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ADVANCES IN NEURODEGENERATIVE AND PSYCHIATRIC IMAGING SPECIAL FEATURE: REVIEW ARTICLE

Towards understanding neural network signatures of motor skill learning in Parkinson's disease and healthy aging

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ABSTRACT

In the past decade, neurorehabilitation has been shown to be an effective therapeutic supplement for patients with Parkinson's disease (PD). However, patients still experience severe problems with the consolidation of learned motor skills. Knowledge on the neural correlates underlying this process is thus essential to optimize rehabilitation for PD. This review investigates the existing studies on neural network connectivity changes in relation to motor learning in healthy aging and PD and critically evaluates the imaging methods used from a methodological point of view. The results indicate that despite neurodegeneration there is still potential to modify connectivity within and between motor and cognitive networks in response to motor training, although these alterations largely bypass the most affected regions in PD. However, so far training-related changes are inferred and possible relationships are not substantiated by brain–behavior correlations. Furthermore, the studies included suffer from many methodological drawbacks. This review also highlights the potential for using neural network measures as predictors for the response to rehabilitation, mainly based on work in young healthy adults. We speculate that future approaches, including graph theory and multimodal neuroimaging, may be more sensitive than brain activation patterns and model-based connectivity maps to capture the effects of motor learning. Overall, this review suggests that methodological developments in neuroimaging will eventually provide more detailed knowledge on how neural networks are modified by training, thereby paving the way for optimized neurorehabilitation for patients.

INTRODUCTION

Parkinson's disease (PD) is a multisystem neurodegenerative disorder affecting mainly the basal ganglia leading to a range of motor and non-motor symptoms.[1] Several studies have shown that PD patients display altered brain connectivity patterns compared to healthy elderly, which underlies some of their motor symptoms.[2–5] Patients typically display a disconnection of the striato-supplementary motor area (SMA) pathway that likely contributes to their bradykinesia,[3,6] while tremor may be the result of a pathological interaction between the basal ganglia and the cerebellothalamic circuit.[3,7,8] PD patients also show altered resting state connectivity in the subthalamic nucleus network (STN) while on their medication, displaying, *e.g.* attenuated coupling between the STN and key executive regions compared to controls,[9] as well as in the striatofrontal pathways, particularly in patients with freezing of gait.[2] Dopaminergic treatment alleviates symptoms and reinstates some degree of sensorimotor control,[10,11] as well as partially normalizes neural connectivity patterns.[2,4,12,13] Nevertheless, treatment effects fade with time, requiring supplementary therapies. Over the past few years, evidence has emerged that neurorehabilitation can reduce functional disability and improve mobility in PD.[14–16] We define neurorehabilitation as motor learning or other modes of training aimed to instigate functional improvements after neural injury and/or long-term neurological damage. The influence of rehabilitation on non-motor symptoms, such as depression, apathy or anxiety, is currently less clear for PD and requires further investigation.[17,18] Hence, for this review, we focus on motor learning and its influence on motor performance only.

Motor learning is defined as the acquisition and optimization of a series of inter-related movements, resulting in more accurate and efficient performance.[19] Consolidated motor learning is characterized by three crucial components: (i) transfer to untrained tasks; (ii) resistance to distraction, *i.e.* automatization; and (iii) retention after a period without practice.[20,21] An important distinction exists between short- and long-term training studies. The former consist of a single training session, sometimes followed by a 24h-retention measurement (offline consolidation). The latter includes multiple training sessions over a period of weeks. In young healthy adults, it was shown that during sustained motor learning a shift in activation occurs from the anterior to posterior striatum with time, indicating consolidation of learning.[22] Due to dopamine depletion, people with PD experience dysfunction of various regions within the striatum, whereby the posterior striatum is particularly affected in contrast to the relatively spared anterior striatum.[23] This would explain why people with PD continue to display difficulties with motor memory consolidation and especially with retention of practice effects, while initial learning is preserved.[24–27] To compensate for the loss of the posterior striatum, PD patients rely more on anterior circuits.[28] Hence, behavioral data can show improvements indicating consolidation, whilst PD patients may still utilize attentional circuits to boost performance. Therefore, brain–behavior outcomes are indispensable to distinguish this "pseudo consolidation," thus allowing to check against the "normal" or near-normal shifts of recruitment inherent to consolidation. Although recent work revealed that motor learning can trigger plasticity-related changes in brain activation and connectivity in PD patients,[29–34] there is a great heterogeneity in PD in terms of disease and symptom severity. As a result not all patients respond similarly to training programs,[25,35,36] highlighting a need for adequate neural circuit-based predictors of motor learning to forecast the effects of neurorehabilitation.

Over the past years, many task-based neuroimaging studies have been conducted which focused on identifying the locality of the BOLD-response changes as a result of motor learning. Yet, interpretation of these studies was hampered by several difficulties: (i) lack of control groups with placebo interventions[37]; (ii) learning-related changes in performance, clouding a clear understanding of the neural correlates; (iii) lack of comparability of difficulty level of learning tasks amongst groups; and (iv) lack of statistical power. This, together with methodological developments in the field of neuroimaging, formed the impetus to shift the focus from examining brain activation patterns towards studying connectivity between brain regions, *i.e.* either (i) anatomical connectivity, a pattern of anatomical links between areas; (ii) functional connectivity, a pattern of statistical dependencies between regions; or (iii) effective connectivity, the causal interactions between regions. With these developments in network analysis, the enormous complexity of the human brain is currently being mapped in both health and disease, including PD. This intricacy is challenged even further when time-dependent interventions need to be captured on top of the baseline status, as is the case in neurorehabilitation studies.

The current review has three aims. First, it will provide an overview of the known changes in neural networks involved in motor learning in healthy elderly adults and PD patients and identify the methodological weaknesses of current approaches. Second, it will explore whether connectivity patterns could serve as predictors for therapy response. Finally, we will discuss and propose future directions on how to use brain imaging to further the field of neurorehabilitation.

METHODOLOGICAL APPROACH TO THIS REVIEW

For our primary aim, we performed a PubMed search looking into motor-learning related connectivity changes in both healthy aging and PD. For our exploratory question, we additionally selected studies using connectivity to predict training-related effects involving mostly young healthy subjects. We combined motor-learning related search terms (motor learning, motor sequence learning, consolidation, automaticity, retention, motor rehabilitation or exercise therapy) with the term "connectivity" and either "Parkinson's disease," "aging" or "predict(ion)" (see Supplementary Table 1). We only included papers that: (i) included either functional or effective connectivity; (ii) included at least a baseline and post-training task-based or resting-state MRI or magnetoencephalograpy/electroencephalograpy (MEG/EEG) measurement; (iii) concerned a motor training intervention and not speech therapy, cognitive training or motor adaptation; (iv) involved either short- or long-term training; and (v) included a minimum of 10 subjects in each group. We excluded studies performed in animals and did not include studies on changes in anatomical connectivity as a result of motor training due to a current lack thereof.

The literature search resulted in 319 articles, of which 12 papers studying changes in connectivity in relation to motor learning or other forms of motor training were selected. After screening of references and citations, four more papers were included. Overall, the selection included five papers on aging, five papers on PD and six on prediction. For an overview, see Figure 1.

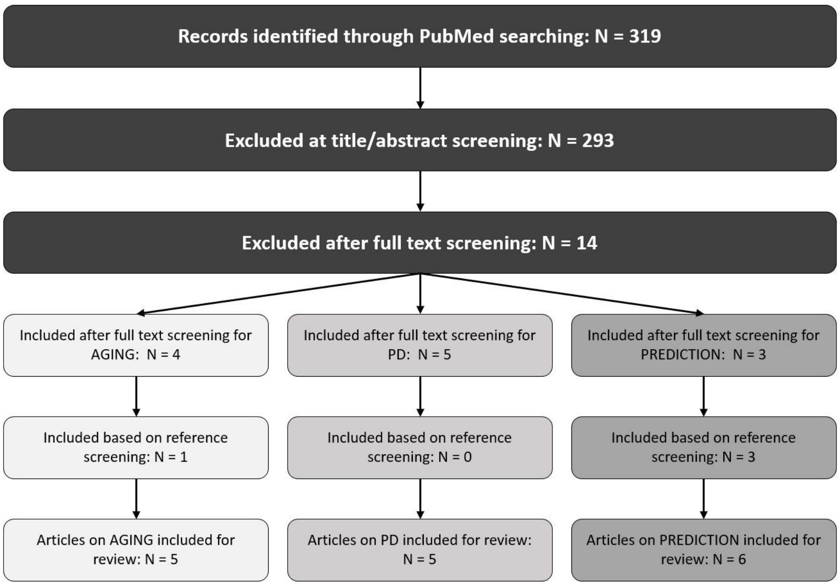
EFFECTS OF MOTOR LEARNING ON CONNECTIVITY

For our main question, we included five articles in healthy elderly adults and five in PD (Figure 1).

Healthy elderly adults

In healthy adults, two motor learning studies were found (Table 1A), both while in resting state, though one using MEG[39] and the other MRI.[38] Although the studies looked at different types of tasks, *i.e.* finger tapping[39] and bimanual tracking,[38] both found a differential pattern of changes in resting-state sensorimotor connectivity as a result of short-term training: while connectivity increased in young adults, decreases were detected in older adults.[38,39] The authors hypothesized that the age-related decrease in within-network connectivity was an indirect result of increased interactions between the motor network and other networks as a compensatory strategy to optimize task performance.[38,40] Brain–behavior correlation analysis further showed differences between young and older adults. While faster learning was associated with increased connectivity between primary sensorimotor cortex and the SMA in young adults, it was related to decreased connectivity in older adults (Table 2A).[39] The increased connectivity in young adults was therefore interpreted as facilitating motor learning. In older

Figure 1. Overview of the literature search.



adults, faster learning was associated with a decreased necessity for compensatory circuits.[39]

Solesio-Jofre et al further investigated changes after 2 weeks of bimanual tracking practice, revealing no age-related modulations of long-term practice.[38] Both groups increased resting-state connectivity within the right hemisphere, possibly reflecting greater interactions amongst motor areas to control the less skilled non-dominant hand in this bimanual task.

In addition, one short-term[41] and two long-term[42,43] studies investigated the influence of aerobic exercise on functional connectivity using resting state fMRI. Weng et al showed that a single session of 30 min of aerobic exercise enhanced the integration of attention and executive networks in both young and older adults compared to passive exercise.[41] However, the increase in functional connectivity was greater in older adults, suggesting a restoration of connections that decreased with aging.[41] On the long-term (≥12 weeks), similar increases in functional connectivity within the default mode network (DMN) and between the DMN and sensorimotor network were found in healthy elderly.[42,43] McGregor et al further showed that these changes were associated with improved motor performance.[43] While these studies did not incorporate motor learning *per se*, it was shown that aerobic exercise can boost motor learning capacities in both older people and PD patients.[29,44] This would argue in favor of investigating the combined effects of aerobic exercise and motor learning on neural networks in the future.

People with Parkinson's disease

People with PD show alterations in neural network connections compared to healthy controls during performance of motor tasks of different complexities.[2,3,5] In brief, strengthened corticocerebellar connectivity, increased connections between the anterior putamen and cortical motor regions and increased connectivity of the sensorimotor network with the attentional networks were found. These abnormalities have been suggested to signify top-down compensatory motor control patterns to overcome altered motor automaticity in the affected posterior corticostriatal circuits.

As for motor learning of finger sequences, a short-term task-based fMRI study by Wu et al revealed that PD patients OFF medication and healthy elderly controls used different brain networks to achieve automaticity of the task (Tables 1B and 2B).[33] In healthy elderly, reaching automaticity was accompanied by strengthening connectivity within the motor network, specifically with the posterior putamen, in combination with a decreased involvement of the attentional networks. Though PD patients were able to reach a degree of automaticity, they displayed a sustained need for attentional control. Connectivity within the motor network also did not increase to a similar extent as in healthy elderly. In a long-term task-based fMRI study, Wu et al further investigated the influence of attention on learning to automatically perform finger movements, practiced over several days (Tables 1B and 2B).[34] After learning and unlike controls, PD patients showed continued connectivity with the dorsolateral prefrontal cortex of the attention network. Interestingly, connectivity with the posterior putamen did not increase in PD, underscoring the significance of basal ganglia dysfunction for automaticity deficits. Once automaticity was achieved, all participants were asked to reattend to the task. While this affected the global attentional and cortical motor networks of patients and controls similarly, this was not the case for the striatal connections. In health elderly, the striatal connections remained stable. In PD, however, connectivity from both anterior and posterior putamen to the primary motor cortex decreased inducing a shift back from the automatic to attention controlled mode.

More recently, Manuel et al looked into short-term changes in resting-state connectivity using EEG after practicing mirror drawing, a task appealing more to sensory integration than Wu et al.'s paradigms (Table 1B).[45] Also, contrary to the studies by Wu et al, this study tested patients ON medication. They found

Table 1. Studies on brain connectivity changes as a result of motor learning in healthy aging and Parkinson's disease

Author	Participants	Design	Task & Training	Training intensity	Imaging method	Connectivity measure
A. Aging						
Mary *et al*. 2017[38]	14 YA 14 OA	Case-control	Task & training: Finger tapping	Short-term: 70 trials in learning phase + 50 trials in retest phase	rsMEG	Seed-based correlation
Solesio-Jofre *et al*. 2018[39]	23 YA 21 OA	Case-control	Task & training: Bimanual tracking	Short-term: 144 trials across six runs Long-term: 1 h/day, 5x/2 weeks	rsMRI	Seed-based correlation
Weng et al. 2016[40]	12 YA 13 OA	Case-control	Task: / Training: Active OR passive cycling	Short-term: 30 min	rsMRI	Seed-based correlation based on gICA
Flodin et al. 2017[41]	22 OA aerobic 25 OA stretch	RCT	Task: / Training: Aerobic exercise OR stretching and toning	Long-term: 30–60 min/day, 3x/week for 6 months	rsMRI	Seed-based correlation + Graph theory +ICA + NBS+MVPA
McGregor et al. 2018[42]	19 OA aerobic 18 OA balance	RCT	Task: / Training: aerobic spin intervention OR balance/strength training	Long-term: 20–45 min/day, 3x/week for 12 week	rsMRI	Seed-based correlation
B. Parkinson's disease						
Wu *et al*. 2010[33]	12 OA 12 PD-OFF	Case-control	Task & training: Finger tapping	Short-term: Until performed from memory 10 times in a row without error	Task-based fMRI	PPI
Wu *et al*. 2015[34]	22 OA 22 PD-OFF	Case-control	Task & training: Visuomotor association	Long-term: 30 min x 4/day, until reaching automaticity (max 5 days)	Task-based fMRI	Granger causality
Shah *et al*. 2016[43]	27 PD-OFF: 14 voluntary 13 forced	RCT	Tasks: continuous fingertip force tracking task & finger tapping Training: Cycling at voluntary OR forced speed	Long-term: 1 h/day, 3x/week, for 8 weeks	Task-based fMRI fcMRI rsMRI	Seed-based correlation
Nackaerts *et al*. 2018[44]	27 PD-ON: 13 writing 14 stretch	RCT	Task: Writing Training: Writing OR stretch (placebo)	Long-term: 30 min/day, 5x/week, for 6 weeks	Task-based fMRI	DCM
Manuel *et al*. 2018[45]	10 OA 9 PD-ON	Case-control	Task & training: Mirror drawing	Short-term: four trials on day 1 and 4 trials on day 2	rsEEG	Imaginary coherence

DCM = dynamic causal modeling; EEG = electroencephalography; MEG = magnetoencephalograpy; MVPA = multivariate pattern analysis; NBS = network based statistics; OA = older adults; PD = Parkinson's disease; PPI = psychophysiological interactions; RCT = randomized controlled trial; YA = young adults; (f)MRI = (functional) magnetic resonance imaging; fcMRI = MRI, during which the subject stimulus is constant throughout the entire acquisition[43]; (g)ICA = (group) independent component analysis; rs = resting state.

increased connectivity of the left parietal cortex with the rest of the cortex in PD compared to healthy elderly, suggesting that learning induced a greater reliance on sensory integration. However, this increased connectivity of the left parietal cortex immediately after learning was associated with worse offline consolidation 24 h later (Table 2B). Although increased connectivity allowed patients to achieve similar initial learning, using these compensatory circuits likely prevented subsequent consolidation of the motor trace.

Only two connectivity studies looked into the effects of long-term motor training in PD, involving several weeks of practice

Table 2. Key findings and interpretation

Author	Key findings	Brain–behavior relation
A. Aging		
Mary *et al.* 2017[38]	In YA short-term rsFC of sensorimotor network increased, while it decreased in OA	• In YA faster learning was correlated with increased post-training rsFC with the SMA, while the opposite was observed in OA • Post-training changes in rsFC were correlated with offline improvement in both YA & OA
Solesio-Jofre *et al.* 2018[39]	• In YA short-term rsFC of sensorimotor network increased, while it decreased in OA • Both YA & OA exhibited increased sensorimotor-related long-term rsFC changes	Increases in the inter hemispheric connection strength across the 2 week period were correlated with greater motor improvement in both YA & OA
Weng et al. 2016[40]	Aerobic exercise increases the integration of attention and executive control networks in YA and OA, although with greater increases in OA	Not applicable
Flodin et al. 2017[41]	There was no differences between groups in resting state network connectivity changes from baseline to post-training	Across groups, post-intervention increases in DMN and sensorimotor network connectivity were related to aerobic capacity improvements
McGregor et al. 2018[42]	Aerobic exercise training increased connectivity between primary motor cortex and DMN compared to balance training	The increase in connectivity correlated with improved motor performance
B. Parkinson's disease		
Wu *et al.* 2010[33]	• In OA automaticity is accompanied by strengthened connectivity in sensorimotor networks, which is less so in PD • Attentional networks became less necessary in OA in automatic stage, while they remained active in PD	Not applicable
Wu *et al.* 2015[34]	• Attentional networks became less necessary in OA in automatic stage, while they remained active in PD • Re-attending to the task resulted in a shift back from automatic to controlled mode in the striatum in PD, but not in OA	Not applicable
Shah *et al.* 2016[43]	Patients who pedaled faster had increased cortico-subcortical connectivity during task performance	A positive correlation was found between pedaling rate and change in FC from the most affected M1 to the ipsilateral thalamus
Nackaerts *et al.* 2018[44]	Writing training enhanced communication in the left visuomotor integration system compared to placebo	No significant correlations between behavioral and connectivity parameters were found
Manuel *et al.* 2018[45]	PD patients exhibited increased rsFC of the left parietal cortex with the rest of the cortex compared to OA	A lower FC of the left parietal cortex with the rest of the cortex correlated with greater offline consolidation gains across both groups

CMA = cingulate motor area; DMN = default mode network; FC = functional connectivity; OA = older adults; PD = Parkinson's disease; rs = resting state; SMA = supplementary motor area; UPDRS = Unified Parkinson's Disease Rating Scale; YA = young adults

(Table 1B). Shah et al studied the effects of 8 weeks of cycling, comparing a voluntary and forced exercise program in a randomized design, using fMRI with a continuous task.[46] However, due to a lack of difference between both groups for pedaling rate, a direct correlation between pedaling rate and connectivity was made, rather than comparing both groups. It was found that patients who pedaled faster, increased their connectivity between the most affected M1 and thalamus during finger tapping (Table 2B). Importantly, this effect was sustained after 4 weeks without practice indicating good retention. Nackaerts et al looked into motor learning of handwriting while patients were tested and trained ON medication.[47] They compared a group that received 6 weeks of intensive handwriting training with a placebo training of stretch and relaxation exercises in a randomized design. Task-based fMRI results revealed an increase in connectivity targeting the SMA by means of enhanced visuoparietal coupling, suggesting more efficient communication in the left visuomotor integration system after real training, rather than sham. As correlations between connectivity changes and behavioral improvements outside the scanner were not significant, a firm interpretation of these findings was not possible.

Overall, the above suggests that motor learning associated increases of connectivity remain largely similar in healthy aging and that also in PD motor network communication is capable of modification, albeit to a lesser extent. Nevertheless, Box 1: Analysis methods used to study motor learning-related changes in brain connectivity

Advantages	Drawbacks
Correlation analysis = model-based method to correlate the time course of a seed region and that of any other brain area	
Advantages	**Drawbacks**
– Easy to implement – Minimal number of assumptions	– No inference on directionality
Coherence analysis = model-based method that quantifies how well one signal can be represented by a linear transformation of another	
Advantages	**Drawbacks**
– Insensitive to regional differences in blood flow and volume	– No inference on directionality
Psychophysiological Interactions = model-based linear regression method to assess how activity in one region predicts/explains activity of another	
Advantages	**Drawbacks**
– Easy to implement	– No inference on directionality
Dynamic Causal Modeling = model-based method to infer hidden neuronal states from measurements of brain activity using a Bayesian framework	
Advantages	**Drawbacks**
– Allows inference on directionality – Tight coupling to biophysical models	– Only a limited number of regions of interest – Direction of connections needs to be pre-specified
Granger Causality = data-driven method to map connectivity using vector autoregressive modeling of fMRI time series	
Advantages	**Drawbacks**
– Allows inference on directionality – No need to pre-specify the direction of connections	– Requires relatively short repetition time for fMRI

training-related alterations in PD mainly involve strengthening of attentional and sensory-motor compensatory circuits rather than achieving increased efficiency of motor automaticity related cortical–subcortical network connections, as such bypassing the affected regions and in particular the posterior putamen.

METHODOLOGICAL CHALLENGES

As can be seen in Table 1, most studies so far had uncontrolled designs, used variable durations of training and task-paradigms and involved relatively small sample sizes. Not only is it difficult to recruit large numbers of patients in the field of neurorehabilitation, neuroimaging studies in PD also suffer from a severe loss of data due to head motion artefacts during scanning. In the studies described above this was up to 15%,[34,47] while this factor is often not taken into account when calculating the required sample size.

The studies described above highlight three major challenges. First, mainly model-based analysis methods were used (Table 1). Box 1 summarizes the advantages and drawbacks of the used methods. In model-based approaches, a region of interest (ROI) is selected as a seed based on prior knowledge and a connectivity map is created between the seed region and the rest of the brain or other selected ROIs. The advantage is that these techniques are easy to implement and straightforward to interpret. However, strong prior knowledge on the possible underlying neural processes is required,[48] as the choice of seed region has a crucial effect on the changes in the connectivity pattern likely to be observed.[49] Finally, it is possible that interesting changes in connectivity were missed simply because the connection or ROI is not included.

Second, four out of five PD studies used task-based measurements (Table 1B). The challenge in these studies is that it is important to obtain a similar performance, not only between groups, but also across sessions, as otherwise the observed neural changes could have been due to performance differences instead of motor learning.[50] In other words, if performance is kept constant, but neural changes are observed after training, these neural changes are likely associated with learning-related plasticity. The study by Nackaerts et al,[47] *e.g.* found similar performance at baseline and after training in the scanner thus making a clean interpretation of motor learning effects possible. Outside the scanner, though, motor gains were apparent after training. Both studies of Wu et al showed changes in performance from early learning to the automatic stage, though this did not differ between patients and healthy controls.[33,34] Shah et al did not report the direct comparison of behavioral results between groups or time points.[46]

A third and final point is the influence of dopaminergic medication. Research has shown that dopaminergic medication, at least partially, normalizes neural networks in PD in the resting-state[12,13] and during tasks.[51–53] Hence, for research purposes it has been recommended to perform neuroimaging while patients are OFF medication.[54] This was the case in three out of five studies (Table 1B).[33,34,46] Though connectivity measured while OFF medication might be more sensitive to detect motor learning-related changes, this does not reflect daily life situations in which the training will occur. Also, it cannot be assumed that practicing while ON medication generalizes to OFF medication and vice versa.[55] This specifically might have influenced the study by Shah et al as there was an incongruence between testing (OFF) and training state (ON).[46] So far, only two studies described the effects of motor learning on connectivity patterns while ON medication,[45,47] demonstrating a need to replicate and extend these findings.

PREDICTING MOTOR LEARNING CAPACITY USING CONNECTIVITY

PD is a highly heterogeneous disorder and studies have shown a variable response to neurorehabilitation. Patients with freezing of gait respond differently to various training modalities than those without, illustrating greater difficulties with consolidation of learning effects, such as with transfer, automatization and retention.[25,26,35,36] This warrants different and personalized training approaches pending the patient characteristics, such as setting the cognitively challenging training conditions to the patients actual level of cognitive functioning. Patients with freezing in particular experience more cognitive difficulties,[56] which might influence their motor learning capacities. Research in healthy elderly and PD patients without freezing has shown that exercise therapy can not only boost motor learning capacities,[29,44] but also has a positive effect on non-motor symptoms such as cognition,[57,58] thereby providing a possible dual advantage. Until now, there is a lack of evidence on whether other PD-phenotypes (*e.g.* tremor-dominant patients) display differential learning effects. However, behavioral work has shown that motor learning, and especially consolidation, is negatively impacted by disease progression across all patients.[24,59] While there are no neural underpinnings to support this yet, this is likely the result of the progressive striatal denervation extending beyond the sensorimotor striatum into the associative regions. A recent behavioral study indicated that high cognitive capacity and low motor ability predicted better dual task training results.[60] As neurorehabilitation requires effort and motivation as well as professional input, predictive biomarkers for neuroplasticity have an important future role to play in allocation of individual patients to varying levels of intensity of training.

For this exploratory question, six articles were selected (Figure 1), which are summarized in Table 3. Resting-state functional connectivity, using MRI, EEG and MEG, was shown to predict short- and long-term motor learning. Studies using tasks that involved a strong visuomotor component revealed that greater connectivity between primary motor cortex, premotor cortex and parietal cortex before training predicted greater motor learning improvements, possibly reflecting a greater capacity for visuomotor integration.[61–63] Conversely, a lower baseline connectivity between the primary sensorimotor cortex and both putamen and cerebellum were linked to greater gains of a finger tapping sequence in young adults.[64] Similarly, reduced connectivity between motor and visual areas predicted faster learning of a finger tapping task in the long term, suggesting that individuals with a greater autonomy of visual and motor processes developed motor–motor associations faster.[65] Using a graph theory-based approach, two predictive biomarkers were uncovered to distinguish high from low learning rates.[66] While high coherence, *i.e.* the spectral analog of a correlation analysis, in the visual cortex was associated with slower learning rates, a high coherence in the parietal operculum and planum temporale was linked to higher learning increments.

At first sight, these results seem inconclusive, as motor learning was predicted by both increased and decreased connectivity at baseline. However, different types of tasks were used. The former group of studies used tasks with a strong visuomotor component, while the latter group involved finger tapping tasks. Importantly, none of these studies compared whether neural predictors indeed explained outcomes better than behavioral ones.

Based on these findings in healthy adults and the findings that connectivity patterns can predict the response to dopaminergic medication in PD,[67,68] we speculate that connectivity measures may be of additional value to predict the response to neurorehabilitation. Two factors should be considered. First, dopaminergic medication may have differential effects depending on the learning stage, specifically in the early stages of the disease.[69] Levodopa can cause an overdose in the relatively intact anterior putamen, thereby worsening the acquisition of a motor task.[70,71] As later stages of motor learning are more dependent on the posterior putamen,[22] that is already affected early on in the disease, dopaminergic medication may be beneficial during these stages as opposed to during early learning.[70,71] Hence, studies addressing early *vs* late learning may not yield the same results. Second, as mentioned above, compensatory mechanisms play an important role in PD.[2,3,5] In healthy elderly, it has been shown that lower baseline connectivity between the sensorimotor cortex and regions involved in visual motion processing, the default mode network and dorsal attentional network are linked with better learning.[64] Hence, less pressure on cognitive resources at baseline, results in enhanced motor learning. In line, we anticipate that PD patients with greater remnants of connectivity between the posterior putamen and other motor regions and those with lower connectivity in compensatory systems, will have greater motor learning capacities. A protocol published on an ongoing study may shed light on these assumptions.[72]

DISCUSSION—FUTURE POTENTIAL FOR BRAIN IMAGING IN NEUROREHABILITATION

Despite the methodological issues identified above, connectivity measures may be more sensitive than brain activation patterns to capture long-term motor learning, as brain regions operate in circuits rather than as single structures.[73] For chronic degenerative conditions such as PD, connectivity measures may be better equipped to distinguish between spontaneous compensation, inducing abnormal activity and entanglement in the brain[28] as well as changes induced by training. As such, several recent developments hold promise to gain a more in depth understanding of learning-related connectivity changes in PD, as described next.

Table 3. Studies on prediction of motor learning outcome based on connectivity measures

Author	Participants	Task	Training intensity	Imaging method	Connectivity measure	Prediction method
Wu *et al.* 2014[61]	17 YA	Pursuit rotor task	Short-term: two practice blocks of 5 min in single session	rsEEG	Coherence	Partial least squares regression model
Bogdanov *et al.* 2017[62]	18 YA	Cued sequence production task	Long-term: 16 sequences, 40 trials/s, 6 runs/ session for 3 days	Task-based fMRI	Graph theory	New approach: combining discriminative subspace learning in network space coupled with significant conserved subgraph mining
Mary *et al.* 2017[63]	14 YA 14 OA	Finger tapping task	Short-term: 1 sequence, 2x/trial for 70 trials	rsMEG	Seed-based correlation	Correlation analysis
Mattar *et al.* 2018[64]	19 YA	Finger tapping task	Long-term: 6 sequences, 150 trials/session, 10 sessions/2 weeks for 6 weeks	rsMRI	Seed-based correlation	Correlation analysis
Manuel *et al.* 2018[65]	24 YA: 12 learning 12 control	Drawing task	Short-term: 12 min/day, 2 days: • Learning: Mirror-drawing task • Control: same task, without mirroring of cursor	rsEEG	Imaginary coherence	Correlation analysis
Wu *et al.* 2018[66]	32 YA	MSL task (wrist extension-flexion)	Short-term: 19-target sequence, 21 times on Day 1, 3 times on Day 2	rsEEG	Coherence	Partial least squares regression model

EEG = electroencephalography; MEG = magnetoencephalograpy; (f)MRI = (functional) magnetic resonance imaging; MSL = motor sequence learning; OA = older adults; rs = resting state; YA = young adults

Particularly, data-driven methods may play an important role as no prior knowledge on the spatial or temporal pattern is required,[48] possibly revealing important, yet unexpected, connections. The difficulty with data-driven methods is that large sample sizes are necessary to obtain sufficient power to detect changes. In the neurorehabilitation field it is difficult to recruit large numbers of patients willing to participate in long-term training, with at least two intensive task-based fMRI sessions. As mentioned above, studies in PD also suffer from a severe loss of data due to head movement, especially in task-based approaches. For this reason, it has been put forward that resting-state measurements may provide a better and more feasible paradigm.[74] As for using resting-state fMRI in the context of motor learning, it is firstly unclear whether participants are actually able to achieve a resting-state immediately following a training session. Second, wakefulness is assumed in resting-state studies. However, recent work showed that 50% of participants undergoes a transition to light sleep at least once over a duration of 10 min, which resulted in increased functional connectivity compared to wakefulness.[75] Overall, both task-based and resting-state studies will have merit when exploring the neural networks underlying neurorehabilitation in PD. The most detailed and skill-specific information will likely come from task-based measures, especially when taking the earlier highlighted methodological difficulties of conducting a training study in the scanner into account. On the other hand, resting-state measures are better able to capture whether similar changes in connectivity patterns occur in connection with learning irrespective of task or skill set. In addition, resting-state measures have the advantage that they can be more easily acquired in large patient samples, which allows for adequate statistical power in prediction models.

In recent years, network neuroscience has also gained importance using graph theory.[73,76,77] In this approach, a complex network is described as a collection of nodes, *i.e.* ROIs, and edges, representing the connections (anatomical, functional or effective) between the nodes.[78,79] The major advantage of using graph theory is that the interactions can be examined at a whole-brain level rather than in *a priori* defined ROIs, while also being able to look at the specific role of a certain node in the network. This introduces a novel vocabulary of measures which capture the quality of network integration: (i) the capacity of networks to become interconnected and exchange information as well as the identification of nodes that are of great importance for this information transfer, and (ii) the degree to which network elements form separate clusters and become segregated.[80] In healthy young adults, motor and visual networks became more segregated over the course of 6 weeks of visuomotor training.[81] More effective performance of a motor task was thus associated with a brain topology, in which the motor network became less entangled. In PD, there is already a reduction in network integration as well as network segregation at baseline, respectively suggesting that less efficient transfer of information as well as exaggerated compensatory communication is apparent.[82,83] Even though Levodopa tends to normalize this disturbed network topology,[84] future research needs to investigate whether such an architectural analysis is sensitive to detect motor learning potential.

A third road for unravelling the potential for neuroplasticity is using a multi modal approach, *e.g.* either using concurrent EEG-fMRI data or combining structural and functional neuroimaging data acquired on the same patients. The advantage of using a multimodal approach is that the cross-information could potentially reveal variations that may only be partially detected using a single modality.[85] Moreover, when attempting to understand and predict individual responses, data gathered simultaneously from several modalities can increase accuracy.[86]

An example of a multimodal approach is the combination of EEG and fMRI measurements offering a high temporal and spatial resolution respectively. As motor learning is a highly dynamic process, a high spatial and temporal resolution is desirable to gain an in-depth understanding of what is happening in the brain. To the best of our knowledge, this is currently an unexplored topic in relation to both motor learning and PD, though several studies have looked into the benefits of EEG-fMRI to characterize the neural dynamics of cognitive processes.[87–90] So far, most studies focused on combining EEG with BOLD activations, though it has been suggested that using EEG-fMRI can also facilitate a fuller understanding of brain connectivity.[91] Recent work has identified both Dynamic Causal Modeling (DCM) and Graph Theory as ideal candidates for data fusion.[92,93]

We did not review changes in structural connectivity as a result of motor learning due to a lack of studies in this domain. However, combining both structural and functional connectivity may provide complementary information on the effects of neurorehabilitation. Still, it has been demonstrated that there is no one-to-one relationship between structural and functional connectivity.[94,95] In healthy adults, Taubert et al were the first to combine structural and functional scans to investigate whether long-term motor training induced changes in functional connectivity coinciding with structural alterations using a multimodal correlation analyses.[96] They found that functional connectivity changed between the SMA/pre-SMA and parietal areas. This change overlapped with microstructural alterations in the white matter tracts and correlated with performance improvements. A recent study from the same group showed that gray matter changes were found to underlie balance training in PD,[97] though a combination with connectivity measures was not investigated.

CONCLUSION

In this review, several consistent findings on brain circuitry changes related to motor learning were highlighted in both healthy people and those with PD. The hallmark of consolidated motor learning appeared to imprint on the degree of entanglement within and between motor and cognitive networks. Even so, current brain connectivity studies reflect variable results and are of methodological insufficient quality to reveal how rehabilitation influences the underlying neural networks in PD. This literature overview uncovered a number of methodological developments that are likely to shed more light on these issues in the future, which in turn can lead to optimized as well as better targeted neurorehabilitation.

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