The Impact of Cholesterol-Lowering Medication Use and Plasma Lipid Levels on Cognitive and Motor Function in Parkinson’s Disease

Kaltra Dhima, B.A.
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National Academy of Neuropsychology

BACKGROUND

- PD is the second most common neurodegenerative disorder
- Cardinal motor symptoms
  - Bradykinesia
  - Rigidity
  - Rest tremor
  - Postural instability
- Heterogeneous presentation & disease progression
- Age at PD onset predicts speed of disease progression
  - Young onset → slow progression
  - Older onset → fast progression
- Risk of cognitive decline unclear
  - MCI in 19-38% of non-demented PD patients
  - ~80% develop dementia eventually

1. PD is the second most common neurodegenerative disorder
2. Cardinal motor symptoms
3. Heterogeneous presentation & disease progression
4. Age at PD onset predicts speed of disease progression
5. Risk of cognitive decline unclear
BACKGROUND

Previous study found protective effect of hyperlipidemia diagnosis on memory function over time in PD

Lipid levels in PD:
- Lower incidence of PD related to abnormal lipid levels (e.g., high LDL)\(^7\text{-}^{10}\)

Statins in PD:
- Lower incidence of PD among statin users\(^{11\text{-}16}\)
  - Anti-inflammatory properties\(^{17\text{-}20}\)
  - Increased striatal dopamine concentration in PD animal models\(^{21}\)
  - Reduced intraneuronal aggregation of alpha-synuclein\(^{22,23}\)

OBJECTIVE

Examine how use of cholesterol lowering medication and plasma lipid levels relate to cognitive and motor function and progression in Parkinson’s disease

Hypothesis:
Cholesterol lowering medication use and/or abnormal plasma lipid levels will demonstrate a neuroprotective effect in this PD cohort.
**METHOD**

- Parkinson’s Progression Markers Initiative ([www.PPMI-info.org](http://www.PPMI-info.org))
- PD cohort
  - *De novo* at enrollment
  - Recently diagnosed (≤2 years)
  - Assessed at baseline (T1) & 3 years later (T2)
    - Demographic & medical information
    - Neuropsychological & motor measures
    - Baseline blood collection (fasting ≥12 hours)
- 93 subjects
  - 423 → 93 (T1 & T2 measures, baseline lipid panel, fasting)

**STATISTICAL ANALYSIS**

- Stepwise linear regressions to predict cognitive and motor function
  - Baseline
    - Baseline predictors & outcome variables
  - Longitudinal
    - Baseline predictors & longitudinal outcome variables
    - Change scores = T2 - T1

- Bonferroni correction for multiple comparisons: α=0.006
PREDICTOR VARIABLES

- Baseline cholesterol-lowering medication use (Y/N)

- Baseline fasting lipid levels from blood plasma (mg/dL)
  - Triglycerides
  - High-density lipoprotein (HDL)
    - “good cholesterol”
  - Low-density lipoprotein (LDL)
    - “bad cholesterol”

- Age at baseline as covariate

OUTCOME VARIABLES

- Animal Fluency
- Benton Judgement of Line Orientation Test (JoLO)
- Hopkins Verbal Learning Test-Revised (HVLT-R)
  - Trials 1-3 total
  - Delayed recall
  - Retention
- Symbol Digit Modalities Test (SDMT), written
- Wechsler Memory Scale-III, Letter-Number Sequencing (LNS)
- Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)\textsuperscript{24} – Subscale III
  - Off state (≥6 hours) at T2
MDS-UPDRS

- Update published in 2008
- Multimodal scale assesses impairment and disability in PD
  - Subscales I-IV

Subscale III: Motor Examination
- Administered by the investigator
- Measures presence and severity of motor symptoms
  - 33 items based on 18 questions
  - Items scored 0-4 (absent – severe)
  - Score range 0-132

MDS-UPDRS SUBSCALE III

1. Speech
2. Facial expression
3. Rigidity
4. Finger tapping
5. Hand movements
6. Pronation-supination
7. Toe tapping
8. Leg agility
9. Arising from chair
10. Gait
11. Freezing
12. Postural stability
13. Posture
14. Bradykinesia
15. Postural tremor
16. Kinetic tremor
17. Rest tremor (amplitude)
18. Rest tremor (consistency)
### Table 1. Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
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<tr>
<td>Age at baseline</td>
<td>62.89</td>
<td>9.14</td>
<td>37</td>
<td>84</td>
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<td>Age at PD diagnosis</td>
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<td>85</td>
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<tr>
<td><strong>Total %</strong></td>
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<tr>
<td>Sex (male)</td>
<td>64</td>
<td>68.8</td>
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### Table 2. Predictor Variables

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<td>Age</td>
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<td>9.14</td>
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<tr>
<td>HDL</td>
<td>57.98</td>
<td>19.55</td>
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<td>LDL</td>
<td>109.52</td>
<td>36.35</td>
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<tr>
<td>Triglycerides</td>
<td>114.41</td>
<td>47.65</td>
<td>47</td>
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<td><strong>Total %</strong></td>
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<td>Cholesterol medication</td>
<td>31</td>
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### Table 3. Baseline Outcome Variables

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<td>51.06</td>
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<td>81</td>
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<tr>
<td>JoLO (ss)</td>
<td>12.57</td>
<td>2.83</td>
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<tr>
<td>HVLT-R - total recall (T)</td>
<td>46.23</td>
<td>10.46</td>
<td>20</td>
<td>69</td>
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<tr>
<td>HVLT-R - delayed recall (T)</td>
<td>44.66</td>
<td>10.79</td>
<td>20</td>
<td>63</td>
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<tr>
<td>HVLT-R - retention (T)</td>
<td>48.10</td>
<td>9.48</td>
<td>28</td>
<td>71</td>
</tr>
<tr>
<td>SDMT (T)</td>
<td>43.78</td>
<td>9.19</td>
<td>16</td>
<td>84</td>
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<tr>
<td>LNS (ss)</td>
<td>11.82</td>
<td>2.75</td>
<td>4</td>
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<tr>
<td>MDS-UPDRS-III*</td>
<td>19.49</td>
<td>7.62</td>
<td>6</td>
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*Raw score, higher is worse

### Table 4. Longitudinal Outcome Variables

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<tr>
<td>JoLO (ss)</td>
<td>-0.64</td>
<td>3.10</td>
<td>-8</td>
<td>6</td>
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<tr>
<td>HVLT-R - total recall (T)</td>
<td>-0.80</td>
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<td>-36</td>
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<td>11.69</td>
<td>-35</td>
<td>23</td>
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<tr>
<td>HVLT-R - retention (T)</td>
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<td>11.90</td>
<td>-38</td>
<td>22</td>
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<td>SDMT (T)</td>
<td>-0.01</td>
<td>9.98</td>
<td>-39</td>
<td>25</td>
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<td>LNS (ss)</td>
<td>-0.24</td>
<td>2.57</td>
<td>-7</td>
<td>6</td>
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<tr>
<td>MDS-UPDRS-III*</td>
<td>10.06</td>
<td>9.76</td>
<td>-12</td>
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Note: Change scores = T2 – T1
*Raw score, higher is worse
Table 5. Significant Regression Models

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<tr>
<th>Outcome</th>
<th>Predictor</th>
<th>p</th>
<th>F</th>
<th>Adj. R²</th>
<th>Beta</th>
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<td>Baseline</td>
<td></td>
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<tr>
<td>HVLT-R retention</td>
<td>age</td>
<td>0.023</td>
<td>5.365</td>
<td>0.058</td>
<td>-0.241</td>
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<td>Longitudinal</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>HVLT-R retention</td>
<td>triglycerides</td>
<td>0.014</td>
<td>6.393</td>
<td>0.067</td>
<td>0.282</td>
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<tr>
<td>HVLT-R delayed recall</td>
<td>triglycerides</td>
<td>0.047</td>
<td>4.057</td>
<td>0.035</td>
<td>0.216</td>
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<tr>
<td>MDS-UPDRS-III</td>
<td>LDL</td>
<td>0.042</td>
<td>4.308</td>
<td>0.045</td>
<td>-0.242</td>
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CONCLUSIONS

- Cholesterol measures did not predict cognitive or motor function at baseline
- Higher age predicted worse memory at baseline
- Higher baseline triglycerides predicted slower memory decline
- Higher baseline LDL predicted slower motor decline

→ Association between hyperlipidemia and better outcomes in cognitive and motor function
→ Hyperlipidemia may slow down disease progression in PD
REFERENCES

THANK YOU!

- Co-authors:
  - Nicholas Holder, BS
  - C. Munro Cullum, PhD, ABPP-CN
  - Laura Lacritz, PhD, ABPP-CN

QUESTIONS?
Neurocognitive Variability Following Treatment for Autoimmune Encephalitis

KELLY COULEHAN, PH.D.
NEUROPSYCHOLOGY FELLOW
MOUNT SINAI EPILEPSY CENTER
10/26/17

Goals
Autoimmune Encephalitides
Case Series
Findings and Conclusions
Future Directions
Autoimmune Encephalitides (AE)

AEs are neuropsychiatric disorders and symptoms can include:

- Flu-like symptoms
- Alterations of consciousness
- Cognitive decline
- Emotional and behavioral disturbances
- Seizures
- Reduced speech
- Abnormal movements
- Autonomic instability
- Hypoventilation

Image: https://www.rarediseasereview.org/publications/2017/2/9/oojx5ip8cd58paslejwgf3hmi9m3nl

Autoimmune Encephalitides (AE)

- AEs are not always cancer or tumor related
  - Younger patients are less likely to have tumors
- Treatments include immunotherapies and resection of underlying tumor
- Early treatment tends to be associated with better outcomes
- 75% full/substantial recovery
- Neurological relapses in 25%
- Mortality rate is ~3-7%
Autoimmune Encephalitides (AE)

- Two theories of how antibodies get into brain:
  - Antibodies are synthesized within the cerebral spinal fluid
  - Pathologically disrupted blood-brain-barrier, likely due to inflammation and stress

Receptors associated with AEs:
- **N-Methyl D-aspartate (NMDA)**
- **Voltage-gated potassium channel (VGKC)**
- $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)
- Glycine
- Dopamine 2
- Gamma-aminobutyric acid (GABA)
- Metabotropic glutamate

Autoimmune Encephalitides (AE)

Clinical features of the acute disease are well characterized; however, neurocognitive long-term outcome has not been examined in detail.

This case-series compares and contrasts the neurocognitive functioning of four patients status/post AE:
- 2 anti-NMDA
- 1 limbic encephalitis
- 1 unknown etiology
Goals
Autoimmune Encephalitides
Case Series
Findings and Conclusions
Future Directions

Case Series: Demographics

<table>
<thead>
<tr>
<th>CASE</th>
<th>AE TYPE</th>
<th>Age at Onset</th>
<th>NP testing from onset</th>
<th>Male/Female</th>
<th>Handedness</th>
<th>Education (years)</th>
<th>Racial Ethnicity</th>
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<tbody>
<tr>
<td>Patient 1</td>
<td>Anti-NMDA</td>
<td>16</td>
<td>1-2 months</td>
<td>F</td>
<td>R</td>
<td>10</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Anti-NMDA</td>
<td>19</td>
<td>4 months</td>
<td>F</td>
<td>L</td>
<td>12</td>
<td>Caucasian/Middle Eastern</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Limbic/VGKC</td>
<td>34</td>
<td>12 months</td>
<td>M</td>
<td>R</td>
<td>18</td>
<td>Caucasian</td>
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<tr>
<td>Patient 4</td>
<td>Unknown</td>
<td>39</td>
<td>2 months</td>
<td>F</td>
<td>R</td>
<td>18</td>
<td>Asian</td>
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Case Series: Medical Presentation

<table>
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<tr>
<th>CASE</th>
<th>AE TYPE</th>
<th>Tumor</th>
<th>MRI</th>
<th>EEG</th>
<th>Onset to Treatment</th>
<th>Treatment</th>
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<tbody>
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<td>Patient 1</td>
<td>Anti-NMDA</td>
<td>N</td>
<td>Unremarkable</td>
<td>Abnormal</td>
<td>2-3 weeks</td>
<td>Steroids, intravenous immunoglobulin</td>
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<tr>
<td>Patient 2</td>
<td>Anti-NMDA</td>
<td>Y</td>
<td>Remarkable</td>
<td>Abnormal</td>
<td>2-3 weeks</td>
<td>Steroids, intravenous immunoglobulin, tumor removal</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Limbic/VGKC</td>
<td>N</td>
<td>Unremarkable</td>
<td>Abnormal</td>
<td>12 months</td>
<td>Steroids, intravenous immunoglobulin</td>
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<tr>
<td>Patient 4</td>
<td>Unknown</td>
<td>N</td>
<td>Unremarkable</td>
<td>Abnormal</td>
<td>1-2 weeks</td>
<td>Steroids, intravenous immunoglobulin</td>
</tr>
</tbody>
</table>

Case Series: Patient 1, 16yo Anti-NMDA

**Presenting Symptoms:**
- Psychosis, delirium, altered mental status, delusions and hallucinations, and agitation

**EEG:** Pronounced right hemisphere slowing

**MRI:** Negative

**Relevant Medical History:**
- Headaches

**Psychiatric:**
- History: Anxiety and ADHD
- Current: mild anxiety, minimal depression

**Neuropsychological Functioning**

<table>
<thead>
<tr>
<th>FSIQ</th>
<th>GAI</th>
<th>VCI</th>
<th>PRI</th>
<th>WMI</th>
<th>PSI</th>
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<td>87</td>
<td>91</td>
<td>107</td>
<td>87</td>
<td>86</td>
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<table>
<thead>
<tr>
<th>Language</th>
<th>Processing Speed</th>
<th>Verbal memory</th>
<th>Attention</th>
<th>Executive Functioning (problem solving, set-shifting, working memory)</th>
<th>Visuospatial skills/nonverbal memory</th>
<th>Bilateral fine motor dexterity</th>
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</thead>
</table>
Case Series: Patient 2, 19 yo Anti-NDMA

Presenting Symptoms:
- Fever, cough, headache, LOC, withdrawn, tearful, seizures
- After 6 weeks, minimal verbal expression, not responding to verbal commands, would not open eyes, increased agitation and delusions of persecution
- After 4 months, ovarian teratoma discovered

EEG: Temporal lobe seizure with secondary generalization; diffuse generalized slowing

MRI: Scattered hyperintensities bright foci

Relevant Medical History: None

Psychiatric:
- History: None reported
- Current: moderate anxiety, moderate depression

Neuropsychological Functioning
Premorbid estimate = Average
Raven’s SPM = 5th %ile

<table>
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<tr>
<th>STRENGTHS</th>
<th>WEAKNESSES</th>
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<tr>
<td>Attention</td>
<td>Processing Speed</td>
</tr>
<tr>
<td>Executive Function (verbal and visual fluency)</td>
<td>Executive Function (set-shifting, inhibition)</td>
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<tr>
<td>Visuospatial skills</td>
<td>Language</td>
</tr>
<tr>
<td></td>
<td>Verbal and visual memory</td>
</tr>
<tr>
<td></td>
<td>Bilateral fine motor dexterity</td>
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</tbody>
</table>

Case Series: Patient 3, 35yo Limbic/VGKC

Presenting Symptoms:
- Blurry vision, motor twitches in arms and legs.
- 6 months later, muscle spasms in right leg and face, vomiting, hallucinations, “heavy headed” feeling, seizures, disorientation, fatigue

EEG: Left temporal sharp waves

MRI: Negative

Relevant Medical History:
- Viral meningitis and migraines

Psychiatric:
- History: Obsessive-Compulsive Disorder
- Current: moderate anxiety, moderate depression

Neuropsychological Functioning
Premorbid IQ = 96th %ile
FSIQ = 81st %ile
VCI = 81st %ile
PRI = 73rd %ile

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<td>Executive Function (Encoding, inhibition, planning, organization)</td>
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<td>Visuospatial skills</td>
<td>Language</td>
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<td>Verbal and visual memory</td>
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<td>Attention/Working Memory</td>
<td>Processing speed</td>
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<td>Executive Function (set-shifting, mental flexibility)</td>
<td>Executive Function (Encoding, inhibition, planning, organization)</td>
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<td>Language</td>
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<td></td>
<td>Verbal and visual memory</td>
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</table>
### Case Series: Patient 4, 39 yo Unknown

**Presenting Symptoms:**
- Headaches, muscle pain, fever, flu-like symptoms for 6 days
- Found unresponsive in her apartment, seizure, auditory hallucinations

**EEG:**
- Occasional left hemispheric discharges
- Occasional right hemisphere sharp waves
- Occasional diffuse sharp waves

**MRI:** Negative

**Relevant Medical History:** None

**Psychiatric:**
- History: None reported
- Current: minimal anxiety, minimal depression

### Neuropsychological Functioning

<table>
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<tr>
<th></th>
<th>Premorbid IQ = 95th %ile</th>
<th>FSIQ = 88th %ile</th>
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<tr>
<td>VCI</td>
<td>79th %ile</td>
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<tr>
<td>PRI</td>
<td>91st %ile</td>
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<tr>
<td>PSI</td>
<td>96th %ile</td>
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<table>
<thead>
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<tbody>
<tr>
<td>Processing Speed</td>
<td>Executive Function</td>
</tr>
<tr>
<td></td>
<td>(mental flexibility, verbal fluency, planning, organization)</td>
</tr>
<tr>
<td>Attention</td>
<td>Language (naming)</td>
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<tr>
<td>Executive Function</td>
<td></td>
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<tr>
<td>(working memory)</td>
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<tr>
<td>Verbal and visual memory</td>
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### Goals

- Autoimmune Encephalitides
- Case Series
- Findings and Conclusions
- Future Directions
Overall Findings

- **Executive Function**: All patients evinced executive dysfunction, including:
  - set-shifting, inhibition, planning/organization, encoding, mental flexibility, verbal letter fluency, problem solving, working memory
- **Processing Speed**: Processing speed difficulties were observed in 3 out of 4 patients
- **Visuospatial Skills**: relative weaknesses compared to verbal skills
  - Perceptual reasoning < verbal comprehension
  - Visual memory < verbal memory
- **Variability**: Inconsistent findings for deficits in language, memory, and fine motor skills
- **Mood**: Three of the four patients endorsed currently experiencing mild to moderate psychological distress.

**NO CONSISTENT PATTERN IN STRENGTHS**

Outline

- **Autoimmune Encephalitides**
- **Case Series**
- **Findings and Conclusions**
- **Future Directions**
Future Directions

NEUROPSYCHOLOGICAL
- Known long-term neuropsychological difficulties
  - Underscores importance of neuropsychological follow up
  - Considering the heterogeneity of outcomes, individualized recovery approach
- Determine predictors of severity and duration of neuropsychological difficulties
- What are the efficacious cognitive interventions
- Optimal time to assess neurocognitive function

GENERAL
- Determine best type and duration of immunotherapy
- What contributes to relapsing/remitting cases?
  - Is long-term immunotherapy needed?
- Mechanisms maintaining duration of recovery
- Mechanisms that initiate illness onset

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- Ilia Lledo
References


Beyond 24hr vEEG: Relying on Neuropsychological Testing to Better Understand Non-epileptic Seizures

Shafer, M.E., Durrett, C., Burghardt, T., Fabiano, R.J., & Yassin-Kassab, M.
PNES Prevalence Rates

- Difficult to accurately determine b/c
  - Guidelines for identifying PNES
  - Overreliance on patient self-report for ES
  - Lack of EEG findings are not 100% indicative of PNES

- 300,000 to 400,000 PNES cases in US (no population studies)
- Among Referrals to neurology centers estimates are
  - 1.5/100,000 to 3/100,000 per year
  - PNES = 10% of outpatient Neurology Visits
  - PNES = 40-50% of Hospital Consultations
- Less than 15% of patients have combination of PNES + ES
- NES about 85% are psychogenic (15% are physiologic)
- 85% of PNES patients are females
- Average age of onset (20 to 25)
- NES = 2 to 33/100,000 in the general population (similar to MS rates)
- Rates increase among individuals with TBI, LD, and NPSY deficits

Neurology vs Psychiatry

- Factors further complicating PNES:
  - 1. EEG are normal for PNES
  - 2. EEG can be normal for ES
  - 3. Patients can have both PNES & ES
  - 4. The average duration for Dx is 7 to 16 years
  - 5. Non-epileptic Sz may be clinically electrographically indistinguishable from epileptic events (Lee, 2010).

- Further Complicated by the fact that neurologist often dismiss PNES (interpreting as a voluntary behavior) and psychiatry/psychologist are afraid of “miss” a genuine seizure disorder.
PNES: Intentional vs. Unintentional

Unintentional

- Somatoform Disorders
- Conversion Disorders
- Panic Disorders
- Dissociative Disorders
- Depersonalization Disorders
- Posttraumatic Disorders (PTSD)

Intentional

- Malingering
- Factitious Disorder

Present Study

- The present study aims to focus on 3 areas:
  - 1. What does motivation look like among individuals with PNES.
    - Are there differences between symptom reports and motivation.
  - 2. Individuals with PNES often complain about impaired cognitive functioning (similar to ES). We wanted to study the accuracy of this concern.
  - 3. What does the psychological profile of PNES patients look like, exploring relationships
Sample

- Total Study = 53
- Approximately 77% of the sample was female (N = 41) (this is slightly slower than the national average which tend to describe to 80 to 90%)
- Sample ranged from 17 to 68 (Mean = 39, SD = 15.99), with males being about 10 years older than female on average (47 years vs 37)-This was NOT considered statistically significant.
- 80% of the sample reported a history of sexual assault.
- All patients completed at least a 24hr vEEG study and were found to meet criteria for PNES.

Symptom Validity vs. Performance Validity

- 44 participants completed the TOMM.
- Mean Score for sample= 45 (i.e., passing score).
- No statistical difference between males and females
- Only 2 participants failed TOMM (both male).
Symptom Validity vs Performance Validity

MMPI T-Scores (Sample)

Mean TOMM Scores

Cognitive Scores (sample)

- IQ Scores:
  - FSIQ = 90.27, SD = 15.36
  - VIQ = 93.72, SD = 15.48
  - PIQ = 91.62, SD = 15.38
  - WMI = 90.24, SD = 16.97
  - PSI = 91.18, SD = 14.95

Academic:
- WRAT-4 = 93.46, SD = 21.40

Information Processing:
- TMT A = 45.95, SD = 14.91
- TMT B = 42.02, SD = 19.97
Memory Systems

- Verbal Memory (CVLT-II)
  - Trial 1 = 43.64, SD 11.32
  - Trials 1-5 = 44.00, SD = 13.46
  - SD Free Recall = 41.70, SD = 15.51
  - LD Free Recall = 42.84, SD = 15.75

- Visual Memory (WMS-Visual Reproduction)
  - I = 8.5
  - II = 8.5
  - Rey 15 Item Test = 14, SD = 1.598

Cognitive Functioning

- CVLT-II scores universally lower (differing from 50).
- Working memory indices were from WAIS correlated with CVLT
- TMT B correlated with CVLT
- TMT A did NOT differ from 50 while TMT did differ from 50.
Gender Differences for Cognition

- Information Processing speed Index was lower among male participants than female (significantly). Women PSD (95) vs males (81)
- As a trend, WAIS scores were slightly higher among women with the exception of WM which was higher for males (none of these met the criteria for statistical significance however).

Attentional Processing

- Trend showing CVLT-II scores were associated with TMT B and WMI which makes sense, we just wonder why among this group is this so prominent
- Scores for TMT B are lower than A (statistically) which shows greater involvement of the executive systems.
No gender differences for scales L & F while males were slightly higher on K (this was statistically significant).

Clinical Scales M/F is statistically different by gender (as expected).

Obsessive Compulsive Scale was statistically higher in woman (M = 70) than men (M = 60).

Social Isolation was higher among women (M = 64) than men (M = 53).

PTSD subscales were higher for women (Keane = 77 vs 65; Schlenger = 69 vs 62).
MMPI-II

- Women report higher rates of PTSD
- Males show a NS trend toward much higher rates of somatization
- CPT scores for detectability were corrected (mild) (.44) with PTSD (positive relationship showing higher rates of PTSD were correlated with a greater capacity for detectability).
- Depression correlates with PTSD-K (.6) and PTSD-S (.8)
- OCD scales correlate with PTSD-K (.75) and PTSD-S (.73)
- Anxiety does NOT correlate with PTSD-K or PTSD-S
- TOMM scores NOT correlated with PTSD scales
- PTSD correlates with F scale (PTSD-K = .722, PTSD-S = .719)
  - Suggesting a relationship between feeling psychological overwhelmed and increased reports of PTSD symptomatology.

Psychological Functioning Cont.

- Age and Psychological Functioning:
  - Older patients in this study reported less PTSD
  - Older patients reported more Anxiety, Somatization
  - Older patients reported less social isolation and mania
  - Older patients exhibited greater levels of defensiveness
Future Research

- Exploring with greater specificity the features of PTSD, dissociative conditions, inherent personality features that may be unique to the PNES profile.
- We have proposed an IRB program at MSU to specifically compare and contrast patient’s with epilepsy, PNES, and PTSD in order to identify unique profiles.
- There is speculation that there may be several unique clusters of PNES (e.g., dissociative, borderline personality) that could respond to various treatments.
- Study how psychiatry can play a more active role in managing and reducing PNES.

Aggression and Anger in Active Duty Service Member with Mild Traumatic Brain Injury

Jason M. Bailie, Ph.D.
Vindhya Ekanayke, M.S.
Mark Ettenhofer, Ph.D.
Angelica Dilay, MPH
Cynthia Boyd, Ph.D.
What is the difference between irritability and aggression?

Anger Spectrum of Emotions

Irritated
Impatient
Annoyed

Internal experience
Thoughts, feelings

Observable behavior
Words, actions

Aggressive

Image source: http://www.bestcollegesonline.com/blog/2012/08/12/10-things-every-teacher-needs-to-know-about-emotions-and-learning/
TBI and Anger

- TBI is associated with anger across severity
  - mild, moderate, severe, penetrating
- Anger problems vary from irritability to overt violence
- Anger often declines with increased time from injury
- Associated with civilian and military-related injury

Anger Prevalence

- Mild TBI, one year after injury: 36% to 47%
- Moderate and severe TBI, one year after injury: 15% to 34%


Aggression after TBI

- Rates of Aggression range from 24% to 34%
  - Physical aggression to another person is rare but verbal aggression is relatively common
  - History of TBI increases the risk for future aggressive behavior and/or violent crime in military veterans

- TBI is associated with other psychological disorders as well...

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apathy</td>
<td>60%</td>
</tr>
<tr>
<td>Depression</td>
<td>10-50%</td>
</tr>
<tr>
<td>Posttraumatic Stress Disorder</td>
<td>11-18%</td>
</tr>
</tbody>
</table>
Objective

To determine the relationship between anger and acts of aggression following mTBI when controlling for depression, post-traumatic stress, and severity of combat exposure.

Participants

25 active duty service members referred for evaluation and treatment of a mild TBI

- Age: $M= 33, SD = 9.02$ (Min = 19, Max = 52)
- Gender: 84% male, 16% female
- 36% High School, 56% Some College, 8% Bachelors Degree
- Years Military: $M= 12.6, SD = 7.09$
- 28% Had Notable Post-Traumatic Stress (PCL-C >50)
- 80% reported history of combat
  - 46% had more than 2 deployments
  - Combat Exposure Scale: $M= 7.8, SD = 5.65$
STAXI-2

State-Trait Anger Expression Inventory, Second Edition (STAXI-2)
• 57 items rated on a four-point Likert scale
• 6 Primary Clinical Scales
• Well validated for clinical assessment of anger problems
• Published normative data
• Strong independent empirical support

<table>
<thead>
<tr>
<th>Scale</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>State Anger</td>
<td>Current Feelings of Anger</td>
<td>I am mad</td>
</tr>
<tr>
<td>Trait Anger</td>
<td>Frequency of angry feelings</td>
<td>I am quick tempered</td>
</tr>
<tr>
<td>Anger Expression-Out</td>
<td>Expression verbal/physical</td>
<td>I do things like slam doors</td>
</tr>
<tr>
<td>Anger Expression-In</td>
<td>Anger is suppressed</td>
<td>I keep things in</td>
</tr>
<tr>
<td>Anger Control-Out</td>
<td>Control outward expression</td>
<td>I control my temper</td>
</tr>
<tr>
<td>Anger Control-In</td>
<td>Calming or cooling off</td>
<td>I take a deep breath</td>
</tr>
<tr>
<td>Anger Expression Index</td>
<td>Sum of Anger Exp/Control Items</td>
<td></td>
</tr>
</tbody>
</table>

Anger Problems after TBI

- **State-Anger**
  - Normal: 39%
  - Elevated: 61%
  - $M = 54.31$, $SD = 13.21$

- **Trait Anger**
  - Normal: 35%
  - Elevated: 65%
  - $M = 61.71$, $SD = 15.25$

- **Anger Expression Out**
  - Normal: 42%
  - Elevated: 58%
  - $M = 52.13$, $SD = 14.92$

- **Anger Expression Index**
  - Normal: 35%
  - Elevated: 65%
  - $M = 61.62$, $SD = 12.54$
### Aggressive Behaviors

<table>
<thead>
<tr>
<th>Aggressive Behavior</th>
<th>Freq. (%)</th>
<th>Aggressive Behavior</th>
<th>Freq. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argue with Family</td>
<td>65.4%</td>
<td>Trouble Controlling Anger</td>
<td>38.5%</td>
</tr>
<tr>
<td>Verbally Threaten</td>
<td>46.2%</td>
<td>Act without Thinking</td>
<td>57.7%</td>
</tr>
<tr>
<td>Damaged Property</td>
<td>46.2%</td>
<td>Argue with Others</td>
<td>34.6%</td>
</tr>
<tr>
<td>Bx “Out of Control”</td>
<td>46.2%</td>
<td>Hit Something Because Anger</td>
<td>61.5%</td>
</tr>
<tr>
<td>Physically Injured Someone</td>
<td>19.2%</td>
<td>Disciplinary Action (i.e. NJP)</td>
<td>7.7%</td>
</tr>
<tr>
<td>Arrested</td>
<td>0%</td>
<td>Problem with a Supervisor</td>
<td>26.9%</td>
</tr>
</tbody>
</table>

### Results

<table>
<thead>
<tr>
<th></th>
<th>S-Ang</th>
<th>T-Ang</th>
<th>AX-O</th>
<th>AX Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggressive Behavior (ABQ)</td>
<td>0.38</td>
<td>0.76</td>
<td>0.69</td>
<td>0.77</td>
</tr>
<tr>
<td>Depression (PHQ-9)</td>
<td>0.25</td>
<td>0.63</td>
<td>0.30</td>
<td>0.41</td>
</tr>
<tr>
<td>Resiliency (CD-RISC)</td>
<td>0.09</td>
<td>-0.52</td>
<td>-0.35</td>
<td>0.42</td>
</tr>
<tr>
<td>Combat Exposure (CES)</td>
<td>0.39</td>
<td>0.33</td>
<td>0.35</td>
<td>0.29</td>
</tr>
<tr>
<td>Post-Traumatic Stress (PCL-C)</td>
<td>0.35</td>
<td>0.74</td>
<td>0.51</td>
<td>0.56</td>
</tr>
</tbody>
</table>

- $r > 0.50$
- $r < -50$
# Results

## Uncontrolled

<table>
<thead>
<tr>
<th></th>
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</tbody>
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## Controlled for Post Traumatic Stress, Depression, & Resiliency

<table>
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<td>0.58</td>
<td>0.67</td>
</tr>
</tbody>
</table>

$r > 0.50 \quad r < -50$

---

# Summary

- In a diverse sample of military members with a history of mild traumatic brain injury, current feelings of anger were related to self-reported aggression.

- Individuals most commonly had problems with high frequency of anger problems (trait anger) as well as difficulty controlling their anger expression.

- Patients most common aggressive behaviors were:
  - Arguing with others
  - Hitting something out of anger

---

"Medically Ready Force...Ready Medical Force"
Summary

- Anger and self-reported aggressive behavior were both highly correlated with other psychological factors such as depression, resiliency, and post-traumatic stress.

- Despite high multi-collinearity the relationship between anger and aggressive behavior following mTBI is independent of depression, resiliency, and post-traumatic stress.

Summary

- Trait Anger and Anger Expression/Control had the most influential relationship with self-reported Aggressive Behavior.
  - Together, Trait Anger and the Anger Expression Index explained 64% of variability in the Aggressive Behavior Questionnaire.
Questions?

References


