

Grapheme-Color Synesthesia is Associated with PTSD Among Deployed Veterans: Confirmation of Previous Findings and Need for Additional Research

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ABSTRACT: *Post-traumatic stress disorder (PTSD) is related to alteration in neuropsychological functioning, including visual and other cognitive processes. Grapheme-color synesthesia is a phenomenon in which a letter or number elicits response of a concurrent image or color perception. Since we earlier reported an association between grapheme-color synesthesia and PTSD, our objective in the current study was to validate this association among a new study group and assess risk factors. For this, we surveyed 1,730 military veterans who have been outpatients in the Geisinger Clinic, a multi-hospital system in Pennsylvania, USA. All the study veterans served in a warzone deployment. The association between PTSD and Grapheme-color synesthesia was evaluated. The average age of veterans was 59.6 years among whom 95.1% were male. Current PTSD prevalence rate was observed to be 7.6% (95% C.I. = 6.5-9.0) and in 3.4% of veterans (95% C.I. = 2.7-4.4) grapheme-color synesthesia was found to be positive. Initial bivariate analyses suggested that synesthesia was associated with current PTSD [odds ratio (OR) = 3.3, $p < 0.001$]. Multivariable stepwise logistic regression evaluating the age, sex, education, trauma exposure, current psychological stress, psychotropic medication use, combat exposure, history of concussion, and current depression, confirmed this association (OR = 2.33, $p = 0.019$). The present study corroborated that Grapheme-color synesthesia was linked to PTSD among a second cohort of deployed military veterans. Further research is recommended in order to validate this observation and to determine whether synesthesia is a risk factor for PTSD.*

KEYWORDS: *Post-traumatic stress disorder, Depression, Synesthesia, Veterans, Risk factors, Trauma exposure*

ABBREVIATIONS

CES: Combat Experience Scale; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; GC: Geisinger Clinic; PTSD: Post-traumatic Stress Disorder

INTRODUCTION

Synesthesia represents a phenomenon in which sensations arise in an unrelated sense modality upon presentation with one sensory modality (Brang & Ramachandran, 2011). Previous studies suggests that synesthesia is prevalent at the rate of about 3-4% among the general population (Asher et al., 2009) with an increased prevalence in first-degree relatives (Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996). Grapheme-color synesthesia is the most common form of synesthesia (Simner & Carmichael, 2015), whereby a number or a letter elicits a concurrent image or a specific color perception (Niccolai, Jennes, Stoerig, & Van Leeuwen, 2012).

Synesthesia may be a marker for underlying neurophysiologic and neuroanatomic changes resulting in cross activation of brain maps (Ramachandran & Hubbard, 2001). Recently it has been suggested that certain mechanisms associated with synesthesia and associated processes may reflect psychopathological symptoms related to enhanced temporo-limbic excitability (Neckar & Bob, 2016). Since brain activity during synesthetic color experiences appears to develop from within the ventral temporal lobe, it has been proposed that the phenomenon of grapheme-color synesthesia manifests from abnormal cross-wiring or feedback between different regions of the brain engaged in extracting visual characteristics of form and color (Mattingley, 2009), although this hypothesis has been questioned (Hupe & Dojat, 2015).

Synesthesia has also been linked to some medical conditions, such as irritable bowel syndrome (IBS), migraine headache, and Asperger syndrome (Alstadhaug & Benjaminsen, 2010;

Carruthers, Miller, Tarrier, & Whorwell, 2012; Neufeld et al., 2013). Individuals with synesthesia also appear to have particular personality traits (Hoffman et al., 2018; Rouw & Scholte, 2016), but further systematic research is required to validate this association.

Nevertheless, synesthesia may confer a benefit to some individuals, noting that synesthetes are more commonly engaged in the arts and that increased creativity has been associated with grapheme- and sound-color synesthesia (Lunke & Meier, 2018). Heightened associative learning (Bankieris & Aslin, 2016) and enhanced visual memory have been found in grapheme-color synesthetes, particularly for visual recognition of abstract images where color can be used to discriminate changes (Rothen, Tsakanikos, Meier, & Ward, 2013). In addition, research indicates that synesthetes have superior visual perception and cognition, as well as increased cortical excitation potential in the primary visual cortex (Banissy et al., 2013; Terhune, Wudarczyk, Kochuparampil, & Cohen Kadosh, 2013; Terhune et al., 2015).

However, when a synesthete is exposed to stressful conditions, such as military combat or other potentially traumatic experiences, we suggest that synesthesia could become a liability. For example, the disturbing sights, sounds, and other sensations experienced during combat could be intensified in synesthetes and thereby increase their risk for developing PTSD. Furthermore, enhanced associative learning, visual perception, and visual memory could predispose synesthetes to flashbacks and rumination about the traumatic exposure. An earlier study conducted among 700 deployed veterans was the first to suggest the association of synesthesia and PTSD, reporting an adjusted odds ratio (OR) of 3.2 (95% CI = 1.3-8.1, $p = 0.015$) (Hoffman, Zhang, Erlich, & Boscarino, 2012). In the current study, our objective was to confirm this association among a second cohort of deployed veterans and to assess additional factors that could confound this association.

METHODS

The population in the present study was obtained by random sampling from a military veterans' community, who were

recruited for an even larger study pertaining to the evaluation of health effect of military service. All the veterans in the study population were outpatients in the Geisinger Clinic (GC), which is one of the largest multi-hospital systems in Pennsylvania (Boscarino et al., 2016). Based upon the medical record numbers, 1,730 previously identified veterans were recruited randomly for interviews in the present study. With patient consent, trained and supervised interviewers conducted structured and diagnostic telephonic interviews from February 2016 through February 2017, for evaluation of mental health. All veterans recruited had one or more warzone deployments and were under 76 years old. Veteran status and deployment history were confirmed based on military records. In the survey, the cooperation rate was estimated to be 55% (Boscarino et al., 2018).

Based on twin and family studies, it was suggested that PTSD is moderately heritable, with genetic factors accounting to about 30% of this disorder (Stein, Jang, Taylor, Vernon, & Livesley, 2002). So far, genetic variations associated with the biological pathways of hypothalamic-pituitary-adrenal (HPA), locus coeruleus/noradrenergic and the limbic system were identified (Boscarino, Erlich, Hoffman, & Zhang, 2012; Broekman, Olf, & Boer, 2007). However, further systematic research is needed to decipher the key risk factors for the manifestation of PTSD (Duncan et al., 2018).

To assess PTSD in the present study, we used a questionnaire based on the Diagnostic and Statistical Manual of Mental Disorder, Fifth Edition (DSM-5) and the checklist of the PTSD (Blevins, Weathers, Davis, Witte, & Domino, 2015; Wortmann et al., 2016). In order to receive the diagnosis of PTSD, veterans had to meet the DSM-5 diagnostic criteria (American Psychiatric Association, 2013). This PTSD scale was used in previous studies (Hoge, Riviere, Wilk, Herrell, & Weathers, 2014). However, since our previous study was based on the DSM-IV PTSD criteria (Hoffman et al., 2012), for consistency in the current study, we converted the DSM-5 diagnostic criteria to DSM-IV criteria, using a formulation developed by (Rosellini et al., 2015). For the current study, the Kappa statistic for DSM-5 vs. DSM-IV was very high (Kappa = 0.893), suggesting strong agreement between these two PTSD scales.

Survey questions described in the studies of Hoffman et al. (2012) as well as Rouw & Scholte (2007) were used in the present study for the assessment of synesthesia. These questions were related to most common form of synesthesia. For example, whether they saw any color upon looking at a certain number or letter. Responses to this question were categorized on a 4-point Likert scale, coded as “strongly disagree,” “disagree,” “agree,” and “strongly agree” (Rouw & Scholte, 2007). Those who responded “strongly agree” or “agree” to this question were classified as synesthesia positive cases. Data pertaining to the military history, medical history, demographic factors, as well as current depression PTSD based on DSM diagnostic criteria (Boscarino, Adams, & Figley, 2011; Boscarino, Hoffman, Pitcavage, & Urosevich, 2015) and combat exposure using Combat Experience Scale (CES) (Boscarino, 1995; Boscarino et al., 2015) and concussion (e.g., ever dazed, confused, saw stars, or knocked out) history (Schwab et al., 2006) during military service were also collected. Use of the mental health service, medication, psychological stress, and trauma exposures measures were evaluated based on standard mental health scales described in previous studies (Boscarino et al., 2011; Boscarino et al., 2015; Boscarino et al., 2018)

Statistical Analysis

Statistical analyses included descriptive statistics and testing of hypothesis. Descriptive statistics of the study population were presented. Multivariable logistic regression was applied for testing the hypothesis whether there is any association between PTSD and synesthesia. Synesthesia was used as a factor to predict PTSD first independently in bivariate analyses and then evaluating the effects of age, gender, marital status, education, psychotropic medication use, current life stress, traumatic stress exposure, combat exposure, depression, and history of concussion using logistic regression.

For descriptive purposes, we review the characteristics of the study population and present these results in Table 1. For analyses testing the study hypothesis that there is an association between PTSD and synesthesia, we used multivariable logistic regression, whereby synesthesia was used to predict PTSD, first, independently in bivariate analyses and then assessing for the effects of age, gender, marital status, education, psychotropic medication use,

Table 1.
Profile of Deployed Veterans in Geisinger Clinic Study (N=1,730)*

Variable (Demographic/health)	(N)†	Percentage (%) or Mean	95% CI
Age (average)	(1729)	59.6	58.9-60.2
Male sex	(1645)	95.1	94.0-96.0
White race	(1655)	95.7	94.6-96.5
Married	(1340)	77.5	75.4-79.4
College graduate or higher	(429)	24.8	22.8-26.9
High combat exposure	(408)	23.6	21.6-25.6
High lifetime trauma exposure	(357)	20.6	18.8-22.6
High current life stressors	(375)	21.7	19.8-23.7
History of in-service concussion	(491)	28.4	26.3-30.6
Use psychotropic meds-Past year	(384)	22.2	20.3-24.2
Major depression-Past year	(143)	8.3	7.1-9.7
PTSD-Past year	(132)	7.6	6.5-9.0
Synesthesia positive	(59)	3.4	2.7-4.4

*The study veterans were comprised of Vietnam veterans (56.2%), Gulf War (15.9%), Afghanistan/Iraq (22.9%), and other warzone veterans (14.2%). Note, some veterans had multiple deployments.

†The N represents the total number of subjects with the demographic or health characteristic.

current life stress, traumatic stress exposure, combat exposure, depression, and history of concussion using a backwards stepwise logistic regression (Table 2). Data analyses were conducted using Stata, version 13.1 software (College Station, Texas). This study was approved by the Institutional Review Boards of the Geisinger Clinic and US Department of Defense.

RESULTS

In the present study, examination of the recruited veterans revealed that 56.2% were Vietnam veterans, 15.9% belonged to Gulf War, 22.9% were veterans of Afghanistan/Iraq, and the rest (14.2%) represented other warzone veterans (Table 1, footnote). As shown in Table 1, the average age of veterans was 59.6 years among which, 95.1% were males, while 95.7% belonged to White race. Also, 77.5% were married, 24.8% had an educational level equivalent to college graduate or higher education and 23.6% of the study group was categorized as having high combat exposure. A total of 28.4% of veterans were screened positive for concussive injury during military service and 22.2% reported taking psychotropic medications in the past year. In the present study, the prevalence rate of current PTSD was about 7.6% (95% C.I. = 6.5-9.0) and the prevalence rate of current depression was found to be about 8.3% (95% C.I. = 7.1-9.7). Among the veterans of the current study, the prevalence of grapheme-color synesthesia was 3.4% (95% C.I. = 2.7-4.4) (Table 1).

The top row in Table 2 shows the unadjusted bivariate results for the association between PTSD and synesthesia. It is evident that the unadjusted odds ratio (OR) for the association between PTSD and synesthesia was significant statistically, with an OR = 3.3 ($p < 0.001$) for PTSD. Multivariable logistic regression results were based on backwards stepwise logistic regression. The model was assessed for age, female sex, marital status, education, current psychotropic use, concussion history, combat exposure, trauma exposure, current life stress, and current depression, with age and sex forced into the final model. As shown, the final regression model resulted in an adjusted OR = 2.33 ($p = 0.019$) for PTSD. These final adjusted results were similar to those reported for our original synesthesia study with a previous cohort of veterans (Hoffman et al., 2012).

DISCUSSION

Based on past research outcomes (Hoffman et al., 2012), we

hypothesized that prevalence of current PTSD among veterans with grapheme-color type synesthesia would be higher. This hypothesis was confirmed in the current study, which assessed additional potential confounding variables. To the best of our knowledge, this study constitutes only the second one in the research literature to report the association of PTSD and synesthesia. As suggested, synesthesia was associated with specific medical conditions (Alstadhaug & Benjaminsen, 2010; Carruthers et al., 2012; Neufeld et al., 2013), as well as symptoms of psychopathology linked to enhanced temporo-limbic excitability (Neckar & Bob, 2016). In addition, research indicates that individuals with synesthesia have superior visual perception and cognition as well as elevated cortical excitability in the primary visual cortex (Banissy et al., 2013; Terhune et al., 2013; Terhune et al., 2015). Previous research, however, suggests that PTSD is related to the opposite traits, including lower intelligence, mixed handedness, attention disorders, and schizophrenia (Boscarino, 2006; Boscarino & Adams, 2009; Boscarino et al., 2012; Duncan et al., 2018; Gurvits et al., 2006). Thus, the reasons for the PTSD-synesthesia association are currently unclear. In the research literature, female sex was observed to be associated with PTSD (Boscarino & Adams, 2009; Boscarino et al., 2012) and synesthesia is reported to be more common among females (Simner & Carmichael, 2015), so this association might be worthy of examination. However, only 5% of veterans in our study were female, so this assessment was not possible in the current study.

Limitations of the current research includes that the interview response data were based on self-reporting and could possibly include recall bias. In addition, there have been inconsistencies in the literature with regard to the underlying bases for synesthesia (Hupe & Dojat, 2015; Melero et al., 2013). Also, estimation of synesthesia was based on a single survey question. However this question was used in the past and our prevalence estimate is consistent with past studies (Hoffman et al., 2012). Moreover, the current study included only deployed veterans constituted predominately with white males. These factors have the potential to induce bias in the results. Another issue is that this study was based on patients from a single multi-hospital system, possibly limiting study generalization. Further, since the present study was cross-sectional, PTSD could not be ruled out as a cause of synesthesia. The prevalence of current PTSD within this sample of veterans was about 8%, which is consistent with

Table 2.
Unadjusted & adjusted results of the association between synesthesia and PTSD: (N=1730)

Logistic Regression Results Predicting Synesthesia*	OR	OR 95% CI	p-value
PTSD-Past year	3.3	1.71-6.40	<0.001
*Unadjusted regression results.			
Stepwise Logistic Regression Results Predicting Synesthesia**	OR	OR 95% CI	p-value
Age (years)	1.0	0.98-1.02	0.84
Female Sex	2.15	0.76-6.08	0.151
College grad or higher	0.44	0.21-0.96	0.038
Concussion history	2.07	1.19-3.61	0.01
PTSD-Past year	2.33	1.15-4.72	0.019

**Final adjusted regression results based on backwards stepwise logistic regression. Model was assessed for age, female sex, marital status, education, current psychotropic use, concussion history, combat exposure, trauma exposure, current life stress, and current depression. The final selected regression results included education level, concussion history, and PTSD, with age and sex forced into the final model results.

the rate observed in previous studies of community-based veterans (Boscarino et al., 2015). Finally, both PTSD and synesthesia are known to be associated with genetics and these need to be further explored (Boscarino et al., 2012; Brang & Ramachandran, 2011).

In spite of these limitations, grapheme-color synesthesia was found to be associated with PTSD in a second larger community-based group of veterans. It is suspected that the PTSD-synesthesia association is probably not specific to combat trauma per se, but may likely be related to noncombat traumas as well. Among these veterans, it is a notable fact that the median age of PTSD onset was 28 years (Hoffman et al., 2012). As evident from Table 1, the average age of veterans in the present study was 59 years, therefore most veterans had PTSD for decades. Recognition of the association between synesthesia and PTSD might lead to new approaches for PTSD diagnosis, such as using the “New York PTSD risk score,” which combines psychosocial risk-factor data with genotype data (Boscarino, Kirchner, Hoffman, & Erlich, 2013). Further longitudinal research is planned to explore these recent discoveries and to determine if this association for PTSD is also present among nonveterans.

CONCLUSION

Based on our study findings, we conclude that grapheme-color synesthesia is likely associated with PTSD. Further research is now planned using the full version of the grapheme-color synesthesia scale, together with longitudinal data. This research may open up neurological windows into a better understanding of PTSD risk, its onset, and its course.

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DECLARATION

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