies to all plots. For illustrative reasons, only a selection of time points is shown.

Fig. 7: Correlations between oscillatory activity over the course of the SRTT and RT gains. Oscillatory beta activity (*EoA* vs. *Random*; *SIn* vs. *Random*) was significantly correlated with **(A)** RT gains from *Random* to *EoA*, thus with acquisition of the sequence and with **(B)** RT gains from *Interference* to *SIn*, thus with susceptibility to interference in patients. **(C)** Correlation between oscillatory theta activity (*EoA* vs. *Random*) and RT gains from *Interference* to *SIn* (susceptibility to interference) in HC. Warm colors indicate positive, cold colors negative correlations. Clusters that show a correlation ($p < .05$) are indicated by white circles. Color bar applies to all plots. For the interpretation of the results, it is important to highlight that larger RT gains from *Random* to *EoA* reflect *better* acquisition. Larger RT gains from *Interference* to *SIn* indicate *less* susceptibility to interference. Please note that for illustrative reasons, not all time points are shown.

Table 1. Characteristics of Parkinson's disease patients and healthy controls

Demographics and cognitive and affective screening measures

Group	n	Gender (male/female)	Age	Years of Education	MDRS	BDI-II	Digit Span	Block-Tapping-Test
Patients	20	9/11	52.85 (± 6.88)	14.68 (± 2.82)	141.90 (± 1.48)	7.21 (± 4.48)	8.45 (± 1.70)	5.45 (± 0.70)
Controls	20	9/11	54.05 (± 7.71)	16.25 (± 4.08)	142.55 (± 1.23)	2.50 (± 4.08)	8.50 (± 2.01)	5.05 (± 0.69)

Clinical characteristics of patients

Side of Impairment (right/left)	Disease Duration (months)	Daily LED (mg)	MDS-UPDRS III
10/10	66.85 (± 36.40)	550.81 (± 265.03)	20.85 (± 6.30)

Demographics and screening measures are presented as group means (standard deviation (SD)). MDRS = Mattis Dementia Rating Scale; BDI-II = German version of the Beck Depression Inventory; LED = levodopa equivalent dose; MDS-UPDRS III = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale motor score on medication.

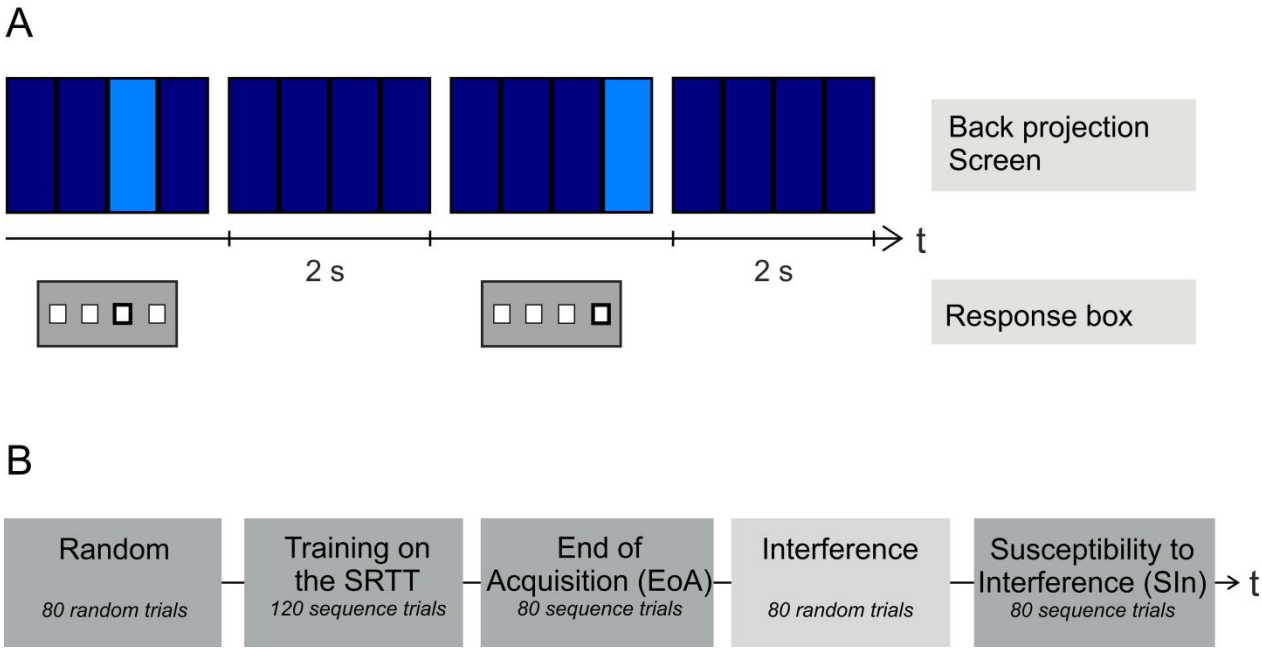

Figure 1

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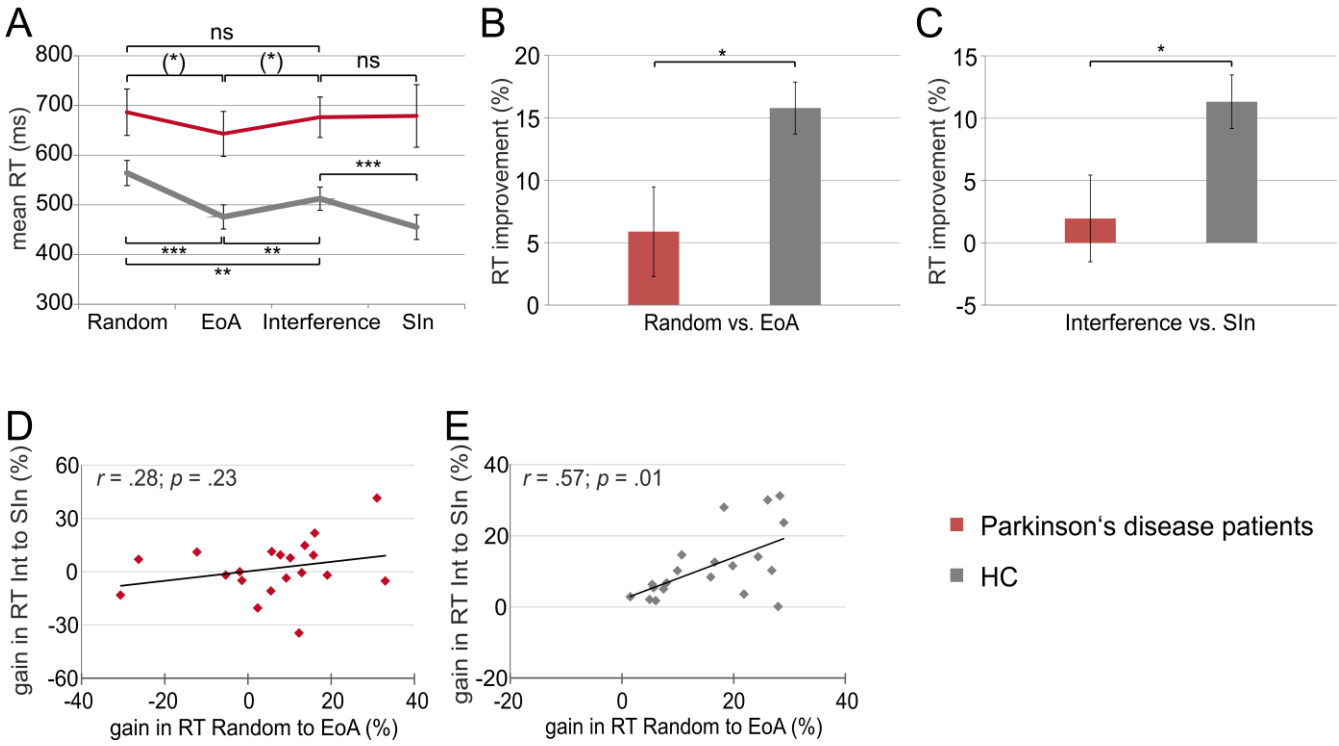

Figure 2

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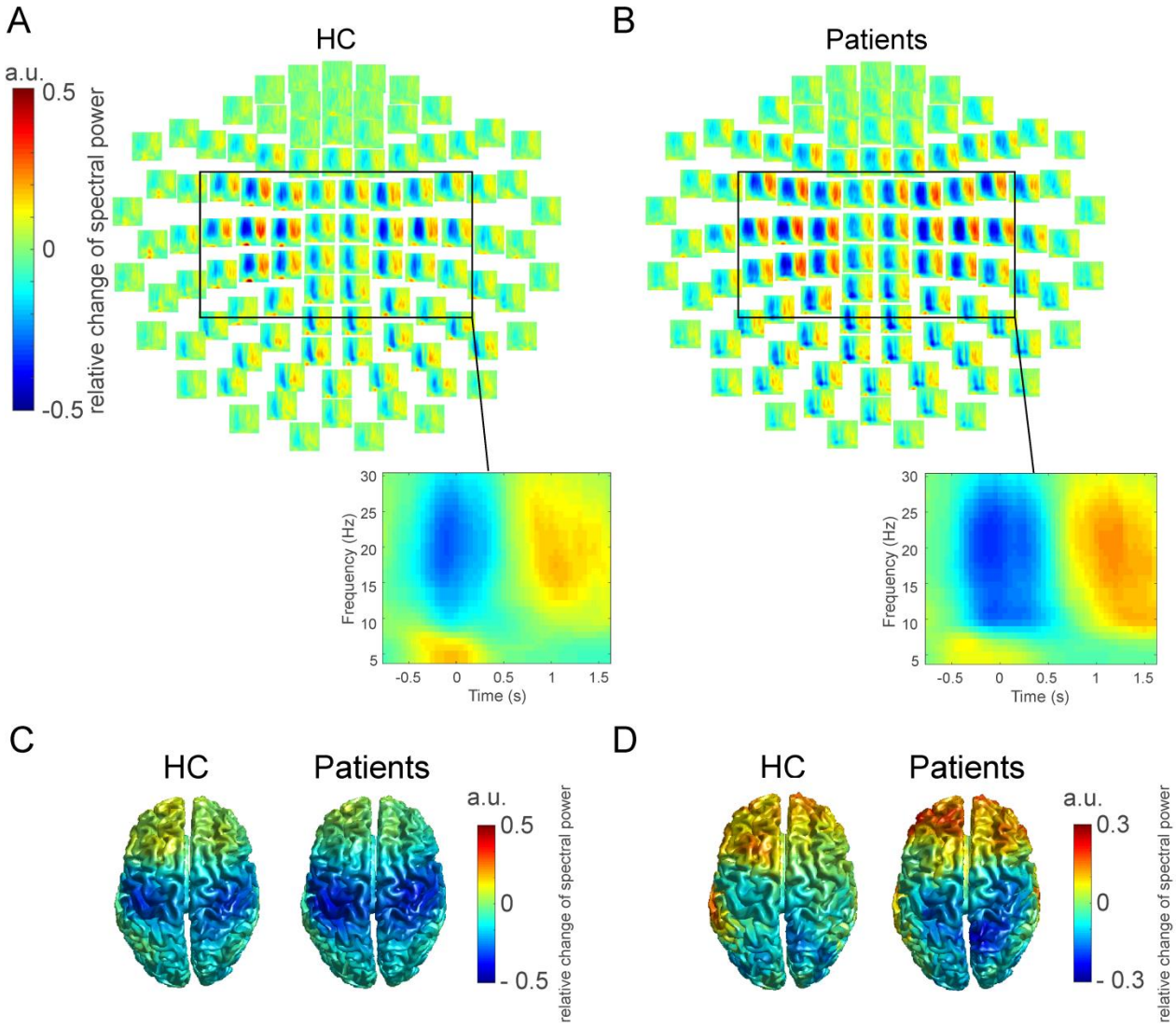

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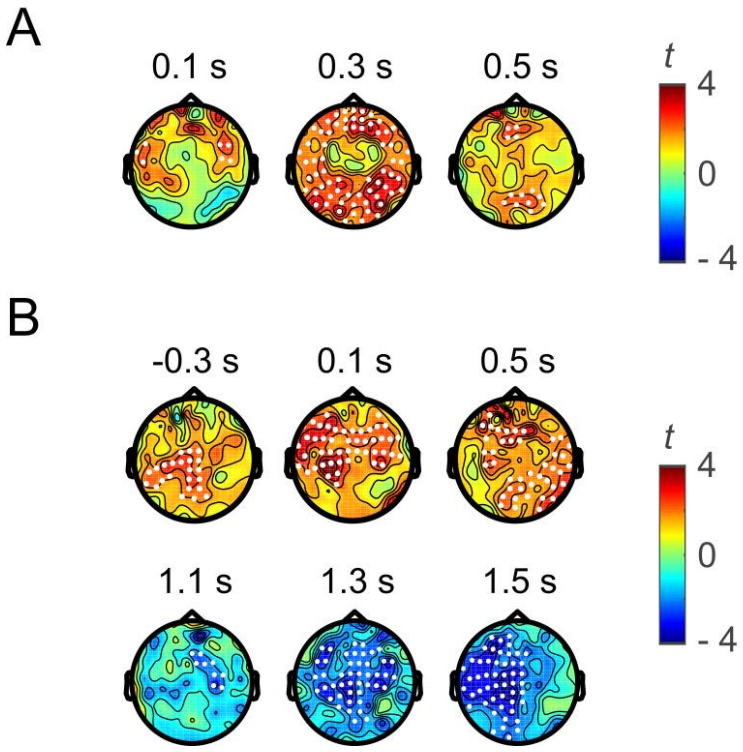

Figure 4

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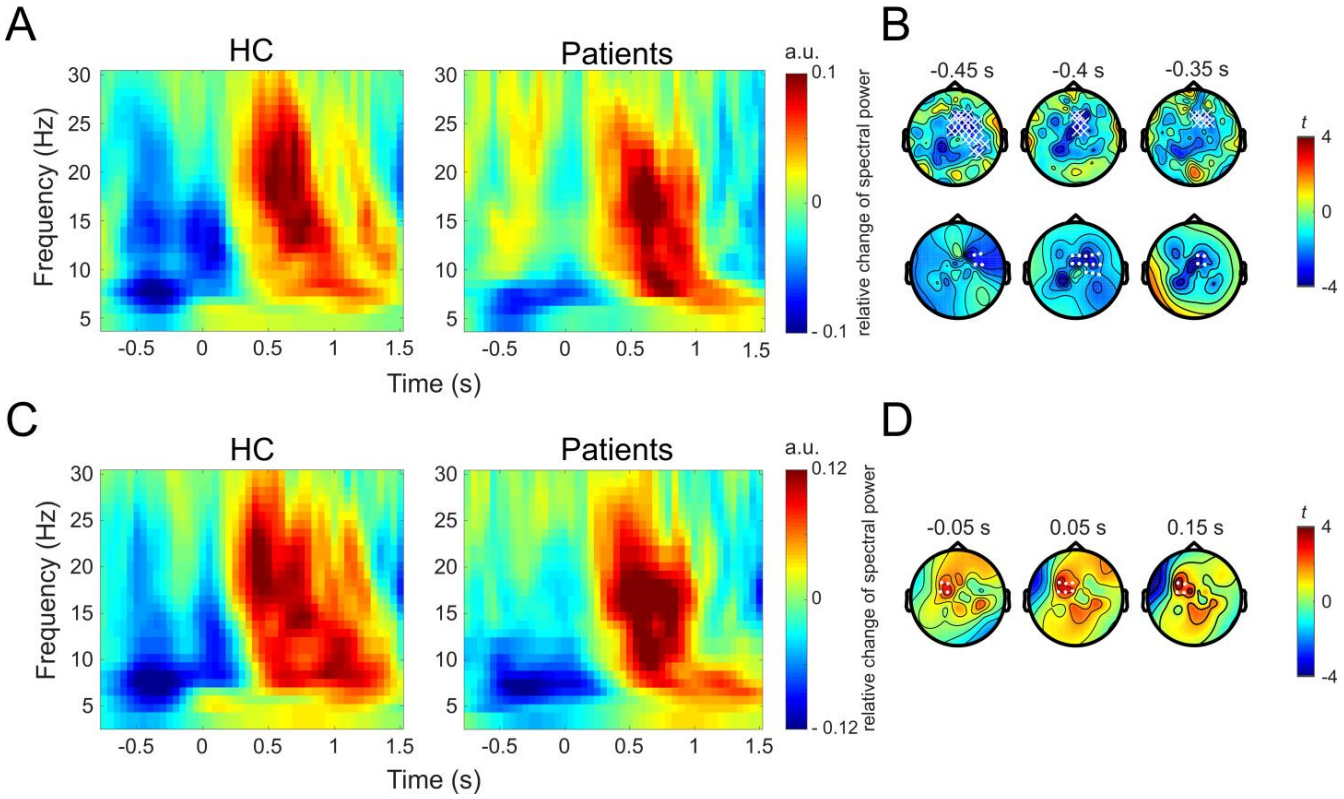

Figure 5

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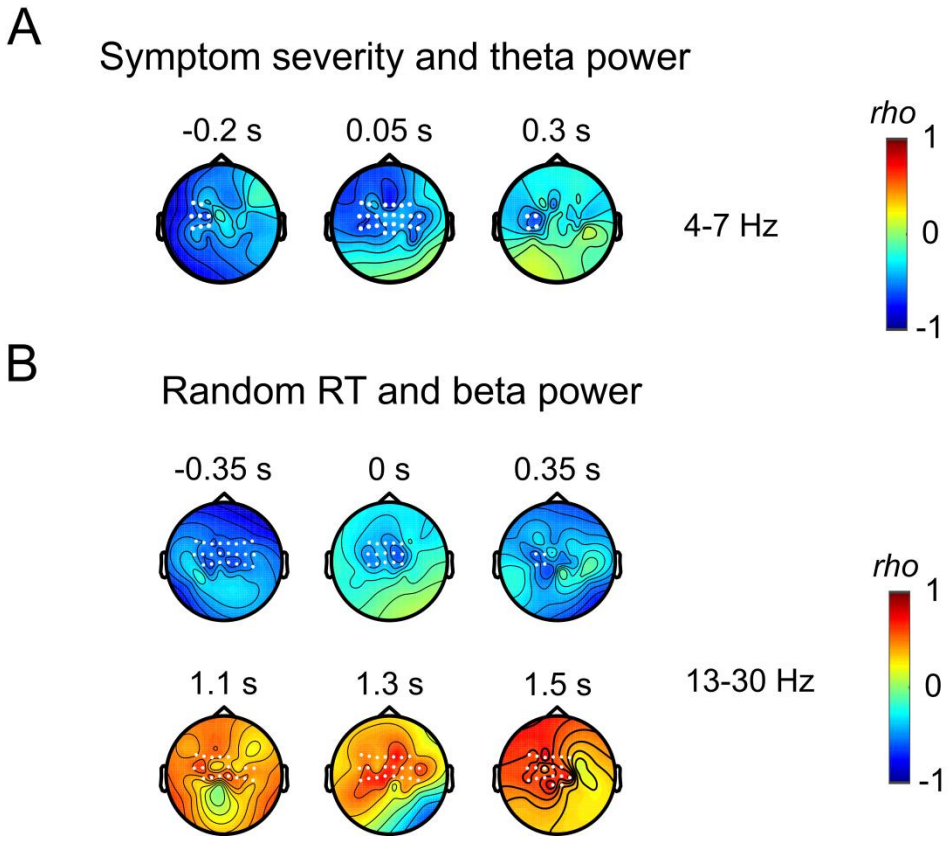

Figure 6

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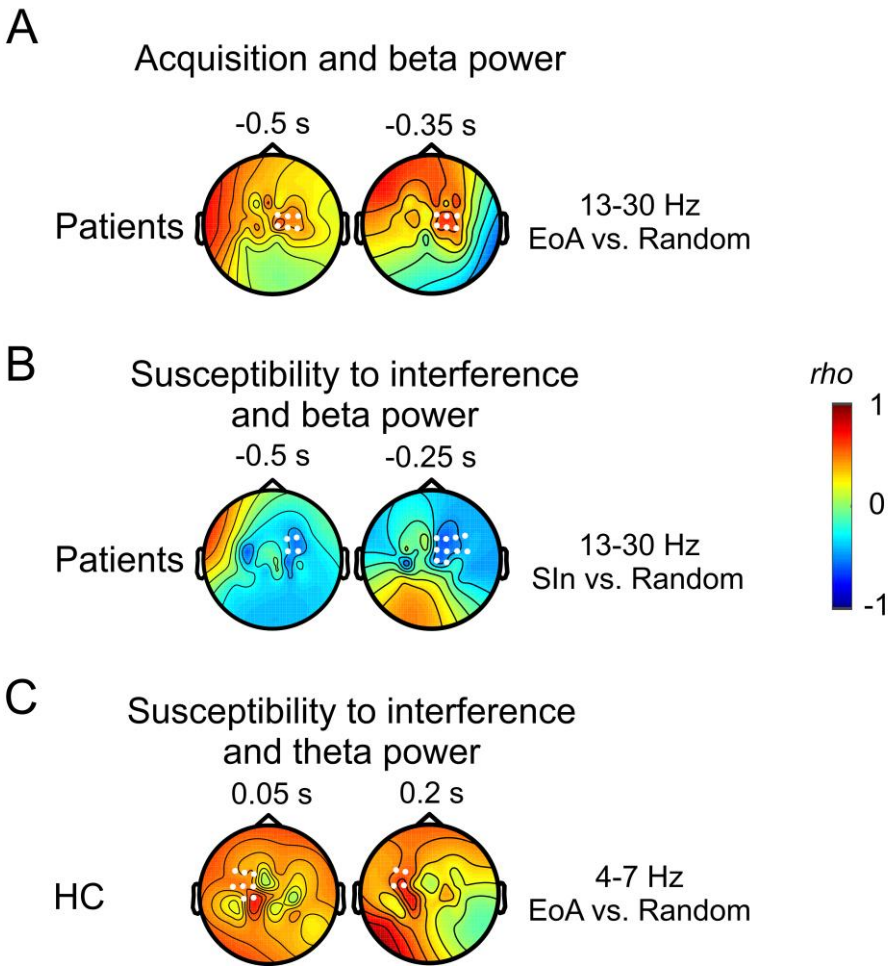

Figure 7

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Research report

Facilitating effects of deep brain stimulation on feedback learning in Parkinson's disease

Sarah Nadine Meissner[a,*], Martin Südmeyer[a,b], Ariane Keitel[a], Bettina Pollok[a], Christian Bellebaum[c]

[a] Institute of Clinical Neuroscience and Medical Psychology, Heinrich-Heine-University, Medical Faculty, Universitaetsstraße 1, 40225 Duesseldorf, Germany
[b] Department of Neurology, Heinrich-Heine-University, Medical Faculty, Moorenstraße 5, 40225 Duesseldorf, Germany
[c] Institute for Experimental Psychology, Heinrich-Heine-University, Universitaetsstraße 1, 40225 Duesseldorf, Germany

HIGHLIGHTS

- STN-DBS improves active feedback learning in PD patients.
- In the absence of trial-by-trial feedback, more impaired patients benefit from DBS.
- STN-DBS tends to improve observational feedback learning.
- STN-DBS might similarly affect active and observational feedback learning.

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ABSTRACT

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) provides an effective treatment for Parkinson's disease (PD) motor symptoms. However, findings of effects on cognitive function such as feedback learning remain controversial and rare. The aim of the present study was to gain a better understanding of cognitive alterations associated with STN-DBS. Therefore, we investigated effects of STN-DBS on active and observational feedback learning in PD. 18 PD patients with STN-DBS and 18 matched healthy controls completed active and observational feedback learning tasks. Patients were investigated ON and OFF STN-DBS. Tasks consisted of learning (with feedback) and test phases (without feedback). STN-DBS improved active learning during feedback trials and PD patients ON (but not OFF) STN-DBS showed comparable performance patterns as healthy controls. No STN-DBS effect was found when assessing performance during active test trials without feedback. In this case, however, STN-DBS effects were found to depend on symptom severity. While more impaired patients benefited from STN-DBS, stimulation had no facilitating effect on patients with less severe symptoms. Along similar lines, the severity of motor symptoms tended to be significantly correlated with differences in active test performance due to STN-DBS. For observational feedback learning, there was a tendency for a positive STN-DBS effect with patients reaching the performance level of healthy controls only ON STN-DBS. The present data suggest that STN-DBS facilitates active feedback learning in PD patients. Furthermore, they provide first evidence that STN-DBS might not only affect learning from own but also from observed actions and outcomes.

1. Introduction

Decisions about how to respond optimally in daily life are often guided by learning from consequences of chosen actions. As revealed by functional neuroimaging in humans, learning processes underlying adaptation to the environment by linking events, actions and their consequences (e.g., positive/negative feedback) appear to involve dopaminergic midbrain structures as well as dopaminergic projection sites in the frontal cortex and dorsal and ventral striatum [1,2]. Single cell recordings in monkeys [3,4] as well as microelectrode recordings in PD patients undergoing deep brain stimulation (DBS) surgery [5] indeed showed that midbrain dopamine (DA) neurons code the discrepancy between expected and actual reward, suggesting a link between DA activity and feedback-based learning. Another fruitful line of feedback learning research has focused on patients diagnosed with PD, as the

* Corresponding author.
E-mail address: sarah.meissner@med.uni-duesseldorf.de (S.N. Meissner).

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0166-4328/

core, although not exclusive, pathology underlying this progressive neurodegenerative disease is the loss of dopaminergic neurons in the substantia nigra and DA depletion in striatal brain areas [6,7]. Although the clinical diagnosis of PD relies on the presence of cardinal motor symptoms such as bradykinesia, resting tremor, and rigidity, PD patients often exhibit also cognitive impairment across a wide range of functions [8,9]. With regard to feedback learning specifically, some studies indeed revealed impairments in PD patients, supporting the assumption that cortico-striatal circuits are involved in these learning processes [10,11]. Interestingly, when addressing effects of dopaminergic medication, learning deficits were often seen in patients ON but not OFF medication [12,13].

When PD motor symptoms cannot be adequately controlled with medication anymore, DBS of the subthalamic nucleus (STN) is a highly effective treatment [14]. However, influences of STN-DBS on cognitive function in general and feedback learning in particular are controversial [15–20]. As cognitive function in PD has been shown to have a substantial impact on quality of life [21], it is important to gain a better understanding of cognitive alterations associated with STN-DBS though. To date, only a few studies have investigated effects of STN-DBS on feedback learning in PD patients [18–20]. Frank and colleagues [18] found speeded responses in PD patients ON STN-DBS when confronted with decision conflict and interpreted this result as evidence that STN-DBS causes impulsive responding during high-conflict situations. But, the authors did not report STN-DBS effects on overall learning performance [18]. By contrast, van Wouwe et al. [19] compared accuracy values during feedback learning tasks in PD patients ON and OFF STN-DBS and reported facilitative effects of STN-DBS on learning, possibly due to a beneficial effect of STN-DBS on the dorsal striatum. However, the study did not entail the testing of healthy controls and could thus not make assertions about a potential learning impairment in PD patients relative to a healthy population. Another recent study assessed learning in a feedback-based classification task (weather prediction task) and did not observe significant STN-DBS effects on overall learning performance in PD patients [20]. But, when the complex cue structure was taken into account, there was evidence for better learning from feedback ON as compared to OFF STN-DBS during implicit (but not explicit) learning. These studies applied feedback-based paradigms that require to link own actions with action outcomes. However, feedback learning can also occur through observation of others by linking outcomes to actions of another person [22]. Neuroimaging studies addressing mechanisms of observational feedback learning suggest that – compared to active learning – dorsal parts of the striatum are less strongly involved [1,23]. Further evidence comes from a recent study reporting a negative learning bias for active but not observational feedback learning in PD patients OFF medication, probably due to the stronger DA depletion in the dorsal than ventral striatum in early PD [24]. Whether STN-DBS affects observational feedback learning has not been investigated.

Although there are first indications of enhanced active feedback learning in PD patients ON as compared to OFF STN-DBS due to a suggested modulatory effect of STN-DBS on the dorsal striatum [19], findings concerning effects of STN-DBS on feedback learning are still inconsistent [18–20]. In the light of these inconsistencies, the present study used a standard feedback learning task in PD patients ON and OFF STN-DBS and compared the patients' performance with the performance of healthy controls (HC). Furthermore, an observational variant of the task was applied which is suggested to involve the dorsal striatum to a lesser extent than the active variant. We assume that STN-DBS may improve feedback learning in PD patients, particularly for active learning.

2. Material and methods

2.1. Ethics statement

The local ethics committee approved the study (study no. 2849), which conforms to the Declaration of Helsinki.

2.2. Participants

Nineteen patients with idiopathic PD (10 akinetic-rigid, 9 mixed-type) and chronic bilateral STN-DBS as well as 18 HC participated in the study. Due to severe motor symptoms OFF STN-DBS, one patient was not able to complete the study, leaving the final $N_{PD} = 18$. PD patients, whose diagnosis was based upon the UK Parkinson's Disease Society Brain Bank Criteria [25], were recruited and tested at the Movement Disorder Center of the University Hospital Duesseldorf between August 2014 and April 2015.

Exclusion criteria were: dementia (Mattis Dementia Rating scale (MDRS; [26]) score ≤ 130), history of neurological disease other than PD, clinically relevant depressive symptoms (Beck Depression Inventory (BDI-II; [27]) score ≥ 18) or history of other psychiatric disorder, additional regular medication affecting the central nervous system, and tremor-dominant PD. The implantation of electrodes was carried out at the Department of Functional Neurosurgery and Stereotaxy of the University Hospital Duesseldorf. The surgical procedure has been described in more detail previously [28]. The DBS electrode placement of each patient was confirmed by stereotactic postsurgical computer tomography. Patients remained on their regular dopaminergic medication during the study with a mean daily levodopa equivalent dose (LED; [29]) of 715.96 ± 349.30 mg and were tested at a minimum of 3 months of STN-DBS treatment.

For each PD patient, an age- and gender-matched HC was recruited and tested. PD patients and HC did not differ significantly with respect to age, years of education, visual spatial (Block-Tapping-Test; [30]) and verbal short-term memory (Digit span; [31]), scores on the BDI-II, and the MDRS (all $p > 0.10$). All participants had normal or corrected-to-normal vision and were right-handed as determined by the Edinburgh Handedness Inventory [32]. Characteristics of patients and HC are shown in Table 1.

Patients and HC participated voluntarily and provided written informed consent prior to the study.

2.3. Learning tasks

All participants performed active and observational feedback learning tasks modified from a previously described task [33,34]. The observational variant, developed by Bellebaum and Colosio [35], was adjusted to closely match active learning. Both the active and observational task comprised three learning phases. Each of the three learning phases was immediately followed by a test phase. In both tasks, participants had to acquire stimulus–response–outcome associations in order to adjust their behavior. Stimulus presentation and response recording (correct responses, misses as well as reaction times) were controlled by Presentation® software (Neurobehavioral Systems, Inc.; http://www.neurobs.com).

2.3.1. Active learning from feedback

During learning phases, each trial began with the presentation of a fixation cross followed by the randomized presentation of one of six abstract Asian symbols (labelled A–F; ten trials per symbol yielding 60 trials in total per phase) in the center of a 17-inch screen of a laptop (Acer, Taipei, Taiwan). Together with the symbol, two red boxes were displayed at the bottom left and right portions of the screen, representing two response options. Participants then

Table 1
Characteristics of PD patients and healthy controls (HC).

Demographics and cognitive and affective screening measures

Group	n	Gender (female)	Age	Years of Education	MDRS	BDI-II	Digit Span	Block-Tapping-Test
PD	18	8	58.83 (±6.76)	16.06 (±4.77)	141.50 (±1.58)	6.39 (±4.93)	7.61 (±1.88)	4.67 (±0.91)
HC	18	8	58.61 (±6.70)	15.89 (±3.50)	141.78 (±2.04)	3.83 (±4.30)	8.11 (±2.08)	4.72 (±1.07)

Clinical characteristics of PD patients

									DBS parameters – left/right STN	
PD Patient	HY	Disease Duration (years)	DBS Duration (months)	Daily LED (mg) before surgery[a]	Daily LED (mg) at testing	UPDRS DBS-ON	UPDRS DBS-OFF	DBS-System (Electrode Model)	Amplitude	Pulse Width (μs)	Rate (Hz)
1	3	7	21	946.50	1213.00	23	47	MDT Activa® PC (3389)	2.8 V/1.7 V	60/60	125/125
2	3	9	3	1189.50	674.00	21	33	MDT Activa® PC (3389)	2.4 mA/2.4 mA	60/60	130/130
3	3	22	48	985.50	672.75	17	43	MDT Activa® RC (3389)	3.5 V/3.6 V	60/60	130/130
4	3	3	12	400.00	100.00	7	19	BSC Vercise™	2.9 mA/2.9 mA	60/60	130/130
5	3–4	20	24	1188.75	482.75	22	34	MDT Activa® PC (3389)	2.2 V/2.8 V	60/60	130/130
6	3	17	60	870.50	985.75	22	58	MDT Kinetra® (3389)	3.6 V/3.8 V	60/60	130/130
7	2	12	18	958.75	928.50	24	40	BSC Vercise™	2.4 mA/3.0 mA	30/30	130/130
8	2.5	13	60	1603.50	398.75	19	45	MDT Activa® PC (3389)	4.9 V/3.9 V	60/60	150/150
9	2	10	16	1057.00	714.25	10	23	MDT Activa® PC (3389)	2.5 V/2.6 V	60/60	130/130
10	2.5	8	7	678.75	500.00	28	45	BSC Vercise™	2.5 mA/2.5 mA	60/60	130/130
11	3	26	35	1856.00	555.00	21	52	MDT Activa® PC (3389)	2.4 V/2.8 V	60/60	130/130
12	1	8	3	960.00	742.00	20	33	BSC Vercise™	2.6 mA/2.2 mA	60/60	130/119
13	1	7	16	872.00	400.00	14	24	MDT Activa® RC (3389)	1.4 V/1.4 V	60/60	130/130
14	3	13	34	1189.00	1210.00	34	43	MDT Activa® PC (3389)	1.7 V/1.6 V	60/60	130/130
15	3	21	21	640.00	970.00	26	35	MDT Activa® PC (3389)	3.5 V/3.1 V	60/60	130/130
16	2	14	18	1587.50	490.50	15	33	BSC Vercise™	1.9 mA/1.9 mA	60/60	130/130
17	2.5	11	23	1520.00	1450.00	24	34	MDT Activa® PC (3389)	3.0 V/2.4 V	60/60	130/130
18	2.5	7	13	1205.00	400.00	19	31	BSC Vercise™	1.8 mA/1.8 mA	60/60	130/130
Mean (SD)		12.67 (±6.26)	24.00 (±17.23)	1095.86 (±370.19)	715.96 (±349.30)	20.33 (±6.35)	37.33 (±10.20)				

Demographics and screening measures are presented as group means (standard deviation (SD)). MDRS = Mattis Dementia Rating Scale; BDI-II = German version of the Beck Depression Inventory; HY = Hoehn & Yahr Scale. LED = levodopa equivalent dose; UPDRS DBS-ON = Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale motor score ON STN-DBS/ON medication; UPDRS DBS-OFF = Movement Disorder Society-Sponsored Revision of the UPDRS motor score OFF STN-DBS/ON medication; MDT = Medtronic (Medtronic Inc., Minneapolis, MN, USA); BSC = Boston Scientific (Boston Scientific. Corporation, Marlborough, MA, USA).

[a] LED at the last check-up before surgery.

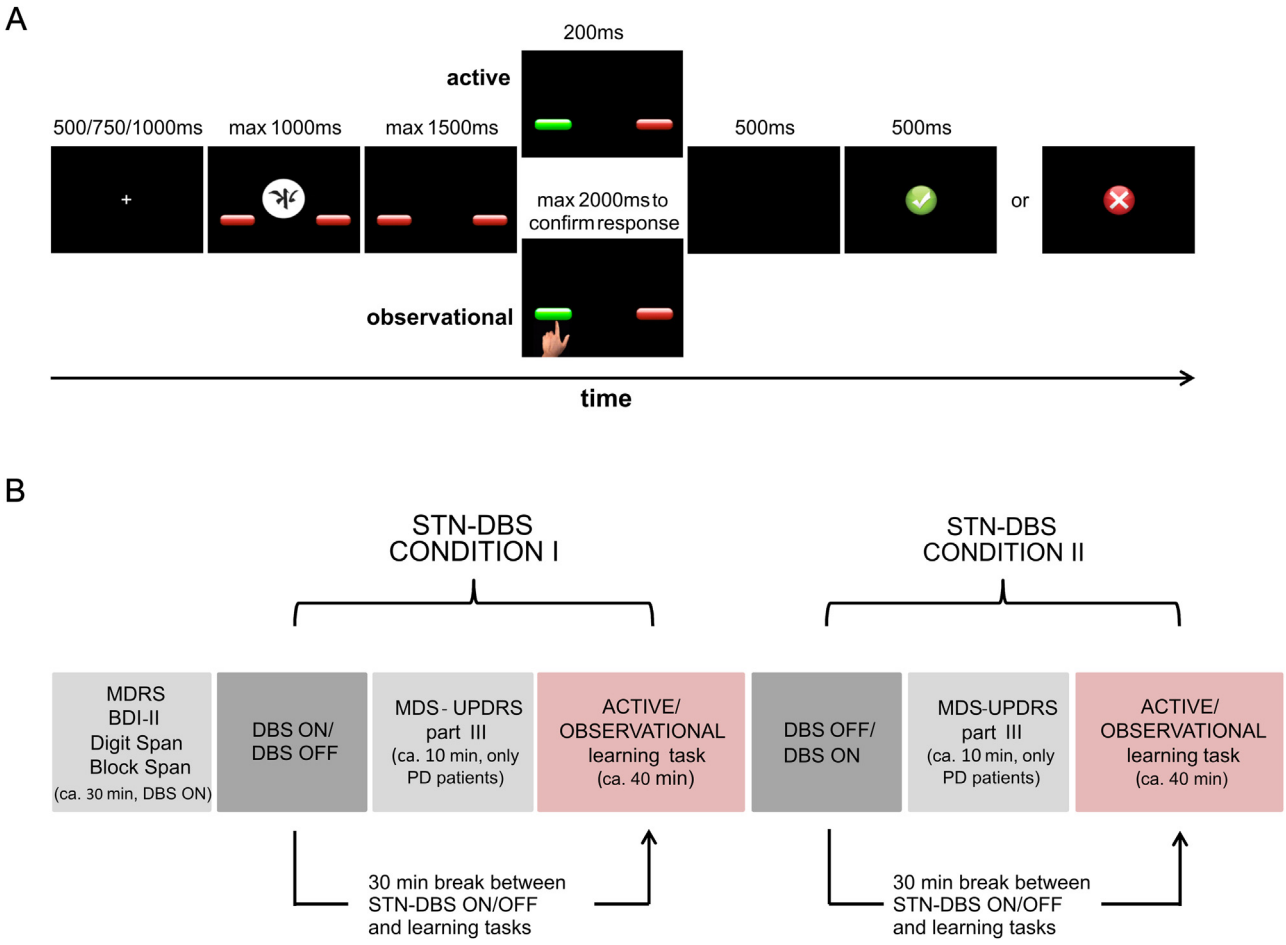

Fig. 1. Overview of the experimental procedure. (A) Sequence of events in one exemplary active (upper part) and observational learning trial (lower part). The central fixation cross which was followed by the presentation of one of six abstract Asian symbols was presented for a randomly varied duration to promote attentive performance. Note that active and observational test trials were similar to active learning trials with the exception that no feedback was provided. (B) Overview of the experimental procedure. Motor function as well as active and observational feedback learning was assessed ON and OFF STN-DBS. MDRS = Mattis Dementia Rating Scale; BDI-II = German version of the Beck Depression Inventory; MDS-UPDRS part III = motor part of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale; STN = subthalamic nucleus; DBS = deep brain stimulation.

had to respond to the presented symbol with a right or left button press (CTRL-keys on the keyboard) using their right or left index finger. Trials with response times > 2500 ms were coded as 'miss', and participants were visually instructed to respond faster. If the response occurred in time, the selected response was indicated by a change in color of the corresponding box on the screen from red to green. After each response, participants received either positive (green check mark) or negative (red cross mark) feedback. Stimulus timing in active learning trials is depicted in Fig. 1A.

For symbols A (left button correct) and B (right button correct), feedback was deterministic with valid feedback (either positive or negative depending on the selected response button) in 100% of the trials. Feedback following the responses to symbols C (left button correct), D (right button correct), E (left button correct) and F (right button correct) was probabilistic: Only 80% (symbols C and D) or 60% (symbols E and F) of the responses in these trials were followed by valid feedback. Responses in remaining trials were followed by invalid feedback. The different conditions will be referred to as 100%, 80%, and 60% contingency conditions. Since symbol-response-outcome associations were unknown to the participants, they had to learn by trial and error.

During test phases, the same symbols as during learning phases were presented (60 trials in total per phase). However, no feedback was provided.

2.3.2. Observational learning from feedback

The observational learning task involved the same stimuli and contingency conditions as the active learning task and differed from the active task only with regard to the learning phases: During observational learning trials (60 trials in total per phase), participants did not select the response to presented symbols themselves but observed responses and accompanying outcomes of another participant. For this purpose, performance patterns of actively learning subjects were recorded and used as templates for the observational learning task. Unknown to observers, one half of patients and HC observed the responses of patients, while the other half observed the responses of HC. The first patient observed the own responses. Each observed response was indicated by a picture of a hand below the selected response button as well as a change in color of the corresponding box on the screen from red to green (Fig. 1A). To see the corresponding positive or negative feedback, participants were instructed to confirm responses within 2000 ms by pressing the left or right CTRL-key with the left or right index finger, respectively. Responses outside of this time window were coded as 'miss', no feedback appeared and participants were asked to respond faster. If the wrong button was pressed, participants were prompted to respond correctly.

Observational learning was assessed during test phases without feedback, which were identical to the test phases used in the active variant of the task and thus consisted of 60 trials per phase as well.

2.4. Testing procedure

Patients and HC completed two parallel versions of each task on the same day. Patients, remaining on their regular dopaminergic medication, performed both tasks ON and OFF STN-DBS with a 30 min delay between tasks. Although longer delays would have been desirable regarding clinical effects, this was not acceptable for ethical reasons.

The order of STN-DBS status (ON vs. OFF) and tasks (active vs. observational) was counterbalanced and randomly determined among patients. Since all participants performed each learning task twice, four different versions of the task were used, each with a different set of symbols. The assignment of stimulus set to task and STN-DBS status was counterbalanced across patients. Each HC performed the tasks in exactly the same order as his/her matched patient. Prior to learning tasks, participants completed cognitive and affective screening measures (see Subsection 2.2) including verbal and visual short-term memory tasks to ensure that potential differences between patients and HC in feedback learning are not caused by deficits in short-term memory. To assess motor function in patients ON and OFF STN-DBS, the motor part of the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS III; [36]) was administered and videotaped (for MDS-UPDRS III scores see Table 1). Before starting the experimental phase of the learning tasks, participants performed eight practice trials and were instructed to pay attention to stimuli, responses and associated feedback to maximize the number of correct responses. For an overview of the experimental procedure see Fig. 1B.

2.5. Data analysis

Learning performance was quantified as percentage of correct responses in learning (active) and test phases (active and observational). For each participant, percentages of correct responses were measured and analyzed separately for each task, stimulation condition and learning/test phase. Since there was no effect of response side in preliminary analyses, data were pooled across hands for further analyses.

2.6. Statistical analyses

Statistical analyses were performed separately for active learning, active and observational test trials using IBM SPSS 22 (IBM Corporation, Armonk, NY, USA). First, Gaussian distribution of data was checked by means of Shapiro-Wilk tests revealing no evidence of significant deviations from Gaussian distribution. To investigate effects of STN-DBS on learning, mixed-design analysis of variance (ANOVA) on the percentage of correct responses in active learning trials with *stimulation* (ON vs. OFF), *learning phase* (1 vs. 2 vs. 3) and *feedback contingency* (100% vs. 80% vs. 60) as within-subjects factors and *group* (HC vs. PD) as between-subjects factor was conducted. Although HC did not receive STN-DBS, their data was analyzed accordingly to parallel the stimulation order of the matched patient [37]. The same analysis strategy was applied for active and observational test trials. In case of violations of sphericity assumptions, the Greenhouse-Geisser correction was applied. To resolve interactions, *post hoc* tests were calculated by means of two-tailed *t*-tests.

To estimate possible effects of symptom severity, patients were divided into groups with rather mild (n = 9; 5 akinetic-rigid) vs. severe symptoms (n = 9; 4 akinetic-rigid) based on a median split on MDS-UPDRS III scores (OFF STN-DBS; m = 34.5). Mixed-design ANOVAs involving *symptom severity* (low UPDRS score vs. high UPDRS score) as between-subjects factor and the within-subjects factors outlined above were conducted for active learning, active and observational test trials. Due to the small sample size of subgroups, these ANOVAs have to be considered as exploratory. To further elucidate possible associations between symptom severity and feedback learning performance, we calculated additional Pearson's correlation coefficients. To this end, learning and test performance difference scores (percentage of correct responses STN-DBS ON – percentage of correct responses STN-DBS OFF; pooled for all phases and contingencies) for active learning, active test and observational test phases were computed for each participant and correlated with individual MDS-UPDRS III scores OFF STN-DBS. Bonferroni corrections for multiple comparisons were applied.

3. Results

Only main effects or interactions involving the factors *stimulation* and/or *group* are reported.

3.1. Active learning trials with feedback

Mixed-design ANOVA with *stimulation* (ON vs. OFF), *learning phase* (1 vs. 2 vs. 3), *feedback contingency* (100% vs. 80% vs. 60%) and *group* (PD vs. HC) as factors revealed a trend towards poorer overall performance in patients ($F_{[1,34]} = 3.51$; $p = 0.07$). The *stimulation* by *group* interaction was significant ($F_{[1,34]} = 4.36$; $p < 0.05$). *Post hoc t*-tests revealed that while patients ON STN-DBS did not differ significantly from HC ($p > 0.40$), OFF STN-DBS they performed significantly worse than HC ($t(34) = 2.52$; $p < 0.05$). Additionally, learning performance was significantly better ON as compared to OFF STN-DBS in patients ($t(17) = 2.19$; $p < 0.05$) whereas in HC no significant difference between measurements was found ($p > 0.30$; Fig. 2A). No other main effect or interaction involving the factors *stimulation* and/or *group* reached significance (all $p > 0.10$). Active learning performance (ON and OFF STN-DBS) for patients and HC for each phase and contingency condition is depicted in Supplementary Fig. S1A and S1B.

3.2. Active test trials without feedback

Mixed-design ANOVA did not yield significant main effects and interactions involving the factors *group* and/or *stimulation* (all $p > 0.10$), indicating no significant difference in overall accuracy between HC and patients regardless of STN-DBS status (Fig. 2B).

Performance accuracy in active test trials (ON and OFF STN-DBS) for patients and HC for each phase and contingency condition is depicted in Supplementary Fig. S1C and S1D.

3.3. Observational test trials without feedback

Mixed-design ANOVA did not yield a significant main effect for *group* ($p > 0.10$). However, the *stimulation* by *group* interaction approached significance ($F_{[1,34]} = 3.30$; $p = 0.07$). In order to see whether the overall pattern of findings was similar to that observed in active learning trials, we decided to further explore this effect, although we realize that the interaction only approached significance. We therefore conducted *post hoc* tests which revealed that, similar to active learning, patients OFF STN-DBS showed poorer performance than HC ($t(34) = 2.32$; $p < 0.05$), whereas ON STN-DBS, they reached a performance level comparable to HC ($p > 0.40$; see Fig. 2C). No other main effect or interaction involving *stimulation* and/or *group* reached significance (all $p > 0.10$).

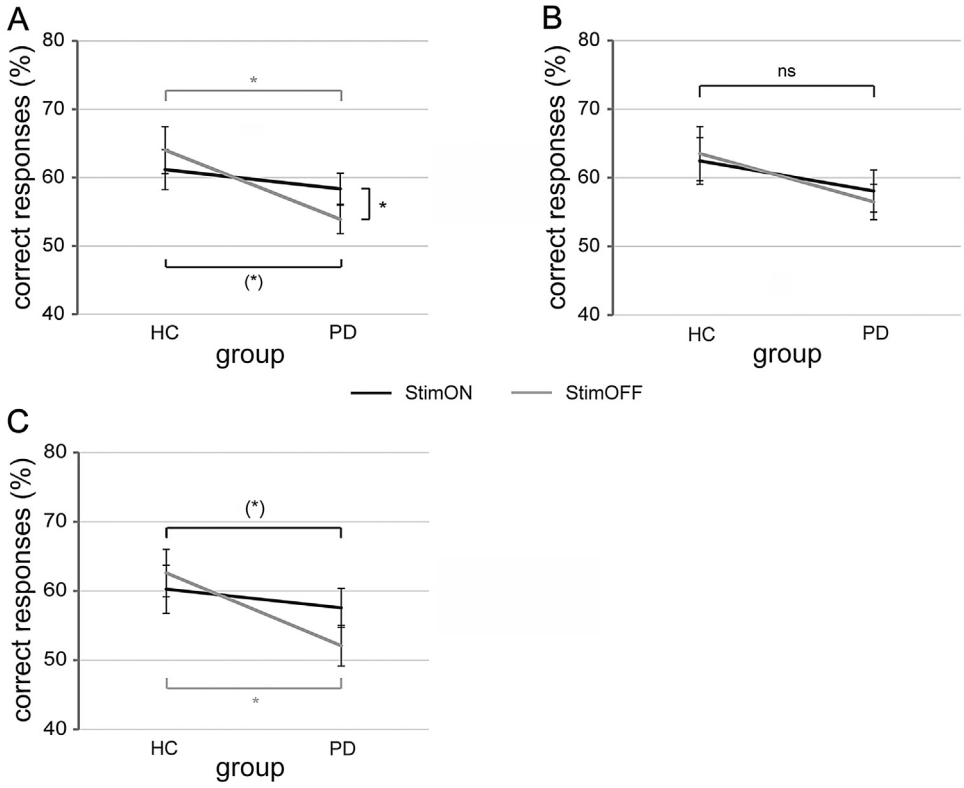

Fig. 2. Learning and test phase performance for active and observational learning tasks. Mean percentage of correct responses in patients (ON vs. OFF STN-DBS) and HC in active learning (A), active test (B), and observational test trials (C). Error bars indicate standard error of the mean (SEM); $^{*}p < 0.05$; $(^{*})p = 0.07$.

Performance accuracy in observational test trials (ON and OFF STN-DBS) for patients and HC for each phase and contingency condition is depicted in Supplementary Fig. S1E and S1F.

3.4. Relation between symptom severity and feedback learning

Analyses for active learning and observational test performance failed to yield significant main effects or interactions involving the factor *symptom severity*. Therefore, the following results relate to active test trials only. Although there was no significant main effect of *symptom severity* ($p > 0.38$), a significant *symptom severity* by *stimulation* interaction emerged ($F_{[1,16]} = 4.70$; $p < 0.05$). *Post hoc paired t*-tests revealed that more severely impaired patients performed better during active test trials ON as compared to OFF STN-DBS ($t(8) = 2.32$; $p < 0.05$). In patients with less severe symptoms this comparison was not significant ($p > 0.10$; see Fig. 3A). To rule out potential confounding effects of disease duration or dopaminergic medication, we compared PD subgroups with respect to LED and disease duration but found no significant differences ($p > 0.14$).

Along similar lines, additional correlational analyses revealed that MDS-UPDRS III scores OFF STN-DBS tended to be positively correlated with active test performance difference scores (STN-DBS ON – STN-DBS OFF; $r = 0.53$; $p = 0.06$; Fig. 3B). This further suggests that the severity of motor symptoms is associated with the amount of improvement (or worsening as indicated by negative difference scores) on active test trials due to STN-DBS. All other correlations failed to reach significance (all $p > 0.73$).

3.5. Basic motor performance and its relation to feedback learning performance

To exclude the possibility that motor improvement due to STN-DBS contributed to the observed differences in feedback learning performance, we performed additional analyses on reaction times as well as number of misses which were recorded throughout the learning tasks. In a first step, reaction times were averaged across phases and contingency conditions for each stimulation condition for active learning as well as for active and observational test phases in each participant. Additionally, we calculated the number of misses for each stimulation condition for active learning and active and observational test phases. Mixed-design ANOVAs on mean reaction times and number of misses were conducted for active learning and active and observational test phases with *stimulation* (ON vs. OFF) and *group* (PD vs. HC) as factors. With regard to reaction times, analyses did not yield significant main effects or interactions involving the factors *group* and/or *stimulation* (mean reaction times in ms ± SEM, ON STN-DBS: active learning trials in HC: 753.64 ± 28.84; PD: 774.68 ± 26.85; active test trials in HC: 747.85 ± 22.41; PD: 747.53 ± 28.05; observational test trials in HC: 761.28 ± 29.57; PD: 783.20 ± 38.70; all $p > 0.08$; OFF STN-DBS: active learning trials in HC: 747.36 ± 30.49; PD: 782.46 ± 31.12; active test trials in HC: 726.86 ± 22.03; PD: 775.00 ± 37.00; observational test trials in HC: 778.09 ± 32.02; PD: 820.22 ± 33.37; all $p > 0.08$), indicating no significant difference in reaction times between HC and patients regardless of STN-DBS status. Analyses on number of misses revealed a significant main effect for group for active learning ($F_{[1,34]} = 7.33$; $p < 0.05$) as well as for active ($F_{[1,34]} = 5.74$; $p < 0.05$) and observational test trials ($F_{[1,34]} = 7.27$; $p < 0.05$) with HC showing less misses than PD patients (mean ± SEM: active learning trials in HC: 0.58 ± 0.24; PD: 3.06 ± 0.88; active test trials in HC: 0.61 ± 0.33; PD: 2.39 ± 0.66;

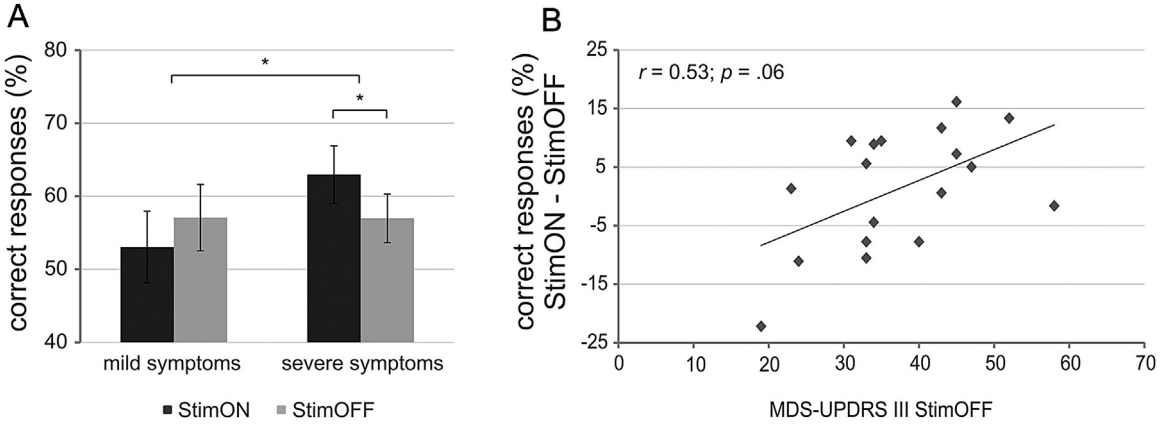

Fig. 3. Symptom severity and its relation to active feedback learning. (A) Mean percentage of correct responses in patients with rather mild vs. severe symptoms (STN-DBS ON and OFF) in active test trials. (B) Correlation between active test performance differences (percentage of correct responses STN-DBS ON – percentage of correct responses STN-DBS OFF; pooled for all phases and contingencies) and symptom severity indicated by MDS-UPDRS III scores OFF STN-DBS in PD patients. Error bars indicate SEM; $^{*}p < 0.05$.

observational test trials in HC: 1.28 ± 0.33; PD: 4.33 ± 1.08). However, there was no significant effect involving the factor *stimulation*, neither for active learning nor for active and observational test trials (all $p > 0.18$).

To further examine whether changes in motor performance on the MDS-UPDRS III due to the manipulation of STN-DBS are associated with changes in learning task performance, we calculated additional MDS-UPDRS III difference scores (STN-DBS OFF – STN-DBS ON) and correlated these scores with active learning as well as active and observational test performance difference scores (percentage of correct responses STN-DBS ON – percentage of correct responses STN-DBS OFF) by calculating Pearson's correlation coefficients. We found no significant correlations between changes in motor performance and changes in learning/test performance due to STN-DBS, neither for the active nor for the observational task (all $p > 0.60$).

4. Discussion

Although improvement of PD motor symptoms by means of STN-DBS is well established, the effect on cognitive abilities including feedback learning is controversial [15,17–20,38]. To achieve a clearer understanding of cognitive alterations associated with STN-DBS, the present study investigated STN-DBS effects on active and observational feedback learning by examining PD patients ON and OFF STN-DBS and comparing their performance with that of HC. Supporting our hypothesis, we found a facilitating effect of STN-DBS on active learning in PD patients. In active test trials without feedback, a similar STN-DBS effect was found for more impaired patients. They benefited from STN-DBS and showed improved task performance, while STN-DBS had no facilitating effect on patients with less severe symptoms. Along similar lines, the severity of motor symptoms tended to be significantly correlated with differences in active test performance due to STN-DBS. For observational feedback learning, the data may hint at a facilitating effect of STN-DBS on task performance.

4.1. Effects of STN-DBS on active feedback learning

The present data suggest a facilitating effect of STN-DBS on active feedback learning in PD, replicating data from van Wouwe and colleagues [19] who further suggested that this facilitation might be associated with a beneficial effect of STN-DBS on the dorsal striatum. The present findings extend these results by showing that PD patients OFF STN-DBS exhibited poorer learning performance than HC, whereas ON STN-DBS they achieved the same performance level as HC. This might suggest that STN-DBS helps to reach "normal" levels of dorsal striatum function, at least for the purpose of feedback-based learning and for the patients with clinical characteristics as those in the present study. Wilkinson and colleagues [20] failed to find improved overall learning performance in PD patients treated with STN-DBS. However, they applied the weather prediction task. Although this task is also based on feedback processing, it involves a stimulus structure that is more complex than the one used in the present study. Thus, crucial differences in task design make the comparison of results difficult.

In contrast to learning trials with feedback, we found no STN-DBS effect on active test trials without feedback, suggesting that STN-DBS may affect the ability to learn and to apply what has been learned differently. Interestingly, in the context of feedback learning, partially distinct roles of the striatum and DA for the learning process itself and for the application of the learned associations in the sense of selection of previously rewarded responses have been proposed [39], which might provide an explanation why the result patterns for learning and test trials were not exactly identical. Furthermore, additional analyses indicated that effects of STN-DBS on test performance varied with symptom severity. Whereas more impaired patients benefited from STN-DBS with regard to performance level – and thereby showed a comparable pattern as in trials with feedback – less impaired patients did not improve ON STN-DBS. These results are further supported and even extended by correlational analyses which revealed that the difference in active test performance between STN-DBS states (STN-DBS ON – STN-DBS OFF) tended to be significantly correlated with MDS-UPDRS III scores OFF STN-DBS. This suggests that with increasing symptom severity, PD patients showed increasingly better task performance ON relative to OFF STN-DBS (and vice versa as indicated by negative difference scores in some of the less impaired PD patients). We realize that these analyses – especially with regard to median split data – have to be interpreted with caution due to the small sample size. Nevertheless, we deem these results as worth reporting, especially as associations between motor symptoms and feedback learning in PD patients with STN-DBS have been reported previously [20]. A systematic investigation of these modulatory influences and underlying mechanisms in larger samples is needed to disentangle STN-DBS treatment effects on cognitive function in general and feedback learning in particular.

4.2. Effects of STN-DBS on observational feedback learning

To our knowledge, this is the first study investigating STN-DBS effects on observational feedback learning. We realize that the interaction between *stimulation* and *group* in the present study only approached significance. Nevertheless, we decided to conduct exploratory *post hoc* tests to further disentangle whether this interaction was driven by similar tendencies as observed during active learning. *Post hoc t*-tests indeed revealed that PD patients ON (but not OFF STN-DBS) reached the performance level of HC, providing first evidence of a facilitating effect of STN-DBS on observational feedback learning. Since ventral striatal structures are suggested to be involved in observational feedback learning [1,23], the present findings are in line with recent results suggesting that STN-DBS improves cognitive function sensitive to ventral striatal function and connected areas [17]. A recent study reported similar observational performance patterns in early-stage PD patients and HC [24]. As our study investigated more severely affected patients in advanced stages of the disease, the present data support the hypothesis that the ventral striatum remains well supplied of DA in earlier stages of the disease but becomes impaired in advanced PD [6]. Similarly, it has been shown that cognitive function depending on the ventral striatum are impaired in late but not early PD [37], supporting this interpretation. As our results regarding observational task performance only tended to be significant, they have to be considered as rather hypothesis-generating and need further investigation and replication in future studies.

4.3. Limitations

Firstly, we realize that with the current design, we can only make clear statements about short-term effects of STN-DBS manipulation. Furthermore, patients remained on their regular dopaminergic medication throughout the study. As there are studies reporting active feedback learning deficits in medicated but not unmedicated PD patients [12] as well as detrimental effects of dopaminergic medication on tasks involving the striatum [40], dopaminergic medication may have – at least partly – contributed to the learning impairment observed in PD patients OFF STN-DBS. With the present design, it is not possible to rule out interfering effects of medication and STN-DBS treatment. However, as the study lasted several hours per patient we didn't regard it as reasonable to measure patients also OFF medication.

Secondly, observed effects – especially with regard to subgroup analysis – have to be interpreted with caution due to small sample size. Nevertheless, even if this analysis is considered as rather exploratory, additional correlational analyses support these findings. Thus, modulatory influences of symptom severity on STN-DBS effects on feedback learning can be seen as first evidence.

Furthermore, we cannot completely rule out that the improvement of motor symptoms due to STN-DBS contributed to the observed improvement on active and observational feedback learning tasks. However, in additional analyses we found no significant differences in reaction times and number of misses between ON and OFF STN-DBS states, neither for active, nor for observational learning tasks. Additionally, motor improvement on the MDS-UPDRS III due to STN-DBS was not significantly associated with performance differences between STN-DBS states in active and observational learning tasks. Thus, we assume that observed facilitating effects of STN-DBS on feedback learning are at least to some extent independent of motor improvement due to STN-DBS.

4.4. Conclusion

The data indicate that STN-DBS used for treating PD motor symptoms also has facilitating effects on important aspects of cognitive function investigated in this study. PD patients benefited from STN-DBS during active feedback learning where links between own actions and outcomes were established. When it came to application of actively learned behavior, only more severely impaired patients improved with STN-DBS. Moreover, the study provides first evidence that STN-DBS might facilitate not only active but also observational feedback learning.

Conflict of interest

M.S. received honoraria for consultancy by Teva, Novartis, Medtronic, AbbVie, St. Jude Medical, and Meda. B.P. was supported by a grant from the Deutsche Forschungsgemeinschaft (DFG; PO 806/3-1). There was no influence of these sources on collection, analysis and interpretation of the data. There was also no involvement in the writing of the report and the decision to submit the article for publication.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2016.06.062.

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