

Disputes & Debates: Editors' Choice

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Editors' Note: In Vivo Distribution of α -Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

In the Systemic Synuclein Sampling Study (S4)—a cross-sectional observational study of 59 participants with early, moderate, or advanced Parkinson disease (PD) and 21 healthy controls (HCs)—Dr. Chahine et al. found lower total α -synuclein levels in the CSF of patients with PD compared with HCs with a reasonable sensitivity of 87%, but this finding had low specificity. On the other hand, α -synuclein immunoreactivity in skin and sub-mandibular gland was specific for PD but not sensitive. In response, Dr. Gibbons et al. cite previous studies that reported much higher sensitivities (80%–95% vs 24.1%) for the detection of α -synuclein in the skin in patients with PD. They argue that this discrepancy cannot be explained by inclusion of late-stage PD in such studies, citing high-detection rates of phosphorylated α -synuclein in patients with early-stage PD and REM sleep behavioral disorder (RBD), and low-false positivity. They propose that the discrepant results in the S4 study may be explained by the study's methodology of formalin fixation of the skin biopsies, which they claim has not gained acceptance in the study of peripheral nerve tissue because of the diminished integrity of peripheral antigen retrieval; paraffin embedding of the tissue, which they argue provides only a fraction of the volume obtained with larger frozen tissue sections; and automated immunohistochemical staining. They suggest that future studies in this area should use more accepted standardized methods for processing skin biopsy tissue for phosphorylated α -synuclein. Responding to these comments, the authors suggest that previous conflicting results have primarily been due to relatively low levels of study rigor in assessing the accuracy of the various immunohistochemistry methods, which, in the S4 study group, included multiple independent slide-reading judges, third-party blinding of such judges, and validation against gold standard neuropathologic diagnosis. They agree that reports of high sensitivity of peripheral α -synuclein detection in patients with idiopathic RBD are encouraging for the early detection of α -synucleinopathies but argue that not all patients with PD have preceding RBD and that those who do tend to have more widespread and severe brain synucleinopathy. They counter that technical differences in para-formaldehyde and formalin fixation are minimal and cite previous methods from S4 authors supporting the use of formalin-fixed, paraffin-embedded (FFPE) tissue. They also argue that the multiple S4 tissue sections that they assessed for each tissue site and subject resulted in sufficient tissue volumes to overcome any limitations of individual paraffin-embedded samples. They note that thick sections and immunofluorescent signal development methods require rare technical expertise, whereas FFPE methods and autostainers are more widely available, with autostaining methods also providing greater replicability and potentially better long-term storage than free-floating immunohistochemical methods. This exchange highlights enduring methodological uncertainties, tradeoffs, and debates regarding the detection of antigens such as synuclein in tissue samples, which need to be more definitively resolved before such detection is adopted into clinical practice.

Aravind Ganesh, MD, DPhil, FRCPC, and Steven Galetta, MD
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Reader Response: In Vivo Distribution of α -Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

Christopher Gibbons (Boston), Vincenzo Donadio (Bologna, Italy), Claudia Sommer (Würzburg, Germany), Rocco Liguori (Bologna, Italy), Giuseppe Lauria Pinter (Milan, Italy), Raffaella Lombardi (Milan, Italy), Kathrin Doppler (Würzburg, Germany), and Roy Freeman (Boston)
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We read with interest the publication entitled “In vivo distribution of α -synuclein in multiple tissues and biofluids in Parkinson disease.”¹ In the article, Chahine et al.¹ discuss the results of the Systemic Synuclein Sampling Study (S4 study). This was an important step toward the in vivo diagnosis of synucleinopathy. Unfortunately, although the detection of phosphorylated alpha-synuclein was highly specific, sensitivity was quite poor, particularly for skin (with a sensitivity of 24.1%). The authors note that there were several explanations for such findings, including the earlier diagnosis of PD in the S4 study compared with the relatively small studies performed at other centers.

At present, there are many studies that include the use of skin for the detection of alpha-synuclein, many with numbers of similar or even larger size than the results of the present study with sensitivities of testing in the 80%–95%+ range.^{2–4} Chahine et al. suggest that the high-positive rates in the previous publications are because of the inclusion of late-stage disease PD. This notion has largely been disproven by the high-detection rates of phosphorylated alpha-synuclein in patients with REM sleep behavioral disorder and in studies only including Hoehn and Yahr stages 1 and 2, which confirm that early detection is not only possible but can be performed with sensitivities much higher than reported in the S4 study.^{1,5–7} The notion of higher rates of false-positive cases in previous studies—as also suggested by Chahine et al.—is opposed to the 100% specificity that has been reported before.^{8,9}

To understand the major discrepancies between the S4 study and the synuclein literature published by several different groups, one must closely compare the methods between the groups. Based on our long experience in skin biopsy processing, the lack of sensitivity in the S4 study can be explained by the following: the methodology used in the S4 study included formalin fixation of the skin biopsies, paraffin embedding of the tissue, and automated immunohistochemical staining.¹⁰

The use of formalin-fixed paraffin-embedded tissue has never gained acceptance in the study of peripheral nerve tissue, where decades of peripheral nerve research have resulted in well-defined, standardized methods for standard skin biopsy processing using only thick, freshly fixed frozen tissue sections.^{11,12} These international standards have been established because formalin fixation reduces the integrity of peripheral antigen retrieval, and therefore, only paraformaldehyde-based fixatives are used.^{3,11,13,14} In addition, there is a need to obtain thicker tissue sections for adequate cutaneous nerve fiber and tissue sampling. As the authors of the S4 study note, the deposition of alpha-synuclein is “patchy.” A standard 4-mm-thick paraffin-embedded tissue section provides only a fraction of the tissue volume obtained with a 20–50-mm frozen tissue section.^{3,13,15} Thus, a significant sampling error is introduced by using paraffin-embedded sections unless much greater numbers of samples are processed. In addition, thin tissue sections disrupt a nerve fiber structure and reduce the ability to visualize intraneural synuclein deposition.

The association between the use of thicker cryosections and the higher sensitivity of phospho-alpha-synuclein detection is reflected in the literature: phosphorylated alpha-synuclein was first reported in premortem skin biopsies of patients with Parkinson disease with low sensitivity by using formalin-fixed paraffin-embedded tissue.¹⁶ In 2013, 3 independent research groups—all

from the field of peripheral nerve research with long experience in the study of cutaneous autonomic and somatosensory small fibers—simultaneously reported the detection of phospho-alpha-synuclein or an increase of total alpha-synuclein in dermal nerve fibers in patients with the Parkinson disease with a much higher sensitivity.^{8,9,17} In the meantime, several studies have been published confirming these data.¹⁸⁻²⁰

The results of the current study simply confirm that formalin-fixed paraffin-embedded tissue sections should not be used in the study of the skin biopsy analysis of peripheral nerve and do not inform about the utility of skin biopsy in the detection of phosphorylated alpha-synuclein. Future studies of this nature should be performed using the accepted standardized methods for processing of skin biopsy tissue for phosphorylated alpha-synuclein.

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Author Response: In Vivo Distribution of α -Synuclein in Multiple Tissues and Biofluids in Parkinson Disease

Thomas Beach (Sun City, AZ), Lana M. Chahine (Pittsburgh), Charles H. Adler (Scottsdale, AZ), and Brit Mollenhauer (Göttingen, Germany)

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We appreciate the opportunity to reply to the letter by Gibbons et al. on our article.¹ Over recent years, there have been many, often widely conflicting reports on the diagnostic accuracy for the Parkinson disease (PD) of immunohistochemical (IHC) staining of pathologic α -synuclein (aSyn) in peripheral tissue biopsies.² We suggest that these conflicts have primarily

been because of the relatively low levels of study rigor in assessing the accuracy of the various IHC methods. Unlike for the S4 study, other published diagnostic IHC methods for aSyn in skin or any other peripheral tissues subjected to rigorous assessments are rare—such as those performed in a series of studies conducted under the sponsorship of the Michael J. Fox Foundation—including the S4 study,¹ which is the subject of the current communications. These rigorous studies have included multiple independent slide-reading judges, third-party blinding of such judges, and validation against gold standard neuropathologic diagnosis.³⁻⁵ We answer specific points mentioned by Gibbons et al. below:

1. Regarding the sensitivity of IHC aSyn methods in participants with idiopathic REM sleep behavioral disorder (RBD), we agree that these are encouraging for the early detection of α -synucleinopathies but point out that not all participants with PD or dementia with Lewy bodies (DLB) have RBD and those who do tend to have more widespread and severe aSyn brain histopathology as compared with those without RBD.⁶ This may also be true for prodromal participants with and without RBD.
2. Regarding the difference between paraformaldehyde and formalin fixation, we believe that this is minimal or nonexistent provided the concentration, in solution, of formaldehyde is equivalent. Most laboratories use commercially obtained 10% formalin in aqueous buffer, which has a formaldehyde concentration of approximately 4%. Many other laboratories, as indicated by Gibbons et al., prepare fixative solutions from solid paraformaldehyde, but this converts on dissolution into formaldehyde, and most laboratories aim for a final formaldehyde concentration of 4%. Because of this, formalin-fixed and paraformaldehyde-fixed tissues cause equivalent antigen (epitope) masking as long as they have equivalent formaldehyde concentrations. Much published work is available that indicates that excellent sensitivity may be obtained in formalin-fixed, paraffin-embedded (FFPE) tissue when optimal antigen exposure methods are used, including published work by some of the S4 authors on aSyn IHC methods.⁷
3. Greater section thicknesses such as those obtained with sliding-freezing microtomes or vibratomes do give additional tissue volume as compared to thinner paraffin sections, and this may give increased sensitivity, but, as Drs. Gibbons, Freeman and co-workers pointed out themselves in their very recent publication,⁸ this is easily made equivalent by staining more paraffin sections to give equivalent tissue volumes. We believe that the multiple S4 tissue sections that we assessed for each tissue site and participant will have given the study sufficient tissue volumes so as to exclude this as a limiting factor for achieving optimal sensitivity. The S4 group has, in fact, conducted follow-up studies that confirmed that additional stained sections did not further improve sensitivity.
4. Although thick sections and immunofluorescent signal development—such as those used by Gibbons et al.—have been used by some (but not all) laboratories for the investigation of peripheral nerve pathology, these methods have distinct and limiting drawbacks. They require technical expertise that a very few laboratories possess, whereas FFPE methods and autostainers are used by virtually every diagnostic hospital pathology unit in the developed world. The use of autostainers and associated standardized reagents provides replicable interlaboratory slide staining that is difficult to obtain with free-floating section methods that are idiosyncratic to each laboratory. The fluorescent slides obtained with the free-floating section methods are not well preserved in long-term storage and would be difficult to exchange between centers.

We therefore disagree with Gibbons et al. in their conclusion that FFPE sections should not be used for skin biopsy analysis, whether for the study of aSyn or other features. We look forward to more rigorous assessments of the free-floating aSyn IHC methods used by the authors, including the usage of third-party blinding, multiple independent judges, and gold standard autopsy diagnosed cases. Such a rigor is especially critical before aSyn detection methods are offered in the clinical setting.

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Editors' Note: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

Dr. Manning et al. found cross-sectional and longitudinal changes in the white matter diffusion measures and resting-state functional MRI network connectivity in 73 concussion-free female rugby players compared with 31 age-matched female swimmers and rowers. They concluded that longitudinal changes occur in the microstructure and function of the brain in otherwise healthy, asymptomatic athletes participating in contact sport and that further research is needed to understand the long-term brain health and biological implications of these changes. In response, Drs. Shahim and Diaz-Arrastia note that repetitive head impacts over decades have been associated with late-life dementia in previous studies of professional contact-sport athletes, but that it is less clear whether participation in such sports at the amateur level poses similar risks. They note that the finding of white matter microstructural disruption seen in the study by Dr. Manning et al. is also seen as a consequence of more severe traumatic brain injuries. While commending the longitudinal data provided by the study, they caution that imaging techniques such as diffusion tensor imaging and rsfMRI may detect small degrees of disruption that are not functionally limiting and also have limited availability and cumbersome processing needs that preclude their use for routine assessment of athletes. They call for further studies of more inexpensive blood-based biomarkers and their correlation with imaging markers of axonal disruption after concussive and subconcussive head impacts. Responding to these comments, the authors agree that cognitive reserve in the individuals studied may be sufficiently high that they are functionally unaffected by the identified MRI markers of tissue and network disruption but argue that they may eventually affect the brain's response to other insults later in life. They agree that these MRI approaches are presently intended for research purposes. Noting that they have undertaken further work on blood-based markers on this cohort, they comment that metabolomic signatures may be more relevant than classical markers of injury while acknowledging the need for better correlation with imaging results and cognitive testing. This exchange underscores our evolving, but incomplete, understanding of the clinical significance of imaging and blood-based markers of axonal injury in otherwise healthy athletes engaged in contact sports.

Aravind Ganesh, MD, DPhil, FRCPC, and Steven Galetta, MD
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Reader Response: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

Pashtun Shahim (Bethesda, MD) and Ramon Diaz-Arrastia (Philadelphia)
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We read the article by Manning et al.¹ with interest. Studies of professional contact-sports athletes have made clear that exposures to repetitive head impacts over decades are associated with late-life neurodegenerative dementia.^{2,3} It is less clear whether participation in contact sports at the amateur level results in comparable risks. The study by Manning et al. found white matter (WM) microstructural disruption—especially in the corpus callosum and impaired functional connectivity in the default mode network over time in concussion-free and asymptomatic female rugby players—using diffusion tensor (DTI) and resting-state connectivity MRI (rsMRI), respectively.¹ These WM tracts are known to be disrupted as a consequence of more severe traumatic brain injuries.⁴ In contrast to the existing studies,⁵ Manning et al. assessed WM and functional changes in female athletes and noncontact sport athletes longitudinally, which is a novel and strong study design. Although the results of the Manning et al. study are compelling, they should be interpreted with caution. Although DTI and rsMRI are sensitive for identifying WM disruption, it is likely that there is substantial cognitive reserve built into brain and that these elegant imaging techniques may detect small degrees of disruption that are unlikely to result in functional limitations. Future studies with larger sample sizes and longer follow-up will be required to answer this important question. Finally, the DTI and rsMRI methods have several limitations, including limited availability and cumbersome image processing, which limits their usefulness for routine assessment of athletes. Future studies should include blood-based biomarkers, such as neurofilament light and glial fibrillary acidic protein, which are inexpensive and straightforward to interpret, as markers of axonal disruption. How well blood biomarkers correlate with the imaging biomarkers of axonal injury after concussive and subconcussive head impacts is a critical issue which remains to be resolved.

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Author Response: Longitudinal Changes of Brain Microstructure and Function in Nonconcussed Female Rugby Players

Kathryn Y. Manning (Calgary, AB) and Ravi S. Menon (London, ON)
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We are in agreement with the caveats put forward by Drs. Shahim and Diaz-Arrastia regarding our article.¹ It is entirely possible that the MRI methods put forward in this paper are so sensitive that they detect changes that are of no functional consequence now. It is also possible that cognitive reserve in these individuals is sufficiently high that these changes have no consequence in the future. However, one could imagine that every life event that chips away at the brain's capacity for recovery and plasticity can ultimately affect the brain's response to a later-in-life insult, such as stroke or plaque formation. It is simply unknown whether this is a linear process or one in which a threshold needs to be surmounted, and hence, whether these

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are important or trivial changes. We would not advocate that these MRI approaches be used in a diagnostic manner. As noted in the comment, these are sophisticated and expensive approaches and are designed to study populations and inform directions for further research (and perhaps policy). One such direction is the use of blood biomarkers. We do have additional publications with data on this cohort in preparation but can note in passing that GFAP showed no changes at the sensitivity threshold of our techniques. In mild TBI or asymptomatic participants, metabolomic signatures may be more relevant than the classical markers such as GFAP or NFL, as we have previously noted.² These would be more appropriate as accessible screening tools once we understand their relationship to the imaging results and perhaps more incisive cognitive testing.

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CORRECTIONS

Long-term Employment Outcomes After Epilepsy Surgery in Childhood

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In the article “Long-term Employment Outcomes After Epilepsy Surgery in Childhood” by Reinholdson et al.,¹ there is an error in figure 1. The blue box (sixth from the bottom) directly below the green and yellow boxes titled “15-year” should read: “Included: 105 Lost: 16.” The authors regret the error.

Reference

1. Reinholdson J, Olsson I, Tranberg AE, Malmgren K. Long-term employment outcomes after epilepsy surgery in childhood. *Neurology* 2020;94:e205–e216.

Quality Improvement in Neurology

Headache Quality Measurement Set

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In the AAN Special Article “Quality Improvement in Neurology: Headache Quality Measurement Set” by Robbins et al.,¹ author Nathaniel M. Schuster was listed incorrectly in the author list. The publisher regrets the error.

Reference

1. Robbins MS, Victorio MC, Bailey M, et al. Quality improvement in neurology: Headache Quality Measurement Set. *Neurology* 2020;95:866–873.

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