Astrocyte Protein Levels Show Differential Changes Based on Clinical Outcome in Depression: Could Astrocytes be the New Star of the Show for Transcranial Magnetic Stimulation?

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BACKGROUND

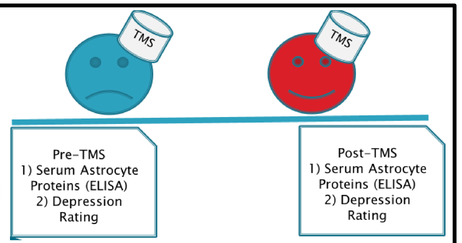
- Transcranial Magnetic Stimulation (TMS) is FDA approved for depression but mechanism of therapeutic action still not fully understood
- Astrocytes have a variety of function, Increasing interest in astrocyte's role in depression
- Astrocyte's role in TMS for depression largely unknown
- Vascular Endothelial Growth Factor (VEGF) is an angiogenic neurotrophic factor produced by astrocytes and has shown promise as serum biomarker for several illnesses including depression
- Glial Fibrillary Acidic Protein (GFAP) is intermediate filament cytoskeletal protein and one of the most widely studied astrocytic protein. It is a marker for reactive astrogliosis, a key pathological hallmark of neuroinflammation, neurodegeneration, and cerebral injury
- S100 Calcium Binding Protein B (S100B) is a calcium binding protein predominantly expressed in the astrocytes and plays a variety of functions including promoting neuroplasticity via neurogenesis and gliogenesis and blood brain barrier permeability.
- Aquaporin 4 (AQP4) is a water channel protein predominantly expressed in the perivascular astrocyte endfeet and several post-mortem and animal studies show some evidence pointing to potential contribution to depression pathophysiology.

METHODS

- Naturalistic Patient Population (N=35)

- Left DLPFC at 10 Hz at
120% motor threshold in 4s trains
3000 pulses/session for 5 sessions/week

- Enzyme Linked Immunosorbent Assay (ELISA) was performed for the various proteins



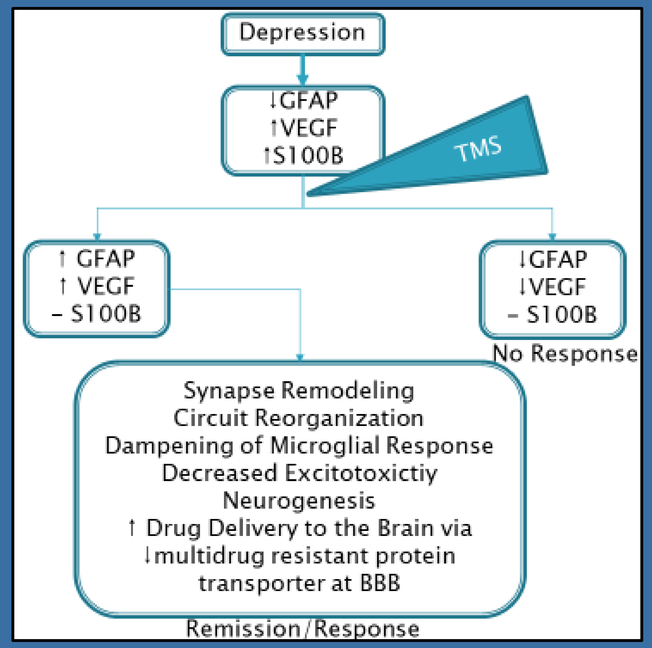
- Inventory of Depressive Symptomatology Self-Report(IDSSR) clinical outcomes
  Remission: final score ≤14 on IDSSR
  Response: 50%<improvement from baseline

Female	Average Age	Pre IDS-SR	Response/Remission rate
21/35 (60%)	50.73 ± 15.86	47.73±12.53	43% (15/35) /29% (10/35)

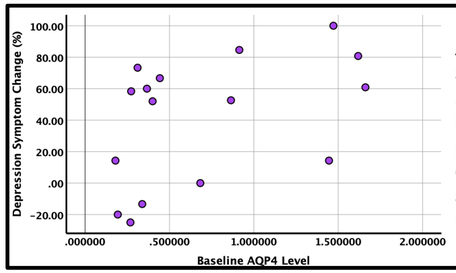
CONCLUSION / DISCUSSION

- Successful TMS outcome had significantly greater increase in VEGF and GFAP compared to non-responders
- Larger increase was associated with greater improvement in depressive symptoms after TMS.
- These patterns were not seen in S100B.
- The functional implications of the differential changes in these astrocytic proteins are yet to be elucidated, but data hint at neuroinflammation, angiogenesis, synaptic remodeling, and blood brain permeability changes.
- This pilot study provides promising exploratory data showing that GFAP and VEGF is an important mediator in the mechanism behind TMS' antidepressant effects.

Degree of GFAP and VEGF changes correlated positively with degree of depression symptom improvement

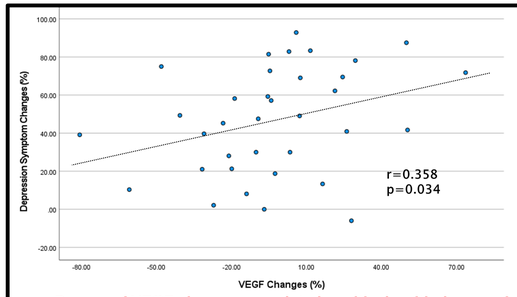


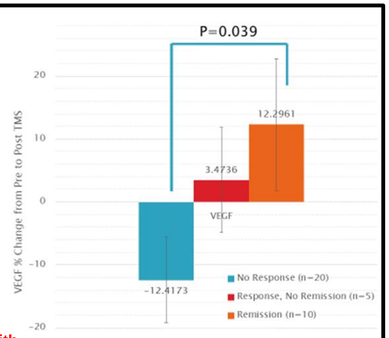
Gliovascular proteins hold promise as peripheral biomarkers and play a role in TMS's therapeutic mechanism of action



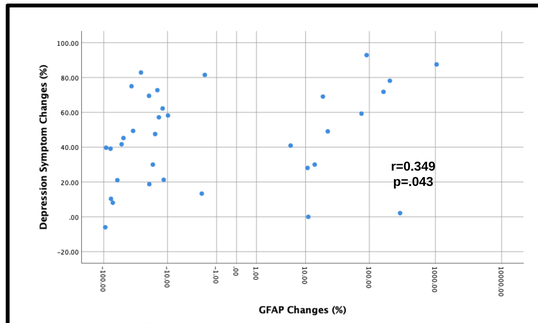
AQP4 was also measured in a subset of the population (n=16, 25% male, 75% female); baseline AQP4 level had a positive correlation with the degree of depressive symptomatic improvement measured (r = .410, p<0.05).

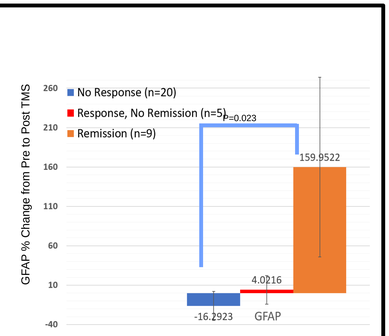
RESULTS



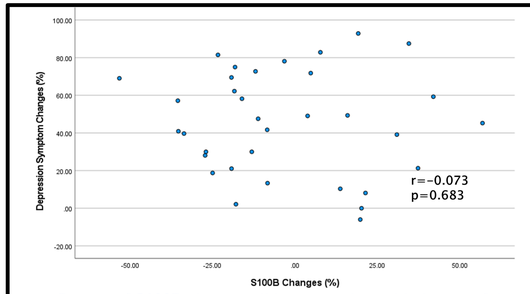


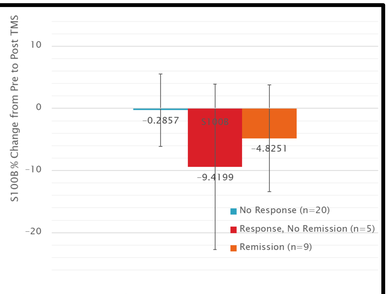
Degree of VEGF changes correlated positively with degree of depression symptom improvement.
Remitters and responders had significantly more increase in VEGF with TMS whereas nonresponders/nonremitters showed a decrease.





Degree of GFAP changes correlated positively with degree of depression symptom improvement.
Remitters and responders had significantly more increase in GFAP with TMS whereas nonresponders/nonremitters showed a decrease.





Degree of S100B changes did not correlate with degree of depression symptom improvement.

Previous Work - Reference
Fukuda, Andrew M et al. "Peripheral vascular endothelial growth factor changes after transcranial magnetic stimulation in treatment-resistant depression." *Neuroreport* vol. 31,16 (2020): 1121-1127.