Catechol-O-Methyltransferase (COMT) and Treatment Response to Meditation and Group Therapy in Veterans with PTSD

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Introduction
• Post-traumatic stress disorder is a chronic and debilitating psychiatric disorder that affects 30% of veterans and 8% of the US population.1
• Approximately 28-49%2 of veterans with PTSD display improvement in PTSD symptoms when treated with non-pharmacologic treatment interventions such as:
  → Mindfulness Based Stress Reduction (MBSR)
  → Transcendental Meditation (TM)
  → Present-Centered Group Therapy (PCGT)
• Catechol-O-methyltransferase (COMT) enzyme catabolizes dopamine and norepinephrine, which regulate mood and anxiety.
• The rs4680 (Val158Met) polymorphism alters the enzyme's structure resulting in reduced activity that is only 25% of the wild type.3
• The Val158Met polymorphism has been associated with PTSD risk, however its influence on treatment outcome is unknown.

Project Aim: Assess the relationships between the Val158Met polymorphism, symptom severity and treatment response in veterans receiving non-pharmacological treatments.

Methods
Study Population: The study cohort utilized participants (n=120) obtained from a previously conducted randomized clinical trial.4 Inclusion criteria included: diagnosis of PTSD and on a stable medication regiment in PTSD treatments.

Genotyping: The COMT Val158Met polymorphism genotyping was performed on blood-derived DNA by a TaqMan Genotyping assay (Life Technologies) analyzed on the Applied Biosystems 7500 Real Time PCR system.

Statistical Analysis: Primary clinical outcomes were MBSR cohort (PCL) baseline and week nine scores; and early childhood/lifetime trauma occurrences. ANOVA, T-test, and Chi-Squared tests were used to test for associations.

Table 1: Study Cohort Demographics and Summary Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>MBSR 7TM</th>
<th>N=71</th>
<th>%</th>
<th>N=120</th>
<th>%</th>
<th>N=49</th>
<th>%</th>
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<tbody>
<tr>
<td>Male</td>
<td>57</td>
<td>80.2</td>
<td>44</td>
<td>89.8</td>
<td>101</td>
<td>84.2</td>
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<tr>
<td>Race</td>
<td>Caucasian</td>
<td>59</td>
<td>83.1</td>
<td>43</td>
<td>87.8</td>
<td>102</td>
<td>85.0</td>
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<tr>
<td>Other</td>
<td>12</td>
<td>16.9</td>
<td>6</td>
<td>12.2</td>
<td>18</td>
<td>15.0</td>
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<tr>
<td>Age</td>
<td>59.4</td>
<td>10.7</td>
<td>58.6</td>
<td>9.9</td>
<td>58.7</td>
<td>10.2</td>
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<tr>
<td>PCL Total Score</td>
<td>63.0</td>
<td>10.3</td>
<td>57.4</td>
<td>13.0</td>
<td>60.8</td>
<td>12.3</td>
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<tr>
<td>PCL Total Change (Week 9)</td>
<td>-9.4</td>
<td>12.4</td>
<td>-2.9</td>
<td>10.1</td>
<td>-6.4</td>
<td>11.52</td>
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<tr>
<td>PCL subset scores</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td>PCL Re-experiencing Baseline</td>
<td>17.8</td>
<td>4.38</td>
<td>15.9</td>
<td>4.25</td>
<td>17.1</td>
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<td>PCL Re-experiencing change (Week 9)</td>
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<td>4.47</td>
<td>-0.84</td>
<td>3.72</td>
<td>-1.60</td>
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<td>PCL Arousal Baseline</td>
<td>19.1</td>
<td>3.69</td>
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<td>3.85</td>
<td>18.6</td>
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<td>PCL Arousal Change (Week 9)</td>
<td>-2.82</td>
<td>4.39</td>
<td>-0.75</td>
<td>3.40</td>
<td>-1.86</td>
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<td>PCL Avoidance Baseline</td>
<td>26.0</td>
<td>4.40</td>
<td>23.5</td>
<td>7.02</td>
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<td>PCL Avoidance Change (Week 9)</td>
<td>-4.85</td>
<td>5.07</td>
<td>-1.37</td>
<td>4.81</td>
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<td>Week 9 Responder</td>
<td>31</td>
<td>43.6</td>
<td>11</td>
<td>22.4</td>
<td>42</td>
<td>35.0</td>
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<td>Childhood Trauma</td>
<td>31</td>
<td>43.6</td>
<td>18</td>
<td>42.9</td>
<td>49</td>
<td>40.8</td>
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Figure 1: COMT Val158Met genotyping by allelic discrimination using TaqMan fluorescence probes

Figure 2: The COMT Gene

Figure 3: Baseline PCL total scores by COMT genotype across participants with or without evidence of childhood trauma

Prior to the treatment intervention, participants with childhood trauma (n=49) who were Met158 carriers exhibited higher baseline PCL total scores (95%CI [-17.276, -0.935]). No differences in baseline PCL total scores were observed in participants without evidence of childhood trauma (n=71).

Figure 4: Baseline re-experiencing symptoms sub-test scores by COMT genotype across participants with or without evidence of childhood trauma

Primary Findings
- We identified a significant relationship between the reduced activity 158Met allele and increased PTSD re-experiencing symptoms in patients with childhood trauma.
- This indicates that dysregulated dopamine or norepinephrine signaling may be involved with mechanisms related to specific symptoms related to re-experiencing those events later in life. COMT genotypes were not associated with response to the treatments examined herein.

Conclusion/Discussion
Underlying the relationship between how genetics can influence PTSD symptom severity and treatment response to certain interventions can help us discover better more effective genetically-tailored treatment options for people with PTSD.

Strength: Longitudinal data from carefully controlled trials provides a unique opportunity to examine genetic relationships with PTSD treatment outcomes.

Weakness: Future studies in larger cohorts are necessary in order to validate potential gene x environment interactions between COMT Val158Met and childhood trauma on PTSD symptom severity.

Translation
Clinical Implication: Identifying potential genetic biomarkers of symptom severity and treatment response may help clinicians improve treatment strategies for patients with PTSD.

Ethical Considerations: Lack of representation in study cohort; potential for discrimination; patient privacy.

Key Stakeholders: Veterans with PTSD and their families; clinicians; PTSD treatment centers; and genetic testing companies.

Acknowledgments
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References
1. US Department of Veterans Affairs. PTSD: National Center for PTSD. Public. 2007; 3-4
3. Rs4680. Rs12913832 – SNPedia
4. 2015;314(5):456–465