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Increased Plasma Serotonin 2A Receptor Autoantibodies Predicts Significant One-year Cognitive Decline in Middle-aged Adult Traumatic Brain Injury

Mark B. Zimering[1,2*], Christine W. Yoe[1], Xena M. Agbolou[1], Valeria M. Kovtun[1] and Tara P. Cominski[1,3]

[1]Veterans Affairs New Jersey Healthcare System, East Orange, New Jersey, USA

[2]Rutgers/Robert Wood Johnson Medical School, USA

[3]Rutgers University, New Brunswick, New Jersey, USA

Corresponding author: Mark B. Zimering, Medical Service (111); Deptartment of Veterans Affairs, 385 Tremont Ave. East Orange, New Jersey, USA, **Tel:** 908 647 0180 x 4426

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Introduction

Traumatic brain injury (TBI) contributes to substantially increased global disability [1] and has been associated with major depressive disorder and dementia [2] through unknown mechanisms. Chronic inflammation increased autoantibodies to a serotonin 2A receptor from older adult TBI patients suffering with accelerated cognitive decline over a two-year period [3]. Because middle-age (post 9/11 military veterans) who were exposed to multiple TBIs can experience even more rapid cognitive decline, here we tested whether baseline plasma serotonin 2A receptor autoantibodies (AA) predicts 1-year rate of decline in global cognitive functions or in pattern separation, a dentate gyrus dependent behavior. Biomarker that could predict subset of younger adult TBI at higher risk for accelerated cognitive decline would be useful in future evaluation of candidate neuroprotective treatments.

Participants and Methods

TBI Patients

Informed consent for the local Institutional Review Board-approved study was obtained from all participants prior to blood drawing or cognitive testing. Thirty-four middle-aged, adult TBI patients (40-60, mean 49.9 years old) including 33 male and 1 female participant enrolled in the study. Many of the post-9/11 U.S. military veterans had experienced repeated TBI exposures including direct force, blast or both kinds of TBI injury. Only one patient had experienced moderately-severe TBI, most of the other injuries were mild TBI. Thirty-three of thirty-four participants had baseline blood drawing for determination of plasma autoantibodies.

Protein-A Affinity Chromatography

Protein-A affinity chromatography was used to isolate the IgG fraction of plasma [4] in thirty-three middle-aged adults who had experienced one or more TBI exposures. The IgG fraction ($1/40^{th}$ dilution=7.5 ug/mL) was stored at 0-4 degree C prior to determination of autoantibody level.

Peptide

A linear synthetic peptide corresponding to the second extracellular loop of the human 5HT2AR (QN..18) was synthesized at Lifetein, Inc (Hillsborough, NJ). The peptide had purity > 95% and was stored under desiccated conditions at −40 degrees C.. On the day of an enzyme-linked immunoassay experiment, an aliquot of lyophilized peptide was dissolved in sterile deionized water prior to immunoassay or bioassay.

Enzyme Linked Immunoassay

Enzyme Linked Immunoassay was performed as previously described using the QN..18 second extracellular loop of the 5HT2AR [5] as the target peptide antigen. Increased autoantibody binding in the QN..18 immunoassay was previously reported to correlate with neurotoxicity in a bioassay employing mouse N2A neuroblastoma cells [5] consistent with an agonist role for the circulating 5HT2A receptor autoantibodies.

Cognitive Tests

One year change in cognitive test performance was calculated as the [One year test score – baseline test score]. Higher one-year change in test score is indicative of improved performance with the exception of the Trail-making Part B in which longer time to task completion reflects worsening executive function.

Statistics

Statistical analysis was performed using unpaired Students' t-test.

Results and Discussion

Baseline Plasma Serotonin 2A R Autoantibodies

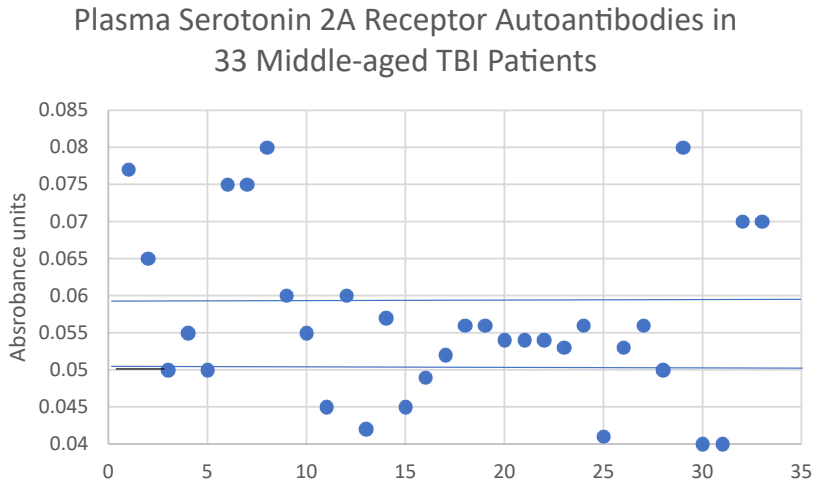
Thirty-three TBI patients underwent baseline determination of

plasma 5HT2AR AAB and completed baseline and one-year cognitive testing: St Louis University Mental Status Test (SLUMS) of working memory; digit symbol substitution test (DSST) of processing speed; and the behavioral pattern separation object task (BPS-O), a dentate gyrus hippocampal- dependent test.

Ten of thirty-three TBI patients (30.0%) had elevated plasma 5HT2AR AAB (i.e. binding of 1.5-fold background or higher; and 10/33 patients had no detectable plasma AAB (binding </= 1.25-fold background) (Figure 1). The mean one-year rate of change in SLUMs test declined significantly in AAB-positive *vs* AAB-negative TBI patients (-2.6 ± 2.47 *vs* 0.6 ± 1.62; P = 0.004) (Figure 2). Two of ten AAB-positive TBI patients experienced large one-year declines in SLUMs score to a level below the cut-off for dementia (not shown in Figure 2). The mean one-year rate of change in performance on the Trail-making Test, Part B (a measure of executive function) also worsened significantly in AAB-positive *vs* AAB-negative TBI patients (9.7 vs -13.4 sec; P = 0.04) (Figure 3). In the TMT-B test increased time (to task completion) is indicative of declining executive function. One-year change in performance on the DSST (-1.5 vs 4.7; P = 0.02) also declined significantly in AAB-positive vs -negative TBI patients (Figure 4).

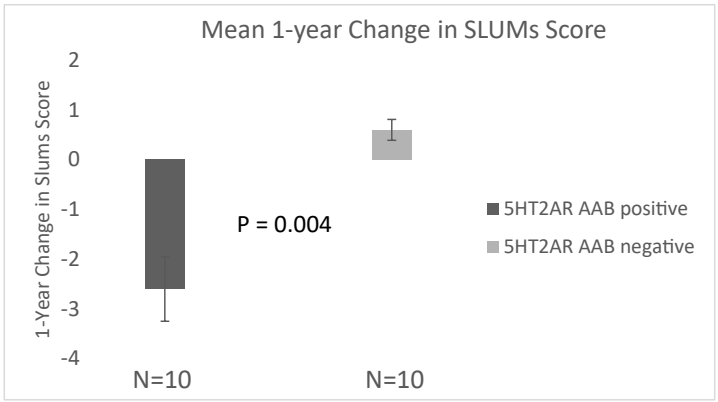
Behavioral pattern separation object task is a dentate gyrus, hippocampal- dependent component of working memory which was reported to be age-dependent [6] and decline significantly with mild cognitive dysfunction in a small subset of older (75 yr old) adults [6]. Dentate gyrus newborn neurons express 5HT2A receptor, and autoantibodies from diabetic depression patients inhibited dendrite extension and decreased survival in cultured rat DG neurons [7]. Here we tested for a possible association between baseline presence of plasma 5HT2AR autoantibodies and 1-year change in performance on the BPS object task. Bias on the BPS task is a measure of the ratio of correct responses to lure (similar object) vs similar responses to the foil (a completely new object). A bias ratio of 1 is indicative of complete pattern separation and a ratio of 0 is consistent with complete loss of pattern separation. In nineteen TBI patients who completed baseline and 1-year pattern separation tests, there was no significant difference in one-year rate of change in BPS-O *in* 5-HT2AR AAB-positive vs -negative TBI patients (5.7 ± 3 vs 3.0 ± 7); (P > 0.05) (Figure 5).

There was no significant association between one-year rate of change in BPS-O and one-year rate of change in SLUMS test (Figure



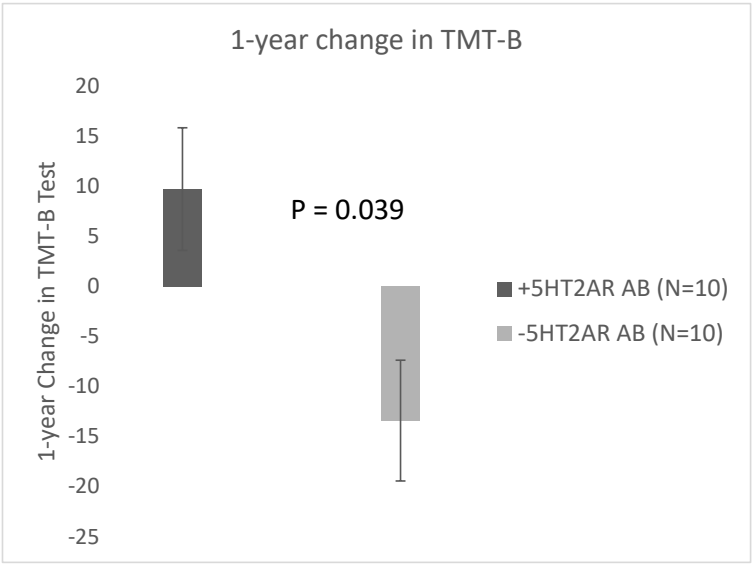
A 1/40th dilution of the protein-A eluate fraction from human TBI plasma was tested for binding to the second extracellular 5HT2A receptor peptide. Background absorbance was 0.04 AU. Undetectable binding was defined as 0-1.25 times background; increase binding was defined as 1.5 times or more above background. The solid lines indicate the upper limits of undetectable (5HT2AR AAB negative) and lower limit of high binding (5HT2AR AAB positive) in the immunoassay.

Figure 1: Distribution of binding to the human 5HT2A receptor second extracellular loop peptide (QN..18) in enzyme linked immunosorbent assay.



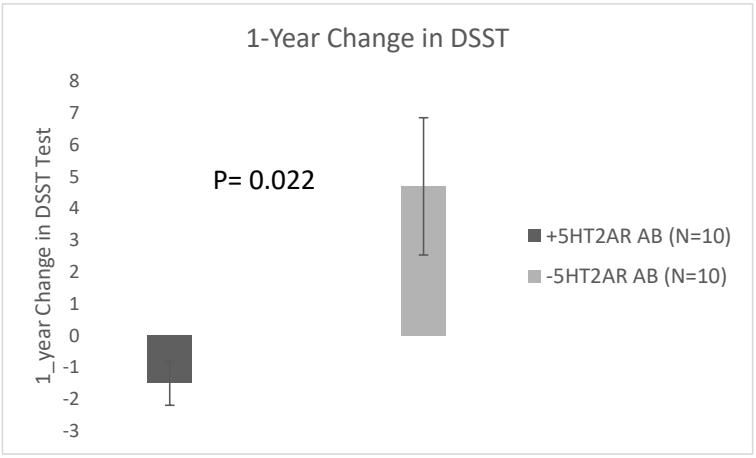
Results are mean ± SD.

Figure 2: Significant association between baseline presence of 5HT2AR autoantibodies and significant mean one-year decline in SLUMs score.



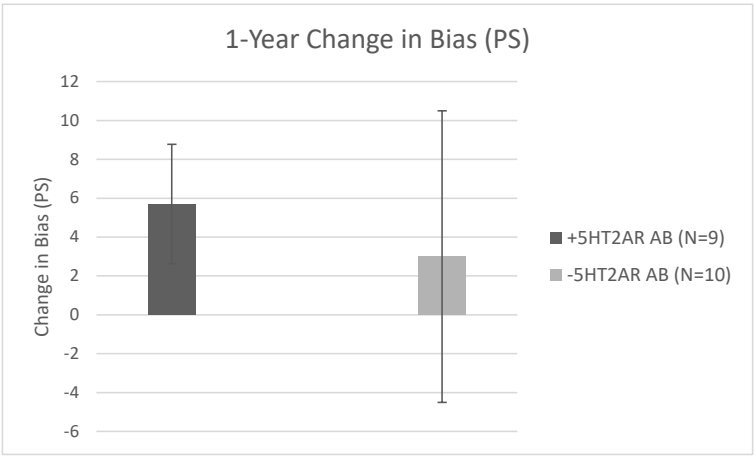
Results are mean ± SD.

Figure 3: Significant association between baseline presence of 5HT2AR AAB and one-year decline in Trail-making Part B test performance.



Results are mean ± SD.

Figure 4: Significant association between baseline presence of 5HT2AR AAB and one-year decline in digit symbol substitution test performance.



Results are mean ± SD.

Figure 5: Lack of significant association between baseline presence of 5HT2AR AAB and one-year change in behavioral pattern separation object task performance.

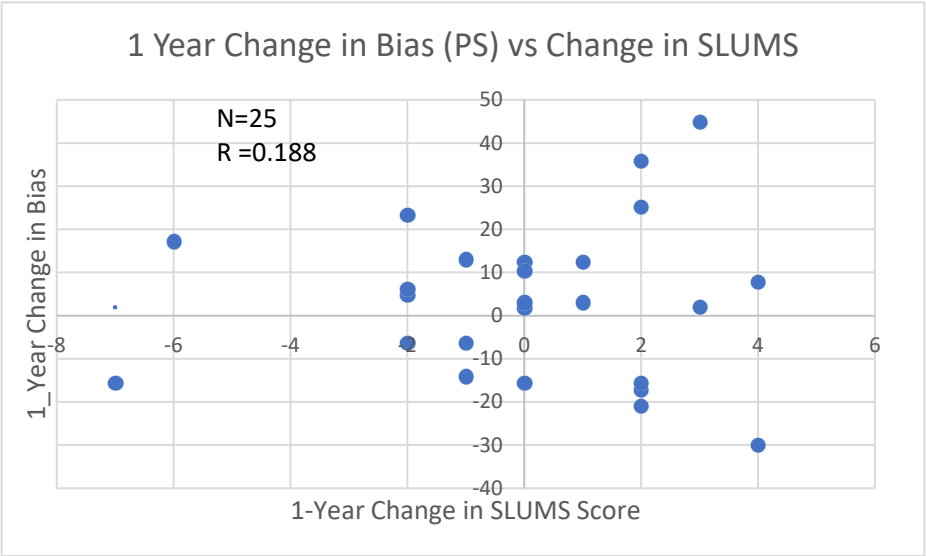


Figure 6: Lack of significant association between one-year rate of change in behavioral pattern separation and SLUMS test performance.

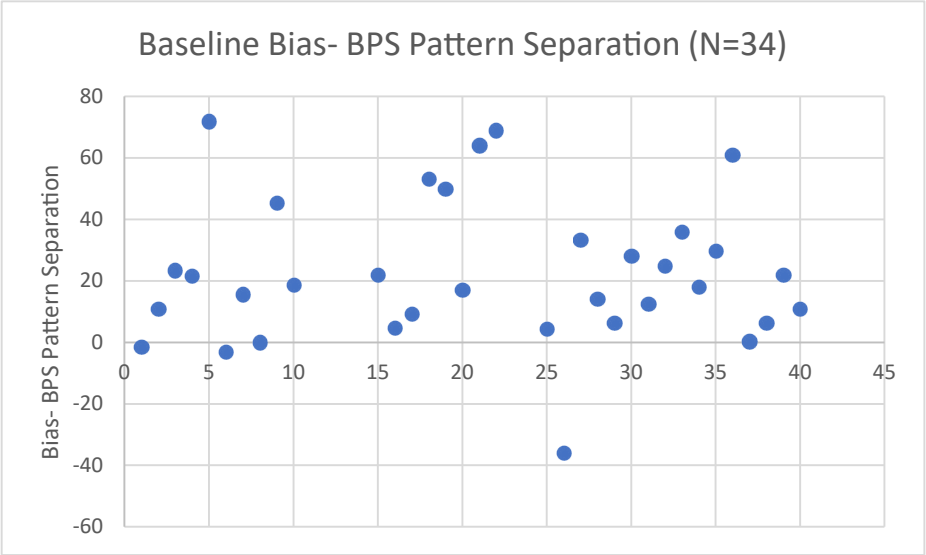


Figure 7: Distribution of baseline behavioral pattern separation test scores in 34 middle aged adult TBI patients.

6). Baseline BPS-O scores were widely- ranging in middle-aged TBI patients consistent with prior report of high degree of individual differences on pattern separation, object task [6] (Figure 7). Many middle-aged TBI patients had relatively preserved one-year BPS scores even though they had already experienced significant declines in the other cognitive tests of memory recall, executive function and processing speed. This suggests that in younger adult TBI population age 40-60, pattern separation may be less useful as an indicator of early cognitive decline than the SLUMS, Trail-making Part B and digit symbol substitution tests.

In summary, the current results suggest that middle-aged adult TBI patients (age 40-60 years) (including those exposed to repeated TBI) can experience significant cognitive decline after a relatively short time period (one year) and that baseline presence of plasma 5HT2AR AAB was a significant predictor of cognitive decline across three different cognitive domains.

Acknowledgments

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The authors report no competing interests with any products or techniques employed in this study.

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