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## Waiting for Godot: Progress in the measurement of human neuroinflammation with existing tools

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Recognition of the impact of systemic inflammation on the integrity of central nervous system structure and function has grown considerably in the last 15 years. In particular, the ability of inflammation in the periphery to provoke neuroinflammation, with potential etiological consequences for psychiatric disorders, has become an intense focus of research (Al-Diwani et al., 2022). As a result, there is accumulating evidence that peripheral inflammation can provoke neuroinflammation and can lead to alternations in brain structure and function, giving rise to cognitive, affective, and motor impairments (Hayley et al., 2021). However, progress in identifying the mechanisms and mediators that underlie these relationships is constrained by methodological limitations in the ability to measure inflammation *in vivo* in the human brain. This has hindered the development of novel treatments for conditions suspected to have an underlying neuroinflammatory component, for which currently available treatments are inadequate, such as depression and dementia. New tools that are sensitive, specific, and comprehensive are needed. In a recent paper in *Brain, Behavior, and Immunity*, De Marco and colleagues (De Marco, 2022) move us a step forward in this regard, both conceptually and methodologically.

Prior work assessing neuroinflammation in humans has relied primarily on brain imaging tools and fluid biomarkers. Positron emission tomography (PET) with tracers for translocator protein (TSPO), which is upregulated in activated glia, has been the most widely used method and has yielded some success in establishing differential glial activation in a variety of psychiatric conditions (Meyer et al., 2020). However, important drawbacks to this approach ultimately limit its utility, including restricted participant samples based on a genetic polymorphism of the TSPO gene, the need for arterial blood for accurate quantification, and a lack of cellular specificity. Perhaps most importantly, TSPO radioligand binding in circulating immune cells and in immune cells in inflamed tissue increases during inflammation (Hatori et al., 2012), potentially impacting the differential distribution of tracer availability in the periphery versus the CNS and confounding the interpretation of changes in the PET signal (Nettis et al., 2020).

In addition to TSPO PET imaging, other brain imaging modalities

have been advanced as tools for quantifying different aspects of neuroinflammation. Some validated evidence exists, for example, for the utility of diffusion-weighted magnetic resonance imaging (dwmMRI) with multi-compartment models (e.g. NODDI) in quantifying changes in microglia density and morphology (Yi, 2019). Quantitative magnetization transfer (qMT), an MR-based imaging technique that can inform the integrity of tissue microstructure, has also shown some success in detecting acute changes *in vivo* attributed to neuroinflammation. Harrison and colleagues, for instance, found an increase in magnetization transfer in the insular cortex following typhoid vaccination that correlated with increased vaccination-induced fatigue (Harrison, 2015). While qMT changes of this nature are typically interpreted as changes in myelin integrity, they can also reflect other aspects of neuropathology including mitochondrial dysfunction and inflammation. Finally, multiple applications of arterial spin labeling (ASL) have been used to non-invasively assess subtle changes in the permeability of the blood brain barrier (Mahroo, 2021), a key mechanism thought to underlie neuroinflammation provoked by inflammation in the periphery. Despite the sensitivity of these measures, there are inherent limitations in their interpretation. The use of ASL to index blood brain barrier dysfunction, for example, is still under development and is prone to error, where minor technical imprecision can lead to substantive differences in signal. Though NODDI measures are sensitive to changes in microglia density and morphology, they can also reflect other microstructural changes. Similarly, qMT appears to be sensitive to a variety of perturbations in brain microstructure, but is not specific to cell types or even to inflammatory processes, and thus its usefulness in shedding light on the mechanisms and mediators that connect central and peripheral inflammation is limited.

Fluid biomarkers of neuroinflammation and neurodegeneration also have a place in quantifying neuroinflammation in humans. Unlike the image-based methods described above, fluid biomarkers can be highly specific. Glial fibrillary acidic protein (GFAP) concentrations, for example, specifically reflect reactive astrocytes (Eng and Ghirnikar, 1994), and neurofilament light chain protein (NfL) and neurogranin

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concentrations reflect axonal and dendritic degeneration, respectively (Gaetani et al., 2019; Kester, 2015). Recent advances in high sensitivity assays have enabled the measurement of GFAP and NfL in plasma, while other biomarkers useful for this purpose, such as sTREM-2 and neurogranin must be assessed in cerebrospinal fluid. Despite the cellular and sub-cellular level specificity that these biomarkers provide, they convey little to no regional specificity and the invasiveness of lumbar puncture for the acquisition of CSF biomarkers constrains their widespread use.

In their recent paper, De Marco and colleagues (De Marco, 2022) provide important proof of concept for another MRI-based imaging tool that improves upon those discussed above, in both its sensitivity and specificity in assessing *in vivo* human neuroinflammation. De Marco et al. used diffusion-weighted magnetic resonance spectroscopy (DW-MRS) to measure changes in microglial activation in the context of LPS-induced systemic inflammation. DW-MRS leverages the highly sensitive properties of water diffusion and exploits the relatively cell-type specific properties of intracellular metabolites. They report increased diffusion of total choline in the thalamus from pre- to post-LPS relative to placebo, suggestive of microglia-specific activation. Importantly, robust correlations between LPS-induced increases in total choline diffusion and deterioration in mood add functional significance to their finding, relating it back to immunopsychiatry and the mechanisms through which inflammation in the body may contribute to psychological dysfunction. DW-MRS is not without its own limitations; its spatial constraints, in particular. Unlike other imaging-based methods, DW-MRS measures are focused on a single or few, relatively small regions of interest (e.g., the thalamus and corona radiata in De Marco et al.) and are unable to provide comprehensive spatial information about regional or circuit-based changes. Nonetheless, the gain in cell-type specificity provided by DW-MRS in this study adds an important tool for assessing neuroinflammation to a toolbox full of relatively sensitive tools that lack such specificity.

None of the measures currently available, when used in isolation, is perfect. There is the temptation in empirical science to lose the forest for the trees and dismiss results based on methodological limitations. While technological and methodological advances are absolutely needed to address mechanistic questions in this area, progress can be made in the

meantime using the available tools in combination, particularly when employed in parallel, within individual. For example, fluid biomarkers can be combined with DW-MRS and other MRI-based metrics to improve the scope, interpretation, and specificity of these data. In this way, we can make progress by triangulating data across these diverse methodologies to create a more complete picture of the neuroinflammatory response to peripheral inflammation and the mediators that give rise to this response, in order to develop targeted treatment strategies.

## References

- Al-Diwani, A., Pillinger, T., Lennox, B., 2022. Immunopsychiatry in 2021: premise to promise, and back again. *The Lancet Psychiatry* 9 (1), 11–12.
- Hayley, S., Hakim, A.M., Albert, P.R., 2021. Depression, dementia and immune dysregulation. *Brain* 144 (3), 746–760.
- De Marco, R., et al., 2022. Diffusion-weighted MR spectroscopy (DW-MRS) is sensitive to LPS-induced changes in human glial morphometry: A preliminary study. *Brain Behav. Immun.* 99, 256–265.
- Meyer, J.H., Cervenkova, S., Kim, M.-J., Kreisler, W.C., Henter, I.D., Innis, R.B., 2020. Neuroinflammation in psychiatric disorders: PET imaging and promising new targets. *The Lancet Psychiatry* 7 (12), 1064–1074.
- Hatori, A., Yui, J., Yamasaki, T., Xie, L., Kumata, K., Fujinaga, M., Yoshida, Y., Ogawa, M., Nengaki, N., Kawamura, K., Fukumura, T., Zhang, M.-R., Gelovani, J.G., 2012. PET Imaging of Lung Inflammation with [18F]FEDAC, a Radioligand for Translocator Protein (18 kDa). *PLoS One* 7 (9), e45065. <https://doi.org/10.1371/journal.pone.0045065>.
- Nettis, M.A., Veronese, M., Nikkheslat, N., Mariani, N., Lombardo, G., Sforzini, L., Enache, D., Harrison, N.A., Turkheimer, F.E., Mondelli, V., Pariante, C.M., 2020. PET imaging shows no changes in TSPO brain density after IFN- $\alpha$  immune challenge in healthy human volunteers. *Transl. Psychiatry* 10 (1). <https://doi.org/10.1038/s41398-020-0768-z>.
- Yi, S.Y., et al., 2019. Detecting microglial density with quantitative multi-compartment diffusion MRI. *Front. Neurosci.* 13, 81.
- Harrison, N.A., et al., 2015. Quantitative magnetization transfer imaging as a biomarker for effects of systemic inflammation on the brain. *Biol. Psychiatry* 78, 49–57.
- Mahroo, A., et al., 2021. Robust Multi-TE ASL-Based Blood-Brain Barrier Integrity Measurements. *Front. Neurosci.* 15, 1–14.
- Eng, L.F., Ghirnikar, R.S., 1994. GFAP and Astroglialosis. *Brain Pathol.* 4 (3), 229–237.
- Gaetani, L., Blennow, K., Calabresi, P., Di Filippo, M., Parnetti, L., Zetterberg, H., 2019. Neurofilament light chain as a biomarker in neurological disorders. *J. Neurol. Neurosurg. Psychiatry* 90 (8), 870–881. <https://doi.org/10.1136/jnnp-2018-320106>.
- Kester, M.I., et al., 2015. Neurogranin as a cerebrospinal fluid biomarker for synaptic loss in symptomatic Alzheimer Disease. *JAMA Neurol.* 72, 1275–1280.