Review of: "The Wernicke conundrum revisited: evidence from connectome-based lesion-symptom mapping"

M MESULAM[1]

1 Northwestern University

Potential competing interests: The author(s) declared that no potential competing interests exist.

Review of: The Wernicke conundrum revisited: evidence from connectome-based lesion-symptom mapping

William Matchin, Dirk-Bart den Ouden, Gregory Hickok, Argye E. Hillis, Leonardo Bonilha, Julius Fridriksson

doi: https://doi.org/10.1101/2021.10.25.465746

Marsel Mesulam

In this paper, Matchin, den Ouden, Hickok, Hillis, Bonilha and Fridriksson present lesion-symptom mapping data with and without DTI (LSM, CLSM) in 218 participants at chronic stages of post-stroke aphasia. This study is conducted by world leaders in neurolinguistics on a large cohort of well characterized patients who were investigated with state-of-the-art imaging methodology. It appears that the principal aim of the study is to address a conundrum, raised by Mesulam et al. [1,2], on the anatomy of language comprehension. Matchin et al. conclude that the conundrum of Mesulam et al. is not a conundrum at all, that it is based on problematic logic, and that the mechanism proposed by Mesulam et al for reconciling the conundrum with stroke-aphasia is wrong.

The conundrum arises from observations on primary progressive aphasia (PPA). This syndrome occurs when one of at least 6 different neurodegenerative diseases asymmetrically targets the language dominant (usually left) hemisphere. Each underlying disease has distinct targets within the left hemisphere and gives rise to corresponding patterns of language impairment. The focality, both behavioral and anatomical, is uncanny. Some patients have dramatically abnormal syntax but perfect word comprehension while others have the converse. In keeping with the clinical specificity, the neurodegeneration, identified as atrophy, can remain completely confined to the left hemisphere for years. Within the left hemisphere some patients have peak atrophy only in the anterior temporal lobe, some only in the general territory of Wernicke's area, and still others in the inferior frontal gyrus where Broca's area is located. Post-mortem studies show that peak in vivo atrophy is a good marker for areas of most severe neurosynaptic abnormality at post-mortem [2-6]. It is easy to see why this 'experiment of nature' would offer irresistible temptations for reinvestigating the anatomy of language using the time-honored approach of clinic-anatomical correlation, but in this instance using peak atrophy to delineate the most

consequential lesion sites. This approach is not without caveat. First, peak atrophy sites are not necessarily the only areas with degeneration. Secondly, the slow disease process offers opportunities for potentially compensatory reorganization of residual neurons even within peak atrophy sites [7]. Stroke-based research is also subject to the second caveat as reorganization occurs outside the lesion site. The first caveat is approached through the principles of plausible inference. For instance, if a function is severely impaired when area 'x' is the seat of peak atrophy and when area 'y' has no detectable atrophy, it is difficult to argue that area 'y' is the actual culprit because it might also contain degeneration undetectable by atrophy or that area 'x' is innocent because there is also sub-threshold degeneration elsewhere.

Atrophy-function correlations in PPA show that severe word comprehension impairment correlates with peak atrophy in the anterior temporal lobe (ATL) not in the temporoparietal region where Wernicke's area is usually sited, that severe word comprehension impairment never occurs without peak atrophy in ATL, that peak atrophy in Wernicke's area leaves word comprehension perfectly intact, and that word and sentence comprehension impairments are resoundingly uncorrelated. These results, being at odds with traditional aphasiology, form the basis of the Mesulam et al. conundrum.

Matchin et al. do not address the conundrum since they do not present data on PPA. Instead of refuting the conundrum itself Matchin et al., address the validity of one of the two 'models' we had proposed for reconciling our findings with stroke-aphasia, namely that deep white matter damage in Wernicke strokes might have led to impairments (e.g., loss of word comprehension) that exceeded the contributions of Wernicke's cortex. So, the Matchin et al. paper comes down to proving that disconnection of ATL is not a sufficiently decisive factor in comprehension impairments caused by Wernicke strokes. If true, such a finding would have no impact on the existence of the conundrum, it would just mean that one of two hypotheses advanced to resolve the conundrum was not proven by the methods that they used. If a hypothesis about the nature of dark matter is not confirmed, that does not negate the existence of dark matter.

A few specifics:

1. *Matchin et al. state on page 2: "Mesulam et al. performed a voxel-based morphometry (VBM) study…"*

My comment: We did not perform a VBM study.

1. *Matchin et al. state on page 9: The 'double disconnection' hypothesis of Mesulam et al. entails that the association between damage to temporal-parietal cortices (roughly Wernicke's area) with word and sentence comprehension deficits in Wernicke's aphasia can be explained via disrupted connections from this area to the ATL and frontal cortex due to damage to underlying white matter. If this were true, then there should be no robust independent contribution of damage to these regions above and beyond the extent of disruption to these connections. To test this, we combined the LSM and CLSM data by assessing whether lesion-deficit correlations for these behavioral measures would still be statistically robust when incorporating connection strength as covariate."*

And then on page 10: "Under the Mesulam et al. hypothesis, we would expect that there would no longer be a significant association between the behavioral scores and damage to middle-posterior temporal lobe regions when these

disconnections are considered."

My comment: The first sentence is misleading. The conundrum does not 'entail' a disconnection at all. The conundrum is there to stay unless the authors have different findings in PPA. The disconnection is one of two suggestions we entertained to explain it. This is but one of the problems with the reasoning of Matchkin et al. They also interpret 'disconnection' in its trivial sense [8]. Being disconnected from a damaged Wernicke's area is a certainty, always present, when Wernicke's area is damaged. We used 'disconnection' to mean something more subtle, namely the accidental undercutting of fibers that interconnect areas entirely outside the lesioned Wernicke's area. This is the process underlying Alexia Without Agraphia where a lesion in the corpus callosum, entirely removed from the right occipital lesion but in the same arterial territory, causes an impairment that cannot be accounted for by the cortical lesion or its axonal output. By double disconnection, we had in mind the destruction of deep fiber bundles not originating in Wernicke's area.

1. *Matchin et al. state on page 11: "Importantly, we found robust correlations between noncanonical sentence comprehension and WAB-R word comprehension, whether or not lesion volume was included as a covariate, unlike Mesulam et al., who found that these variables were not correlated. This supports the classic view in stroke-based aphasia that word and sentence comprehension deficits coincide with similar patterns of damage to Wernicke's area. We also found that WAB-R repetition was very robustly correlated with WAB-R word comprehension, whereas Mesulam et al. found that word comprehension and repetition were not correlated."*

My comment: Exactly! Matchin et al. confirm the conundrum. There is no question whatsoever that in PPA word and sentence comprehension, on one hand, and word comprehension and repetition, on the other, have absolutely no significant correlation. In PPA, patients who cannot understand the meaning of simple words such as 'orange' or 'grass' can have perfect repetition whereas logopenic PPA patients who have terrible repetition can be perfectly normal in word comprehension. So Matchin et al. confirm the conundrum, i.e., that things are different in stroke-aphasia.

1. *On page 18 Matchin et al. state: "Thus, the fundamental prediction of Mesulam et al. that sentence comprehension deficits associated with damage to Wernicke's area are explained by a frontal disconnection pattern, and that word and sentence comprehension deficits dissociate, was disconfirmed."*

My comment: First, it cannot be a 'fundamental prediction' since we proposed an alternative in the form of diaschisis[9]. Again, the logic here is difficult to penetrate. Matchin et al. report results on stroke aphasia, not PPA. Mesulam et al. never disagreed with the stroke aphasia literature where it is crystal clear that the two types of comprehension impairment are correlated. They are not correlated in PPA. This is exactly why we have a conundrum, unless one would argue that persons afflicted with PPA have a perverse brain organization that lends itself to unnatural dissociations. The second point is even more important. Essentially what Matchin et al. have done is a variant way of proving a null hypothesis. Namely, that a hypothetical disconnection we had proposed as one of two suggestions to reconcile the conundrum is not all that relevant for explaining the effects of Wernicke strokes on comprehension. In addition to the logical problems in proving that something is not important, the methodology is potentially subject to questions. First, there are no measures of specificity and sensitivity. In other words, what is the threshold of detection by DTI. How much of a loss of a pathway do

you need to detect it? Secondly, ATL is subject to susceptibility artifacts so a signal-to-noise-ratio (SNR) map would be desirable. Thirdly, it is important to point out that DTI is not a true anatomical method and that it relies exclusively on the movement of water molecules in a magnetic field.

1. *Matchin et al., in a summary paragraph on page 22 state that: Overall, our combined VLSM and CLSM results speak against the hypothesis of Mesulam et al. (2015) of a double dissociation syndrome underlying sentence/syntactic comprehension deficits in post-stroke aphasia. Rather, our results support the classic concept of Wernicke's area as directly supporting both word and sentence comprehension, although our results do suggest that anterior temporal lobe and inferior parietal networks bolster core linguistic processing through semantic and phonological working memory resources."*

My comment: Matchin et al. have shown that an investigation of stroke-aphasics gives results consistent with the literature on stroke-aphasics. Their study does not resolve the conundrum, in fact reinforces it. Its main claim to have debunked the 'disconnection' model is a straw man argument since the conundrum is not contingent on proving that double disconnection is the reason why things are different in PPA and stroke. In fact, the title for a figure in the 2019 paper where we outlined the disconnection model was *"Two models for reconciling lesion-symptom relationships of the Wernicke area in neurodegenerative vs cerebrovascular lesions"*[9]. We had also proposed another realm of reconciliation through diaschisis that the authors do not mention. Both were proposals to stimulate awareness of the conundrum and motivate proposals for resolving it since we cannot have one type of neurolinguistics for stroke and another for PPA. The conundrum is not contingent on any of these two models. If the explanation offered to explain a phenomenon cannot be proven, the phenomenon does not disappear.

Overall, the logic of Matchin et al. is confused and confusing. Their massive data simply confirms what has been known on stroke-aphasia and has no relevance to PPA. Mesulam et al. never questioned the internal consistency of the stroke literature, we just think it is incomplete.

So far in my review, I focused on the soundness of the Matchin et al. critique of the conundrum concept. There is also massive evidence in favor of our PPA-based version of the language network. The relevant papers are quoted in our two Wernicke papers and more recent publications[10]. Let me mention one[11] where we report that the severity of word comprehension impairment in PPA is correlated inversely with the strength of functional connectivity between ATL and a middle-temporal region that appears to overlap Matchin et al.'s Wernicke's area. Perhaps rsfMRI is more sensitive than DTI?

If I had been asked to referee this paper, I might have suggested to change the title to "Stroke Aphasia Revisited", in which case I would have awarded it 5 stars. Alternatively, I would have advised the authors to withdraw this paper and join hands with us to do some constructive thinking on the conundrum.

1. Mesulam M-M, Thompson CK, Weintraub S, Rogalski EJ. The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia. *Brain.* 2015;138:2423-2437.

2. Mesulam M-M, Rader B, Sridhar J, et al. Word comprehension in temporal cortex and Wernicke area: A PPA perspective. *Neurology.* 2019;92.

3. Ohm DT, Fought AJ, Rademaker A, et al. Neuropathologic basis of in vivo cortical atrophy in the aphasic variant of Alzheimer's disease. *Brain Pathology.* 2019.

4. Kim G, Ahmadian SS, Peterson M, et al. Asymmetric pathology in primary progressive aphasia with progranulin mutations and TDP inclusions. *Neurology.* 2016;86:627-636.

5. Kim G, Bolbolan K, Gefen T, et al. Atrophy and microglial distribution in primary progressive aphasia with transactive response DNA-binding protein-43 kDa. *Ann Neurol.* 2018;83:1096-1114.

6. Kim G, S. V, Gefen T, et al. Asymmetric TDP pathology in primary progressive aphasia with right hemisphere language dominance. *Neurology.* 2018;90:e396-e403.

7. Mesulam M-M, Rogalski E, Wieneke C, et al. Primary progressive aphasia and the evolving neurology of the language network. *Nature Reviews Neurology.* 2014;10:554-569.

8. Catani M, Mesulam M-M. What is a disconnection syndrome? *Cortex.* 2008.

9. Mesulam M-M, Rader B, Sridhar J, et al. Word comprehension in temporal cortex and Wernicke area: A PPA perspective. *Neurology.* 2019;92.

10. Mesulam M-M, Coventry C, Rader B, et al. Modularity and granularity across the language network- a primary progressive aphasia perspective. *Cortex.* 2021;141:482-496.

11. Bonakdarpour B, Hurley RS, Wang A, et al. Perturbations of language network connectivity in primary progressive aphasia. *Cortex.* 2019;121:468-480.