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# Response to "Neuromelanin? MRI of Noradrenergic and Dopaminergic Neurons"

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# Response to "Neuromelanin? MRI of Noradrenergic and Dopaminergic Neurons"

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To the Editor:

We thank the authors of the editorial comment[1] on our review article[2] for drawing attention to a paper by Privoulos et al[3] regarding interpretation of the higher water content and long T1 of the locus coeruleus (LC). We also appreciated their in-depth discussion of whether neuromelanin (NM) is being directly imaged or not.

A previous comment by Watanabe[4] on Privoulos et al's paper[3] elegantly summarized exactly what we believe is seen with the low flip angle (FA) data, that is, high water content of gray matter tissues with long T1. The work by Privoulos et al[3] shows little magnetization transfer (MT) effect and their analysis suggests a small macromolecular fraction in the LC. Along these lines, this commentary[1] refers to several 2019 publications[5,6] and notes specifically that: "These indicate a decreased transfer of magnetization from the bound pool to the free water pool as well as from the free water pool to the bound pool." Indeed, as a result, the MT contrast (MTC) data look very much like spin density-weighted images in the sense that cerebrospinal fluid (CSF) has high signal (no macromolecules and, hence, no suppression of the signal) while the contrast between gray matter and white matter is improved because the white matter is suppressed more than the gray matter. The commentary also discusses matters related to the presence of both intracellular and extracellular water. The authors close their first editorial comment paper with a suggestion of what might happen with aging (in which increasing T1 of the LC would suggest further reduction of the bound pool). The authors note that, under these conditions, even if there is an unchanged MTC signal intensity: "Accordingly, extracellular water fraction must increase to compensate for the reduced macromolecular fraction (as long as the volume of the LC is not different)." Clearly, these types of changes with aging or physiological changes associated with Parkinson's disease are critical to investigate.

Now let us briefly discuss the limit of low flip angle spoiled gradient echo imaging. We note that, as long as the FA is less than the Ernst angle of white matter (ideally, much less), the images will become more and more spin density-weighted (and with negligible contributions from T1). To obtain a true proton density-weighted image actually requires that the FA is much less than the lowest Ernst angle for all tissues—this is on the order of 6° with a repetition time of 25 msec, since the T1 of CSF is on the order of 4500 msec. Of course, in very low FA images, CSF is indeed brighter than the LC. Our first estimates of the water content and T1 of the LC yield roughly 80% and 1300 msec (in reasonable agreement with Privoulos et al[3] of roughly 1400 msec). These values are, in fact, similar to most gray matter without high iron content. If a 3D MTC pulse with low FA is used, then the white matter will be further suppressed more than the LC while the CSF will be unaffected making this appear "super spin density weighted" so to speak. Knowing the tissue properties of the LC makes it possible to optimize the contrast with or without an MT pulse.[7]

However, understanding the actual relationship between these signals and the presence of NM is another story altogether. This was the effort made by Watanabe and Privoulos in their elegant papers.[3,4] The second piece of information that appears to give some consistency to this interpretation from an MRI perspective is that the loss of NM in Parkinson's disease patients corresponds also to an increase in iron content and, hence, a loss of the N1 sign.[8] Generally, water content drives T1 but other factors (such as the presence of iron or exchange processes with macromolecules) can reduce T1. However, this does not appear to be the case for the LC. The main point in our review was that the water content seen with low FA imaging correlates with the MT-NM results and with the loss in MT-NM contrast seen in Parkinson's disease patients.

Given the above-mentioned detailed findings about the LC regarding its response to an MT pulse, the commentary[1] suggests that it is not the NM per se that has increased water content. Indeed, we probably should have referred to this as being from the increased water content in the NM-containing tissue (whether it is from the larger noradrenergic neurons or not is not the question here). There could indeed be secondary or association effects that the presence of NM correlates with high water content in the tissues; however, upon degradation, this water-driven contrast disappears. The potential role of intracellular and extracellular water effects in explaining this behavior is amply discussed by Watanabe.[4,5] Further, given the sensitivity to water content, the authors close their comment on our review paper[2] with "reduced LC/SN signal intensity suggests reduced amount of intracellular water, e.g., as a result of NA/DA neuron loss. Thus, LC/SN signal intensity is, although not attributable to NM, likely to correlate with NM (as well as with intracellular water) because NM as an effective metal chelator provides neuronal protection and decreases with NA/DA neuron loss." We are in agreement that the LC contrast seen in MR is associated with tissue containing NM but not directly from the NM itself.

Keren's work[9] is a key paper in the field that set the stage for the community's choice of nomenclature, that is designating the LC contrast seen with MR as "NM imaging." Their excellent paper shows a colocation of NM cells in the LC that corresponds to norepinephrine neurons with the MTC NM-MRI data. They remark: "Thus, neuromelanin appears to serve as a natural contrast agent for nucleus LC that can be used to localize nucleus LC and may have the potential to characterize neurodegenerative disease." In Keren's figure 5, they show a clear correlation between the density of staining of the tyrosine hydroxylase and LC neurons with the MR enhancement seen in the LC. So, it is not unreasonable that they have assumed the source of contrast is NM. But as mentioned above, it is more of an association rather than a direct measure of NM, as suggested by Watanabe. Keren's histological staining also contained cadaver brain samples from subjects with Alzheimer's disease and Lewy body disease. Evidently, they found consistent

 

correlations in all cases. These results suggest again that it is the high water content producing this contrast. Taken together, the available information points to the same idea, that the MR LC imaging (whichever approach is used) is associated with the noradrenergic neurons and the presence of NM. Keren concludes: "We have demonstrated that neuromelanin is a primary contributor to LC-MRI contrast that is observed in neuroimaging studies of human subjects." and "These results indicate that neuromelanin serves as a natural contrast agent for identifying the location of nucleus LC." So, you cannot blame the neuroimaging community for designating these findings as NM imaging.

Similarly, Kitao et al[10] studied NM MRI in the SN and compared these findings to histology. However, their conclusion is stated more as an association: "Based on the direct correlation between postmortem NmMRI and neuropathological findings, signal intensity in the SNc is closely related to the quantity of neuromelanin-containing neurons but is not influenced by iron deposition." Therefore, we agree that this enhanced contrast from water is indeed associated with the NM-containing neurons and not necessarily caused by the direct presence of the NM but, rather, its association with these neurons.

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**Level of Evidence:** 5
**Technical Efficacy:** Stage 1