VIEWPOINT

The Concept of Motor Reserve in Parkinson's Disease: New Wine in Old Bottles?

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Across neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD), a disparity between the clinical expression and the extent of pathophysiological burden has been observed. This has fueled the establishment of resilience concepts such as cognitive reserve (CR) and brain reserve (BR) at the beginning of this millennium.[1] Since the introduction of these concepts, a plethora of studies have aimed at identifying mechanisms predominantly associated with the mitigation of cognitive decline despite neurodegenerative changes associated with multiple sclerosis, dementia, or healthy aging (ie, resilience).[2,3] In comparison, resilience mechanisms in PD have received far less attention even though they seem equally important given the clinical heterogeneity and long prodromal phase. With the emerging concept of motor reserve (MR), new avenues have opened up focusing on potential neuronal processes providing resilience (ie, relative preservation of motor function) in PD, which can potentially be harnessed for interventional therapies. Importantly, this requires a common understanding of the principles of how to assess resilience in observational studies and how to quantify its underlying mechanisms. Given the head start in identifying pitfalls and precisely delineating the concept of resilience in the AD field, the opportunity lies at hand to benefit from this knowledge for investigations of MR in PD.

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Cognitive Reserve: Lessons Learned

The literature on the neurobiological underpinnings of reserve was relatively inconsistent because methodologies, proxies of reserve, and the cohorts used greatly varied across studies. To establish a well-defined nomenclature and to generally improve study designs and interpretation of results, a framework was recently introduced by a work group of the Alzheimer's Association.[4] According to this framework, cognitive and brain reserve refer to resilience mechanisms of the brain, thus coping with neurodegeneration. CR thereby reflects a more dynamic process, sometimes compared with the "software" running on the brain. This software is associated with the adaptability of cognitive processes to maintain functionality through, for example, changes in network efficiency. Functional magnetic resonance imaging can be used to study underlying CR processes. In contrast, BR, in a more passive form, accounts for differences in brain integrity (eg, number of neurons) and reflects the "hardware" of the brain, which can be captured by structural magnetic resonance imaging or positron emission tomography (PET). These two concepts are not mutually exclusive, but interconnected, and both appear to be associated with lifetime factors, including education, risk factors (eg, genetic or vascular risk), and sex, which modulate the association between pathology, neuronal dysfunction, and subsequent functional impairment. According to the framework's definitions, MR may hence be considered as a process that relatively preserves motor function by adaptations of motor-relevant networks despite increasing pathophysiological burden. Thus, the neuronal underpinnings of MR may best be

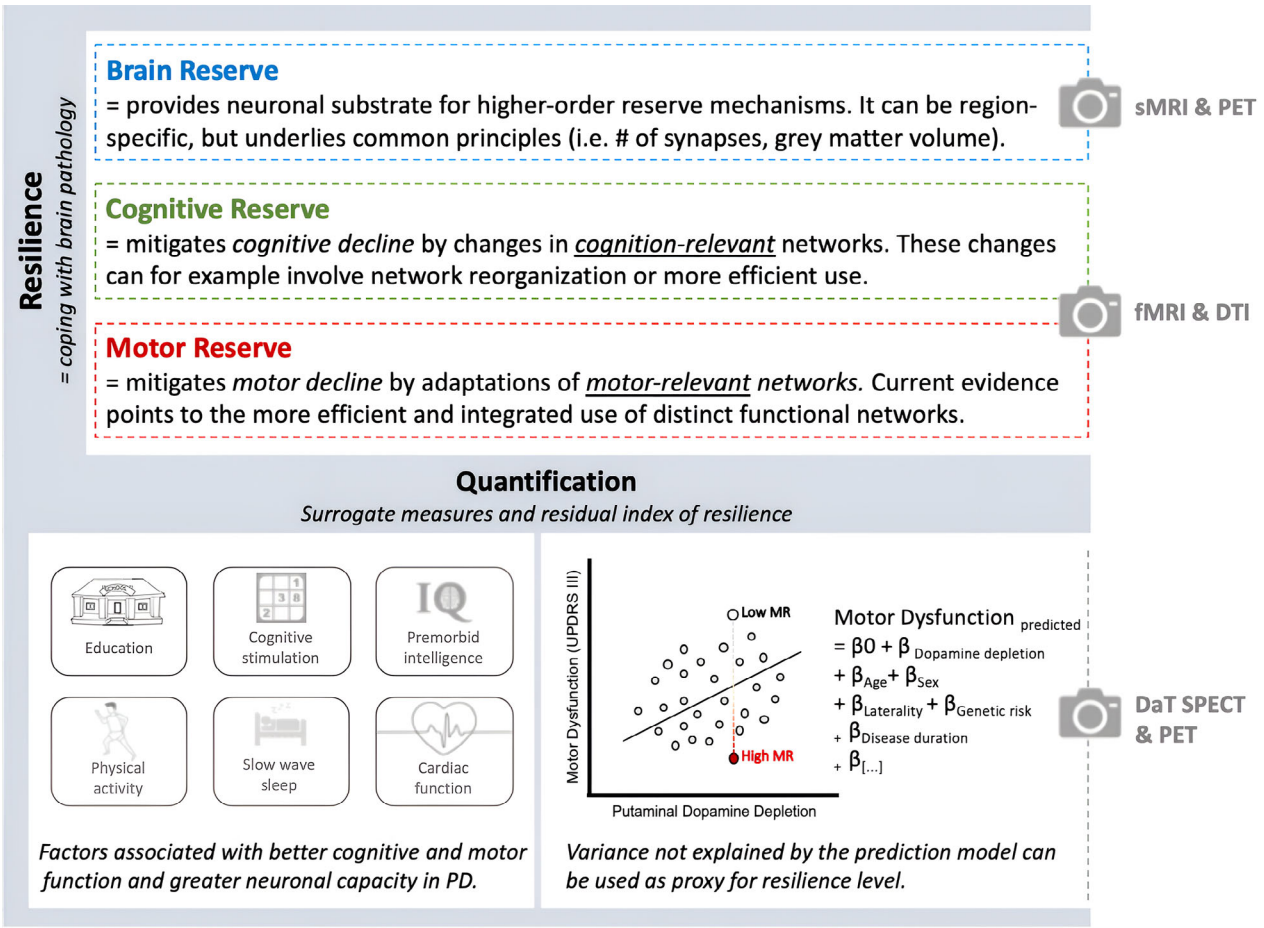

FIG. 1. Summary of resilience concepts and how they can be quantified by neuroimaging techniques and surrogate measures. fMRI, functional magnetic resonance imaging; MR, motor reserve; PET, positron emission tomography; sMRI, structural magnetic resonance imaging; DTI, diffusion tensor imaging; DaT SPECT, dopamine transporter single-photon emission computed tomography; UPDRS III, Unified Parkinson's Disease Rating Scale, Part III. [Color figure can be viewed at wileyonlinelibrary.com]

captured by structural or functional connectivity analyses (see Fig. 1 for summary).

The Emerging Concept of Motor Reserve: A New Chapter in PD Research?

Because the topic of MR is still relatively new, literature of the neurobiological underpinnings and associated (non) modifiable factors is still scarce. Yet, available evidence points to a more efficient and integrated use of functional brain networks being associated with MR in patients with PD.[5-8] Also, morphological differences, such as greater gray matter volume[6,9,10] or striatal dopamine release,[7,10] have recently been suggested to mitigate cognitive and motor decline, albeit progressive dopamine depletion. In regard to the disease course, it was shown that initial MR level[8,11] and higher structural network strength associated with MR[12] modulated disease progression, indicating that it may carry a prognostic value potentially relevant for treatment regimens and disease management. Yet, the physiological principles underlying these neuronal imprints and their association with lifestyle factors remain relatively unknown. Intriguingly, recent post-mortem evidence indicated that an active lifestyle was related with improved dopamine synthesis and structural striatal protein expression, as well as a decrease in astrocyte activation.[13] These findings are in accordance with rodent studies pointing toward lower neuroinflammation[14,15] and increase in dopamine function[16,17] when exposed to an exercise regimen. Overall, it appears that lifetime factors may contribute to the buildup of resilience mechanisms such as lower neuroinflammatory response and greater neuronal substrate, which in turn may actively foster network adaptations to counteract motor decline in PD.

The Role of Modifiable Factors: We Are What We Do?

Several modifiable factors have already been identified to be linked with resilience capacity, such as education,[18]

premorbid intelligence,[6] physical exercise,[7] sleep,[19] or cardiorespiratory fitness.[20] Recent efforts have attempted to summarize the current evidence on potential modifiable and nonmodifiable factors associated with MR in PD.[21] In the summary paper, the authors argue that factors such as age at onset, sex, comorbidities, and lifestyle factors are invariably associated with MR. However, caution needs to be taken in terms of whether these factors are actually associated with resilience, aging processes, or differences in the disease course. For example, the authors concluded that older age at onset was associated with lower MR. Age at onset, however, just represents an inevitable metric of time and may not directly contribute to the buildup or waning of reserve. Agreeably, older age at onset is related with progressive neurodegenerative processes, which may impede on the MR level.[22] Yet, individuals with the same age at onset but different lifestyles or genetic imprints may nonetheless present differences in resilience level.[23] The same holds true in terms of comorbidities such as rapid eye movement sleep behavioral disorder (RBD). Notably, RBD is associated with a more progressive disease course and thus greater motor dysfunction.[24] Still, the conclusion cannot be drawn that RBD is associated with lower MR per se, unless MR is solely defined as motor performance at a specific point in time.

Thus, when considering the role of (non)modifiable factors, the interindividual variability of underlying neuronal mechanisms needs to be investigated rather than the pure behavioral output. Furthermore, reserve needs to be considered as a dynamic mechanism that is built up over life, which interindividually varies. This way we can gain insights into whether a demographic or (non)modifiable factor is actually associated with either a resilience-related (ie, relative preservation of functionality) or a disease-related mechanism (ie, subtypes with more malignant disease course). Moreover, caution needs to be taken when reporting results and classifying them based on resilience concepts (MR vs. CR vs. BR) or compensation. These terms appear actually related to different active and passive neuronal processes. Notably, these concepts are closely interlinked, rendering it sometimes difficult to disentangle mechanisms associated with either one of them.

MR Versus CR: Can We Kill Two Birds with One Stone?

In the past, motor and cognitive function have been viewed as separate entities. Novel accounts, however, argue that networks involved in cognition and motor function are closely intertwined. In particular, cost–benefit considerations and reward processes may play a crucial role in voluntary movement.[25] Given this close interaction between motor and cognitive function, it is conceivable that a boost of structures associated with cognition (ie, CR) may also serve the preservation of motor function (ie, MR). Indeed, several studies investigating the role of CR, using surrogate measures such as education or intelligence quotient, demonstrated that these factors were associated with both lower cognitive and motor symptom severity in patients with PD (for review, see Hindle et al.[18]). The current neurobiological evidence of resilience in PD further points toward the involvement of brain areas knowingly involved in motor function (eg, basal ganglia) but also in motivational (eg, ventral striatum) and planning domains (eg, orbitofrontal areas).[6,8] Based on the current evidence, it thus remains unknown whether a strict distinction between CR and MR is necessary or helpful. Moreover, given that PD is also characterized by nonmotor symptoms, solely focusing on MR may not reflect the entire resilience spectrum toward the pathophysiology of PD. Therefore, the distinction between CR and MR may potentially become obsolete as the underlying mechanisms concomitantly contribute to the relative maintenance of both the cognitive and motor function. Nonetheless, with regard to the development of interventional therapies, it will be important to examine whether targeting primary motor circuitries is more efficient in the mitigation of motor decline rather than targeting cognition-relevant structures or vice versa. Results of these future studies will provide insights into whether different terminologies in terms of CR and MR are actually relevant or redundant.

Compensation Versus Resilience: Same, Same but Different?

Although little evidence is provided in terms of resilience, many studies have reported on compensatory mechanisms in PD. Although we agree that compensatory mechanisms are certainly part of resilience, the individual level and extent to which these compensatory mechanisms vary actually reflect resilience capacity. For example, it was argued that patients with PD tap into MR by means of novel area recruitment and enhanced activation of underlying motor networks.[26] Yet, in this study, the neuronal adaptations were not associated with an explanatory variable (eg, certain lifestyle) that would explain resilience capacity. Thus, although the involvement of additional brain areas may allow compensation of PD, it remains to be assessed whether this compensatory mechanism is generally present up to a certain extent in the majority of patients (for review, see [3]) or whether it is associated with individual resilience level that variably occurs in a subset of patients and is explained by a moderator variable. Importantly, these analyses require carefully selected study designs because the disease itself can induce

maladaptive network changes such as hyperconnectivity of distinct network hubs.[27] These adaptations are, however, not associated with a mitigation of motor and cognitive symptoms. Hence, to assess the nature of a compensatory mechanism, the following questions may be addressed: (1) Does the compensatory mechanism have a positive effect on motor and cognitive function? If not, it cannot be a resilience mechanism. (2) Can an explanatory variable be identified that is associated with the degree of compensation? If so, the explanatory variable introduces variance in the degree of compensation, which relates to resilience. Because much has already been learned about compensating PD, future studies will be required that focus on identifying compensatory mechanisms that provide resilience in a subset of patients. Moreover, in contrast with disease-related compensatory mechanisms, resilience-related mechanisms may potentially be similar across neurodegenerative diseases.

Quantification of Motor Reserve: Many Roads Leading to Rome?

Although lifestyle measures may provide information on interindividual differences that can easily be obtained in the clinical setting, a general issue of these proxies is that they present static surrogate markers. These static markers may not be sensitive enough for the determination of resilience mechanisms at different disease stages. The residual approach was more recently introduced in CR research to circumvent this drawback.[28] Recent studies have also used this approach to quantify MR level in PD.[8,11] This approach thereby considers the variance in motor function (eg, Unified Parkinson's Disease Rating Scale, Part III score) that is not explained by demographic characteristics and dopamine signal loss (eg, dopamine PET/SPECT) as MR measure. By associating the residuals with neuroimaging parameters, the neuronal underpinnings of MR, but also CR or BR, can, respectively, be determined, as recently done.[8] An advantage of this approach is that it can be quantified at different time points and may thereby yield a more dynamic MR measure. However, it also contains several disadvantages. The residual approach is based on the error of the linear model, which may be influenced by nonlinear associations, collinearity, and incomplete surrogates. Also, factors being associated with symptom severity, such as laterality[29] or genetic risk (eg, GBA mutations[30]), have so far not been included in the employed models and may thus have led to poor MR estimates. Moreover, it has been suggested that dopamine transporter could be downregulated as a compensatory mechanism.[31,32] Thus, solely using the association of putaminal dopamine transporter binding and motor function as an MR measure may not encompass the actual individual MR level. Therefore, it is crucial to first assess the nature of the relationship between independent and dependent variables (ie, nonlinear vs. linear) and to carefully consider the degree of explained variance by the predictor variables (ie, the R2) to avoid poorly fitted models.

In summary, the residual approach in contrast with static surrogates may provide a valuable dynamic measure to identify neurobiological signatures of resilience, if adequately used. Yet, it does not directly inform on which moderators actually support these signatures. The ultimate goal in resilience research is to identify modifiable mechanisms that can be targeted by interventional treatment strategies. Hence the residuals still need to be explained in subsequent analyses by means of lifestyle, molecular, cellular, or genetic factors, as recently done in AD research.[33] Moreover, it was recently argued that interaction analyses may be more useful in identifying resilience signatures rather than solely determining resilience levels by the error in the model.[34]

Aside from this, machine learning or covariance network analyses may yield novel pathways in resilience research. In terms of machine learning, the brain age gap (ie, chronological − predicted biological age based on neuroimaging data) may offer a data-driven neurobiological proxy of resilience, which can subsequently be used to determine molecular or genetic resilience signatures.[35] Moreover, covariance network analyses may be employed to identify a common resilience network that becomes activated during multiple tasks and is supported by lifestyle factors.[36] Collectively, it will be crucial to examine the mitigating effect of the identified resilience signatures in longitudinal designs to determine its power in slowing the disease course.

Conclusion

Although first progress has already been initiated in the field of resilience in PD, further research on structural, functional, and molecular resilience signatures are warranted. A better understanding on common, as well as potentially varying, resilience principles (ie, MR, CR, and BR) will require carefully constructed study designs comprising patients with different neurodegenerative diseases (eg, AD vs. PD), different disease subtypes (eg, body first vs. brain first), different lifestyles (eg, sedentary vs. highly physically active), and different disease stages (prodromal or clinical). These studies will collectively provide crucial information for individually-tailored strategies increasing resilience toward neurodegenerative processes. Moreover, findings of these studies will not only be relevant for PD but also other movement disorders, such as supranuclear palsy, multiple sclerosis, or amyotrophic lateral sclerosis. ■

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