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Brain pathologies are associated with both the rate and variability of declining motor function in older adults.

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A higher burden of mixed-brain pathologies in aging brains is related to faster motor decline. [3] We employed a novel approach to determine if brain pathologies account for other facets of motor decline such as motor variability [Supplementary Methods and Figure 1, online resource]. We analyzed data from 1229 older decedents followed for an average of 9 years (Supplementary Table 1, online resource).[1] Linear mixed-effect models showed that global motor scores decreased on average by -0.04 units/year (Estimate -0.037 , S.E. 0.0008 , $p < 0.001$). From these same models we calculated motor variability as within-person variability of annual global motor scores relative to person-specific trend of motor decline. On average, the annual person-specific motor variability was 0.013 units/year (Range 6×10^{-5} to 0.182).

To examine the role of brain pathologies, we added terms for each of ten brain pathologies to the prior models alone and together. In separate models, AD pathology, nigral neuronal loss, Lewy bodies, macroinfarcts, atherosclerosis, arteriolosclerosis and cerebral amyloid angiopathy were associated with more rapid motor decline (Supplementary Table 2, online resource). In a single model, AD pathology, nigral neuronal loss and macroinfarcts were associated with motor decline (Supplementary Table 3, online resource). Figure 1a contrasts the person-specific linear trajectories of global motor decline in adults with (light red lines) and without (light blue lines) moderate-severe nigral neuronal loss. Figure 1b contrasts the fitted-person specific trajectories of annual motor decline in adults with (light red lines) and without (light blue lines) moderate-severe nigral neuronal loss.

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Availability of Data

Data used in this study are available through request via the RADC research resource sharing hub (<https://www.radc.rush.edu/>).

We extracted metrics for annual motor variability from these same models. AD pathology, nigral neuronal loss, Lewy bodies, macroinfarcts and atherosclerosis were associated with the person-specific annual motor variability in separate models (Supplementary Table 2, online resource) and together in a single model (Supplementary Table 3, online resource). For example, exponentiation of the estimate of motor variability for nigral neuronal loss suggests that the presence of nigral neuronal loss is associated with a 33% increase in motor variability compared to an individual without nigral neuronal loss. Figure 1c contrasts global motor variability for adults with (light red lines) and without (light blue lines) moderate-severe nigral neuronal loss.

Next, we examined if the effects for the summary AD pathology metric was due to β -amyloid, tangles or both. Both β -amyloid and tangles were associated with the rate of motor decline when we examined separate models. The association of β -amyloid with motor decline is attenuated and no longer associated with motor decline when a term for tangles is included in the same model. The marginal association of β -amyloid with annual motor variability is also mediated by inclusion of a term for tangles in the same model. Thus, the association of AD pathology with annual motor decline and variability is driven by tangles and not β -amyloid (Supplementary Table 4, online resource).

Given the complexity and diversity of motor performances, the annual rate of change does not capture all facets of declining motor function. Variability is inherent in the motor system and its minimization may be crucial for optimizing motor performances.[5] The current study applied a novel statistical approach to conventional linear modeling to quantify both the annual rate of motor decline and the annual variability of repeated motor performances.

Another innovative aspect of this study was that we examined the extent to which the rate of motor decline and its variability were related to mixed-brain pathologies in the same individuals. A higher burden of mixed-brain pathologies including AD pathology, nigral neuronal loss, Lewy bodies, macroinfarcts, atherosclerosis, arteriolosclerosis and cerebral amyloid angiopathy were associated with more rapid motor decline. Some but not all of these neuropathologies were also associated with the annual rate of motor variability in these same individuals. These data suggest that the impact of neuropathologies on motor decline is heterogeneous: some may affect motor decline but not motor variability and some may affect both. Further work is needed to elucidate the biologic substrate and molecular mechanisms underlying these findings.

The current study suggests that the association of neuropathologies with fluctuations in motor performance is not specific to a single pathology.[4] Analyses with a continuous summary measure of AD pathology provides more power than using a dichotomous measure of AD pathology and showed that AD pathology was associated with both motor decline and variability. Further analysis supports the notion that tangles link β -amyloid with motor decline and variability.

These data highlight that several analytic techniques may be needed to capture the varied facets of complex phenotypes like motor decline. These analyses highlight that without more detailed characterization of motor phenotypes and individual motor performances the full

extent to which brain pathologies contributes to late-life motor impairment may be underestimated. Further work is needed to determine the neural mechanisms and sites underlying motor variability and to what extent motor variability and decline are independent facets that may be amenable to different targeted interventions. These findings provide additional evidence that there is much greater heterogeneity in the motor manifestations of individual brain pathologies than previously recognized which may contribute in part to the observed phenotypic heterogeneity of late-life motor impairment.[2]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Associations of nigral neuronal loss with motor decline and motor variability.

1a contrasts the person-specific linear trajectories of global motor decline in adults with (light red lines) and without (light blue lines) moderate-severe nigral neuronal loss. **1b** contrasts the fitted-person specific trajectories of global motor decline in adults with (light red lines) and without (light blue lines) moderate-severe nigral neuronal loss. The dark red and blue lines represent the average global motor decline for the entire group of participants with and without moderate-severe nigral neuronal loss. **1c** contrasts global motor variability for adults with (light red lines) and without (light blue lines) moderate-severe nigral neuronal loss. The dark black line represents the annual decline of global motor score for all individuals. The dark red and blue lines represent the 95th percent confidence interval for global motor variability for individuals with and without moderate-severe nigral neuronal loss. The red lines are more widely displaced than the blue lines showing more variability.