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Epigenetic Signatures May Explain the Relationship Between Socioeconomic Position and Risk of Mental Illness: Preliminary Findings from an Urban Community Based Sample

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Abstract

Low socioeconomic position (SEP) has previously been linked to a number of negative health indicators, including poor mental health. The biologic mechanisms linking SEP and mental health remain poorly understood. Recent work suggests that social exposures influence DNA methylation in a manner salient to mental health. We conducted a pilot investigation to assess whether SEP, measured as educational attainment, modifies the association between genomic methylation profiles and traumatic stress in a trauma-exposed sample. Results show that methylation × SEP interactions occur preferentially in genes pertaining to nervous system function, suggesting a plausible biologic pathway by which SEP may enhance sensitivity to stress, and, in turn, risk of post-traumatic stress disorder.

Introduction

Epigenetics refers to the stable yet modifiable regulation of gene function that occurs through non-DNA encoded mechanisms. Epigenetic mechanisms include histone modifications such as acetylation, phosphorylation, and ubiquitination, which causes structural changes to chromatin and makes surrounding DNA sequences inaccessible (Tsankova et al. 2007); DNA methylation, which typically involves methylation of cytosine residues at CpG positions and often results in repression of nearby genes (Eckhardt et al. 2006); and non protein coding RNAs such as micro-RNAs, which can interact with other epigenetic mechanisms to regulate epigenetic processes such as chromatin modification (Mattick et al. 2009) and DNA methylation (Havecker et al. 2010).

DNA methylation in particular has received attention as a potential epigenetic mediator and moderator of environmental exposures on health-related outcomes. Much of this interest originally stemmed from the now well-established links between environmental chemical

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exposures and both global and locus-specific changes in DNA methylation (reviewed in (Hou et al. 2012)), and has since grown in light of the demonstrated ability of DNA methylation to change in response to ageing(Bjornsson et al. 2008; Wong et al. 2010) and experiences early in life (Champagne et al. 2006; Weaver et al. 2004). Interest in the contribution of environmentally induced DNA methylation changes to mental illness has been particularly pronounced, as numerous examples exist of epigenetic associations with schizophrenia (Abdolmaleky et al. 2006; Abdolmaleky et al. 2005), suicide (McGowan et al. 2008), and bipolar disorder (Mill et al. 2008), as well as with illnesses that are more closely associated with environmental conditions (Shih, Belmonte and Zandi 2004), such as depression (Uddin et al. 2011b) and post-traumatic stress disorder (PTSD) (Koenen et al. 2011; Smith et al. 2011; Uddin et al. 2010; Uddin et al. 2011a). Such examples, however, do not typically assess important social determinants that may act as environmental exposures contributing to risk for mental illness.

There is abundant literature showing that social exposures are associated with health (e.g. (Due et al. 2011; Safaei 2006). Of particular interest in this regard is socioeconomic position (SEP), a fundamental determinant of health (Galea et al. 2011; Link and Phelan 1995). Two major pathways have been identified in the literature as possible routes linking SEP to health: from a material perspective, individuals of relatively higher SEP may access resources, such as health insurance, quality of food consumed, and higher education, that promote health (Lynch et al. 2000); from a psychosocial perspective, individuals of relatively lower SEP may be exposed to a greater number of stressful events and/or be more vulnerable to the consequences of these events, ultimately resulting in poor health (McEwen and Seeman 1999). The material and psychosocial pathways are not mutually exclusive. Although the link between low SEP and a number of stress-sensitive negative health outcomes (Ahern and Galea 2006; Cairney and Krause 2005; Dowd, Aiello and Alley 2009; Dowd et al. 2008; Evans and Kim 2007; Nicklett and Burgard 2009; Toumbourou et al. 2007; Zajacova, Dowd and Aiello 2009), including poor mental health, (Ahern and Galea 2006; Brewin, Andrews and Valentine 2000; Cairney and Krause 2005; Nicklett and Burgard 2009) may be considered in support of the psychosocial pathway, material resources are often also associated with psychosocial processes suggesting that it is likely a combination of the two pathways that ultimately links SEP and mental health. (Kawachi, Subramanian and Almeida-Filho 2002). Both mechanisms, however, rely on the assumption that some biologic process (or processes) exists that explains how exogenous factors, in this case SEP, ultimately manifest as endogenously determined phenotypes. It remains an open question how exposures on either pathway effect their downstream influence(s) on health.

The modifiable yet non-transient nature of epigenetic signatures makes them plausible biologic candidates that account for how exogenous factors that change, like social status, are associated with poor health indicators, including poor mental health. Indeed, recent work suggests that social exposures can influence epigenetic marks in a manner salient to health in general(Borghol et al. 2012; McGuinness et al. 2012; Talens et al. 2012), and mental health in particular. One prominent example pertinent to the latter involves a large, population-based epidemiologic study of the legacy of the Dutch Hunger Winter of 1944-45, which recently established an association between social deprivation and methylation status in the insulin-like growth factor II gene (*IGF2*),(Heijmans et al. 2008; Tobi et al. 2012) with those exposed to nutritional insufficiency during the periconception period showing lower methylation at this locus. The *IGF2* locus plays a key role in development and growth (Delaval, Wagschal and Feil 2006) and defects in methylation at this locus are known to contribute to several imprinting-related disorders, such as Silver-Russell syndrome and Beckwith-Wiedemann syndrome (Bartholdi et al. 2009; Riccio et al. 2009). Notably, brain weight in males is positively correlated with DNA methylation at *IGF2* (Pidsley, Dempster and Mill 2010); and, in turn, low brain weight has been associated with schizophrenia

(Harrison, Freemantle and Geddes 2003), including within the Dutch Hunger Winter cohort (Hulshoff Pol et al. 2000). Together, these observations suggest that social exposures may influence DNA methylation in a manner salient to mental health; however, studies explicitly testing this hypothesis have, to our knowledge, yet to be reported.

To address this issue, here we conduct a pilot investigation of whether SEP, measured as educational attainment, modifies DNA methylation profiles to predict traumatic stress in a trauma exposed sample. We focus on SEP due to its strong association with a range of health indicators in the literature, (Ahern and Galea 2006; Cairney and Krause 2005; Dowd et al. 2009; Dowd et al. 2008; Evans and Kim 2007; Nicklett and Burgard 2009; Steptoe et al. 2010; Toumbourou et al. 2007; Zajacova et al. 2009) including those related to traumatic stress (Brewin et al. 2000; Koenen et al. 2002; Koenen et al. 2007; Kulka et al. 1990); emerging work also indicates that SEP is linked to modifiable molecular variation (Miller et al. 2009), including DNA methylation(Borghol et al. 2012; McGuinness et al. 2012). Drawing on samples from an urban, community-based cohort, the Detroit Neighborhood Health Study (DNHS), we assess methylation × SEP interactions at over 27,000 CpG sites, representing over 14,5000 genes on the HM27 BeadChip to predict traumatic stress, and characterize the biological significance of the profiles showing nominally significant methylation × SEP interactions.

Methods

Participants

Our analyses are based on a subsample of 100 persons who were exposed to one or more potentially traumatic events (PTEs) and who were participants in wave 1 of the longitudinal DNHS. The DNHS is a survey-based investigation of mental health correlates in population-representative cohort of adult Detroit residents. At wave 1, 1,547 participants were surveyed; the full survey sample was representative of the Detroit population on key sociodemographic variables including age, gender, race, income, and educational attainment (Uddin et al. 2010), Respondents were also asked to provide blood specimen either by way of venipuncture or blood spot; 612 samples were collected from consenting participants. Two-tailed chi-square tests comparing our blood sample to the full survey sample showed that their sociodemographic characteristics were comparable to the complete sample. Similarly, we compared the 100 individuals in our final sample to the 612 consenting participants of the blood draw and found that the two samples differ only on age – our final sample consisted of slightly higher proportion of younger individuals.(Uddin et al. 2010)

For the analyses described below, methylation data were obtained as described previously (Uddin et al. 2010). Briefly, bisulfite conversion of previously extracted, whole blood-derived genomic DNA from 100 individuals was performed on 1ug of each sample using the EZ-96 DNA Methylation™ Kit from Zymo Research (Orange CA) and following the manufacturer's recommended protocol. Bisulfite converted DNA was subsequently assessed for methylation status at 27,578 CpG loci covering more than 14,000 genes using the humanmethylation27 (HM27) DNA Analysis BeadChip by Illumina (San Diego, CA). The resulting data were background normalized using Ilumina's BeadStudio software and exported for subsequent analysis using the R package v2.9.0 and SAS software v9.2. Methylation microarray data were validated in a subset of loci as previously described. (Koenen et al. 2011; Uddin et al. 2010) Peripheral blood mononuclear cells (PBMCs) were isolated and quantified (Uddin et al. 2010; Uddin et al. 2011b). Data on participants' use of over the counter and prescription medication, including anti-anxiety and anti-depressants, was also collected by clinicians during the in-home visits during which the venipuncture specimens were collected. This study was approved by the Institutional Review Board (IRB) of the University of Michigan, and all participants provided written, informed consent.

Mental health assessment and other survey-based variables

Participants were administered a 40 minute telephone assessment which included questions on exposure to traumatic events, socio-demographic and behavioral characteristics, and a standardized assessment of PTSD, depression, and generalized anxiety disorder (GAD), as previously described (Uddin et al. 2010).

Briefly, presence or absence of lifetime PTSD was assessed using the PTSD checklist (PCL-C) (Weathers and Ford 1996), a 17-item self-report measure of post-traumatic stress symptoms based on DSM-IV criteria, augmented by additional questions about duration, timing, and impairment or disability due to the symptoms in order to identify PTSD cases that were compatible with DSM-IV criteria. Participants were initially asked to identify PTEs that they experienced in the past from a list of 19 events that had previously been implemented in an earlier epidemiologic study to assess PTSD in the Detroit area (Breslau et al. 1998), and an additional question that allowed the participant to briefly describe any other extraordinarily stressful situation or event. We then asked those participants who had experienced at least one traumatic event to choose which one they considered to be the worst. Participants rated each of the 17 PTSD symptoms on a scale indicating the degree to which the respondent had been bothered by a particular symptom as a result of this trauma from 1 (not at all) to 5 (extremely) in reference to this event. An additional PTSD section assessed symptoms based on a randomly chosen traumatic event (excluding the worst event) for those participants who had experienced more than one PTE. Respondents were considered affected by lifetime PTSD if all six DSM-IV criteria were met in reference to either the worst or the random event. The PTS symptom severity measure was then defined as the sum score of symptoms based on the worst event, which can range from 17 to 85.

To validate our identification of PTSD obtained from the telephone interview responses, we conducted clinical in-person interviews among a random subsample of 51 participants. A licensed clinician conducted one-hour clinical interviews after obtaining signed consent from participants, utilizing the Clinician-Administered PTSD Scale for DSM-IV (CAPS) for PTSD. The counselor was blinded to the information obtained from the participants during the telephone interview. Analysis of data from the in-person interviews showed that the PCL-C used during the telephone interviews had excellent internal consistency and high concordance. The PCL-C yielded a Cronbach coefficient alpha (α) of 0.93. Using clustering scoring based on DSM-IV criteria (i.e. to be a case, the participant's symptoms had to meet all six criteria), the instrument had a sensitivity (SE) of 0.24, specificity (SP) of 0.97, positive predictive value (PPV) of 0.80, negative predictive value (NPV) 0.72, and an area under the ROC curve (AUC) of 0.76. Low sensitivity values imply that our survey-based PTSD prevalence estimates are conservative. Importantly, the high specificity insures our PTSD group is made of true cases. All 100 individuals included in this pilot study were exposed to at least one PTE; among these, 23 were affected by lifetime PTSD and 77 were trauma-exposed but unaffected.

Additional survey-based variables included in this study were: demographic variables including race, sex, and age; number of traumatic events, which was a count of the different types of trauma event and ranged from 0–19 for each person; and whether a participant had ever smoked, due to the known influence of smoking on DNA methylation levels (Breitling et al. 2011). SEP was assessed via participants' reported highest level of educational attainment in order to capture cumulative social exposures, including both the educational opportunities of the individual participant, as well as the opportunities and constraints encountered by the participant's parent(s) when making choices that influenced their children's socioeconomic circumstances.(Galobardes, Lynch and Smith 2007) Consistent with the evidence that attainment of more than a high school education is associated with improved health (Rogers et al. 2010), analyses were performed with SEP dichotomized

according to more than high school (high SEP) or high school or less (low SEP). High SEP was used as the referent group in the analyses described below.

Analytic methods

In this study we assess traumatic stress not only as a dichotomous outcome (i.e. PTSD), but also as a continuous (i.e. PTS symptom severity) outcome in order to (i) ensure our results are robust to qualitative and quantitative assessments of PTSD and (ii) ascertain biologic processes that may be operating at subthreshold levels, i.e that may not be apparent based on a strictly dichotomous PTSD diagnosis (Hawk et al. 2000). Presence/absence of lifetime PTSD was modeled using logistic regression. PTSD symptom severity was modeled using a general linear model. The severity measure was log-transformed for normality. We assessed main effects of each outcome across all CpG sites on the array using the methylation beta value and SEP as predictors, controlling for demographic characteristics (age, race, sex), behavioral characteristics (smoking, depression, GAD, medication use), and peripheral blood mononuclear cell (PBMC) count. Methylation beta values were centered to the mean in both the PTSD and PTS symptom severity models. Following main effect analyses, we assessed the presence/absence of methylation × SEP interactions across all CpG sites on the array by including an interaction term in the main effects model using high SEP was the reference group. In the main effects model, coefficients for gene methylation value and SEP were accepted as significant if $p<0.01$ (uncorrected for multiple testing). In the interaction models, methylation X SEP interaction terms were accepted as significant if $p<0.01$ (uncorrected for multiple testing).

Functional analyses of genes showing significant methylation × SEP interactions were performed using the functional annotation clustering (FAC) tool in DAVID (Database for Annotation, Visualization and Integrated Discovery) (Huang da, Sherman and Lempicki 2009). DAVID is a publicly available resource that provides a comprehensive set of functional annotation tools to help investigators understand the biological meaning behind large sets of genes. In this study, results were obtained using the FAC tool, which clusters similar annotations based on the co-occurrence of particular gene sets. The tool also calculates an associated enrichment score for each cluster based on the geometric mean of the *P* values determined for each of its component annotations (which is then reported in -log scale). For the FAC analyses reported here, options were set to their default values and annotations were accessed as indexed on July, 2011. Clusters were identified by selecting overrepresented annotations that conveyed broad biological meaning within each FAC.

Results

Descriptive statistics and bivariate comparisons of participants with and without PTSD are presented in Table 1. The majority of the study sample was female and African American. The average PTS symptom severity was 38.7 (SD=16.01). Participants with PTSD did not differ significantly from those without the disorder on age, gender, race/ethnicity, PBMC count, ever smoking, medication use, or SEP (education).

In main effect models assessing lifetime PTSD, significant coefficients (uncorrected $p<0.01$) were obtained for methylation beta values in 118 CpG sites, corresponding to 116 unique genes. In main effect models assessing PTS symptom severity, significant coefficients (uncorrected $p<0.01$) were obtained for methylation beta values in 80 CpG sites, corresponding to 79 unique genes. Results for the top three FACs for genes showing significant methylation beta value coefficients are summarized in Table 2 for both outcomes. Two of the three FACs (secreted, response to nutrient) were comprised by very similar annotations for both lifetime PTSD and PTS symptom severity, although their rank order differed slightly. Significant coefficient estimates (uncorrected $p<0.01$) for SEP were

obtained for only a few CpG sites in main effect models assessing lifetime PTSD (n=1) and PTS symptom severity (n=6), precluding analysis with the FAC tool.

In interaction models assessing lifetime PTSD, significant methylation × SEP interaction coefficients (uncorrected $p<0.01$) were obtained for 119 CpG sites, corresponding to 119 unique genes. In interaction models assessing PTS symptom severity, significant methylation × SEP interaction coefficients (uncorrected $p<0.01$) were obtained for 55 CpG sites, corresponding to 55 unique genes. Nine CpG sites, corresponding to nine different genes, showed significant interaction effects for both outcomes; results of the main study predictors (i.e. CpG methylation, SEP, and their interaction if applicable) for both main effect and interaction models are shown for these nine genes in Tables 3-6. Full results are presented for main effect and interaction models for these nine genes in Supplementary Tables 1-4, which are available upon request from the authors.

Results for the top 3 FACs for genes showing significant methylation × SEP interaction terms are summarized in Table 7 for both PTSD and PTS severity. Both outcomes showed evidence of SEP effect modification characterized by FACs relating to the nervous system; however, in contrast to the main effect results, the specific annotations comprising these FACs differed between PTSD and PTS symptom severity: the top three FACs for PTS symptom severity were comprised of annotations relating to synapse (e.g. postsynaptic cell membrane, synapse part), GTPase regulator activity and oxidation reduction (oxioreductase, mitochondrion). In contrast, the top three FACs for PTSD were comprised of annotations relating to hippocampus development, forebrain development, and RNA transport.

Further investigation of the CpG sites associated with significant interactions in the lifetime PTSD model revealed that 46 of the 119 sites showed positive interaction coefficients, i.e. were associated with increased risk of the PTSD. FAC analyses of the 46 genes associated with these 46 sites determined that the top-ranked cluster was characterized by the nervous-system related annotation of synaptic transmission (Table 8); in contrast, FAC analyses of the 73 genes associated with the 73 CpG sites showing negative interaction coefficients did not reveal any annotations relating directly to nervous system function in the top 3 clusters.

Similarly, in the PTS symptom severity model, 38 of the 55 CpG sites associated with significant interactions showed positive interaction coefficients, i.e. were associated with increased risk of PTS symptom severity. FAC analyses of the 38 genes associated with these 38 sites determined that, among the top 3 highest ranking clusters, the nervous-system related annotation of neuron projection characterized FAC 3 (Table 9); in contrast, FAC analyses of the 17 genes associated with the 17 CpG sites showing negative interaction coefficients did not reveal any annotations relating directly to nervous system function in the top 3 clusters. Results of all FAC analyses are listed in Supplementary Tables 5-12, which are available upon request from the authors.

Discussion

Converging evidence from epidemiologic, molecular genetic, and animal model studies suggests that social exposures can influence DNA methylation in a manner salient to mental health. Using a subsample of participants from the Detroit Neighborhood Health Study, we conducted a pilot investigation of whether SEP modifies the association between genomic DNA methylation profiles and traumatic stress in a trauma-exposed cohort. We found that significant (uncorrected $p<0.01$) methylation X SEP interactions occur preferentially in CpG sites associated with genes relating to nervous system function (which were notably absent from main effect analyses). Furthermore, when functional significance was assessed separately for CpG sites associated with significant positive and negative interaction

coefficients, nervous-system related functions were especially apparent in the positive (i.e. risk-enhancing) gene set. Although the brain is the central organ mediating stress processes (McEwen 2007), many of the brain regions hypothesized to link SEP-related stress to health also regulate peripheral stress-response axes that are important for health, including peripheral physiological reactivity (McEwen and Gianaros 2010). Taken together, these preliminary results suggest that SEP may preferentially modify DNA methylation profiles in biologic pathways that enhance stress sensitivity and reactivity which may, in turn, increase risk of PTSD.

Among the many annotations relating to nervous system function identified in this study, the identification of hippocampus-related annotations in the PTSD-based analyses is particularly noteworthy. The hippocampus is a brain region that originates from the telencephalon portion of the forebrain during development (Lagali, Corcoran and Picketts 2010), is involved in memory, learning and emotional regulation (McEwen 2001, 2007), and is known to be affected by stress (Sapolsky et al. 1990), including PTSD (Zhang et al. 2011b). Evidence from animal models has shown that chronic social stress can remodel this brain region (McEwen 2007), and human imaging studies indicate that chronic stressors are associated with decreased hippocampal volume even in otherwise healthy individuals (Gianaros et al. 2007). Of importance to this study, recent work has found that children from lower income households show lower hippocampal gray matter density, controlling for gender, age, parental education, and whole brain volume (Hanson et al. 2011). This finding is consistent with previous hypotheses regarding the likely neurobiological pathways that translate social stress, and in particular socioeconomic stress, into cognitive and health-related outcomes (Gianaros and Manuck 2010; Hackman and Farah 2009; McEwen and Gianaros 2010). Our own work, which is based on DNA methylation levels assessed in peripheral blood, cannot be tied directly to these brain-specific findings; nevertheless, a growing literature is exploring the concordance between molecular signatures obtained in central and peripheral tissues, (Kato, Kakiuchi and Iwamoto 2007; Kurian et al. 2011; Le-Niculescu et al. 2009; Rollins et al. 2010) due, in part, to the existence of receptors for neurotransmitters that are expressed on both neurons and lymphocytes, including glucocorticoid receptors, dopamine receptors, GABA-A receptors, muscarinic and nicotinic receptors, serotonin receptors, and beta-adrenergic receptors.(Gladkevich, Kauffman and Korf 2004) Given the ready availability of peripheral samples, and the scarcity of CNS tissues from living individuals, additional studies in this area are warranted.

Our study should be interpreted in light of a number of limitations. Chief among these is that our results were determined based on analyses that were not corrected for multiple testing; indeed, had we done so, none of our findings would have reached statistical significance. Instead, we adopted an uncorrected p value of $p<0.01$ as a cutoff for subsequent functional analyses in order to aid our primary goal of identifying biological pathways that may be associated with DNA methylation modifications by SEP. In addition, while biologically meaningful interactions were detected between SEP and methylation in our study, the analyses presented in this work are cross-sectional and thus unable to determine whether SEP exposures are truly causative of the increased risk of PTSD. Our reliance on education as our SEP measure, however, is consistent with this hypothesis, as it is thought to represent a more cumulative index of SEP exposure (Galobardes et al. 2007) that shapes health indicators throughout adult life. In addition, while we assessed DNA methylation variation at thousands of sites across the genome, providing a comprehensive picture of genome-scale variation, there are likely additional significant methylation X SEP interactions that we were unable to detect due to our relatively small sample size and incomplete coverage of the genome. Our findings would thus be strengthened through replication in larger, independent cohorts and through using more recently developed microarrays that provide greater genomic coverage. Finally, our findings were based on a sample consisting predominantly

of African-American participants. Although the extent of race/ethnic stratification in DNA methylation is currently unknown, this phenomenon is known to exist for DNA sequence variation (Li et al. 2008), which is known to affect DNA methylation(Hellman and Chess 2010); and race/ethnic variation in DNA methylation has been previously reported(Lee et al. 2007; Zhang et al. 2011a). The extent to which our findings are generalizable to other populations thus remains to be determined.

In conclusion, results presented here provide preliminary evidence that SEP modifies the relation between methylation and risk of PTSD in genes predominantly related to nervous system function. This pattern was observed for both dichotomous and continuous measures of PTSD, confirming that the observed effect modification by SEP is consistent across qualitative and quantitative assessments of this disorder. Taken together, results from both PTSD and PTS symptom severity analyses help to shed light more broadly on how SEP interacts with epigenotype to predict risk of mental illness. These findings await confirmation from future studies conducted in independent cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Descriptive statistics and bivariate comparisons of participants with and without PTSD

	Overall Sample		PTSD (n=23)		no-PTSD (n=77)		Test
	n/mean	%/sd	n/mean	%/sd	n/mean	%/sd	p-value
Age	45.32	16.78	46.70	15.19	44.91	17.29	0.66
No. traumatic events	6.04	3.60	7.57	3.65	5.58	3.48	0.02
No. PBMC	23.3376	8.05	23.29	7.25	23.35	8.31	0.97
Female	60	60	15	65.22	45	58.44	0.56
White	14	14	4	17.39	10	12.99	0.61
African American	79	79	17	73.91	62	80.52	
Others	7	7	2	8.7	5	6.49	
Any medication	48	48	12	52.17	36	46.75	0.65
Ever smoke	58	58	17	73.91	41	53.25	0.08
PTSD	23	23	–	–	–	–	–
PTS symptom severity	38.7	16.01	56.70	11.86	33.32	12.88	**<.0001**
Generalized anxiety disorder diagnosis	17	17	10	43.48	7	9.09	**<.0001**
Depression diagnosis	33	33	12	52.17	21	27.27	**0.03**
Low education	50	50	14	60.87	36	46.75	0.23

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Table 2

Functional annotation cluster[¶] analysis of genes showing significant[*] methylation beta value coefficients in main effect analyses

Outcome	Cluster	No. of Genes in Cluster[+]	Enrichment Score
PTSD	Cell adhesion	12	2.43
	Response to nutrient	8	1.88
	Secreted	37	1.34
PTS Symptom Severity	Secreted	22	1.26
	Response to nutrient	4	1.23
	Cell fraction	10	1.17

[¶]Functional annotation clusters (FAC) were bioinformatically inferred using DAVID (see methods for more details).

[*]Assessed at the $p<0.01$ level.

[+]All genes are identified in terms of DAVID IDs; genes can appear in more than one FAC.

Table 3

Main effect logistic regression model results of SEP and methylation predicting lifetime PTSD (n=100).

CpGsite	Gene Symbol	RefSeq	b_{educ}	Se_{educ}	p_{educ}	b_{meth}	Se_{meth}	p_{meth}
cg04958389	*PRSS2*	NM_002770	1.07	0.65	0.10	0.75	2.51	0.77
cg06917325	*SLC22A8*	NM_004254	1.06	0.67	0.11	-0.49	2.47	0.84
cg08573687	*TH*	NM_199292	1.10	0.65	0.09	-2.21	2.82	0.43
cg14870461	*AER61*	NM_173654	1.13	0.65	0.08	-4.55	5.01	0.36
cg16426459	*MLPH*	NM_024101	1.07	0.65	0.10	0.87	3.25	0.79
cg16869108	*VHL*	NT_022517	1.12	0.65	0.08	-1.24	1.67	0.46
cg22753768	*BAP1*	NM_004656	1.11	0.64	0.09	4.44	5.20	0.39
cg26049501	*STARD13*	NM_052851	1.08	0.64	0.09	-2.70	4.41	0.54
cg26912636	*TMEPAI*	NM_020182	1.10	0.64	0.09	-0.13	2.91	0.96

Note: covariates are age, gender, race, sumpbmc, smoke, anymed, dep, gad, sumpte, SEP (education), and gene methylation value.

b=beta coefficient; se=standard error; p=pvalue

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Table 4

Main effect linear regression results of SEP and methylation predicting lifetime PTS Symptom Severity (n=100).

CpGsite	Gene Symbol	RefSeq	b_{educ}	Se_{educ}	t_{educ}	p_{educ}	b_{meth}	Se_{meth}	t_{meth}	p_{meth}
cg04958389	*PRSS2*	NM_002770	0.15	0.07	2.02	0.05	0.13	0.27	0.50	0.62
cg06917325	*SLC22A8*	NM_004254	0.16	0.08	2.12	0.04	0.11	0.29	0.39	0.70
cg08573687	*TH*	NM_199292	0.15	0.07	2.07	0.04	-0.19	0.45	-0.42	0.67
cg14870461	*AER61*	NM_173654	0.15	0.07	2.05	0.04	0.42	0.48	0.89	0.38
cg16426459	*MLPH*	NM_024101	0.15	0.07	2.10	0.04	0.54	0.41	1.31	0.19
cg16869108	*VHL*	NT_022517	0.15	0.07	2.08	0.04	0.03	0.20	0.15	0.88
cg22753768	*BAP1*	NM_004656	0.16	0.07	2.13	0.04	0.72	0.56	1.29	0.20
cg26049501	*STARD13*	NM_052851	0.15	0.07	2.09	0.04	-0.34	0.47	-0.71	0.48
cg26912636	*TMEPAI*	NM_020182	0.16	0.07	2.11	0.04	0.31	0.34	0.92	0.36

Note: covariates are age, gender, race, sumpbmc, smoke, anymed, dep, gad, sumpte, SEP (education), and gene methylation value.

b=beta coefficient; se=standard error; t=tvalue; p=pvalue

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Table 5

Interaction effect logistic regression model results of SEP X methylation predicting lifetime PTSD (n=100).

CpGsite	Gene Symbol	RefSeq	b_{educ}	Se_{educ}	p_{educ}	b_{meth}	Se_{meth}	p_{meth}	b_{Int}	Se_{Int}	p_{Int}
cg04958389	*PRSS2*	NM_002770	0.85	0.73	0.24	-3.51	2.34	0.13	16.23	6.29	<0.01
cg06917325	*SLC22A8*	NM_004254	1.18	0.74	0.11	-12.46	5.01	0.01	19.87	7.43	<0.01
cg08573687	*TH*	NM_199292	0.17	0.80	0.83	-197.48	62.00	0.00	194.55	61.54	<0.01
cg14870461	*AER61*	NM_173654	1.12	0.79	0.16	13.05	6.80	0.06	-44.06	15.36	<0.01
cg16426459	*MLPH*	NM_024101	1.65	0.76	0.03	24.24	8.45	0.00	-30.48	10.55	<0.01
cg16869108	*VHL*	NT_022517	1.52	0.80	0.06	-6.76	2.57	0.01	15.64	5.17	<0.01
cg22753768	*BAP1*	NM_004656	1.27	0.77	0.10	-11.95	8.50	0.16	40.17	14.94	<0.01
cg26049501	*STARD13*	NM_052851	1.79	0.82	0.03	-25.19	10.04	0.01	34.02	12.78	<0.01
cg26912636	*TMEPAI*	NM_020182	1.62	0.80	0.04	-14.98	5.72	0.01	23.69	7.61	<0.01

Note: covariates are age, gender, race, sumpbmc, smoke, anymed, dep, gad, sumpte, SEP (education), and gene methylation value.

b=beta coefficient; se=standard error; p=pvalue.

Table 6

Interaction effect linear regression results of SEP X methylation predicting lifetime PTS Symptom Severity (n=100).

CpGsite	Symbol	RefSeq	b_{educ}	Se_{educ}	t_{educ}	p_{educ}	b_{meth}	Se_{meth}	t_{meth}	p_{meth}	b_{Int}	Se_{Int}	t_{Int}	p_{Int}
cg04958389	*PRSS2*	NM_002770	0.13	0.07	1.87	0.07	-0.37	0.30	-1.22	0.22	1.68	0.55	3.06	<0.01
cg06917325	*SLC22A8*	NM_004254	0.14	0.07	1.95	0.05	-1.01	0.50	-2.00	0.05	1.58	0.59	2.68	<0.01
cg08573687	*TH*	NM_199292	0.00	0.09	0.01	0.99	-16.07	5.01	-3.21	0.00	15.96	5.01	3.18	<0.01
cg14870461	*AER61*	NM_173654	0.16	0.07	2.28	0.03	2.04	0.72	2.81	0.01	-2.76	0.96	-2.88	<0.01
cg16426459	*MLPH*	NM_024101	0.16	0.07	2.25	0.03	2.60	0.73	3.57	0.00	-2.85	0.85	-3.34	<0.01
cg16869108	*VHL*	NT_022517	0.15	0.07	2.17	0.03	-0.43	0.24	-1.76	0.08	1.25	0.40	3.11	<0.01
cg22753768	*BAP1*	NM_004656	0.16	0.07	2.32	0.02	-0.48	0.66	-0.73	0.46	3.76	1.19	3.16	<0.01
cg26049501	*STARD13*	NM_052851	0.16	0.07	2.17	0.03	-1.32	0.58	-2.26	0.03	2.60	0.97	2.69	<0.01
cg26912636	*TMEPAI*	NM_020182	0.16	0.07	2.22	0.03	-0.60	0.45	-1.33	0.19	1.94	0.65	2.97	<0.01

Note: covariates are age, gender, race, sumpbmc, smoke, anymed, dep, gad, sumpte, education, and gene methylation value.

b=beta coefficient; se=standard error; t=tvalue; p=pvalue

Table 7

Functional annotation cluster[¶] analysis of genes showing significant[*] methylation × SEP interactions

Outcome	Cluster	No. of Genes in Cluster[+]	Enrichment Score
PTSD	Hippocampus development	6	1.88
	Forebrain development	8	1.60
	RNA transport	4	1.50
PTS Symptom Severity	Synapse	6	1.18
	GTPase regulator activity	5	1.13
	Oxidation reduction	8	0.89

[¶]Functional annotation clusters (FAC) were bioinformatically inferred using DAVID (see methods for more details).

[*]Assessed at the $p<0.01$ level.

[+]All genes are identified in terms of DAVID IDs; genes can appear in more than one cluster

Table 8

Functional annotation cluster[¶] analysis of genes showing significant[*] methylation × SEP interactions in PTSD

Interaction Coefficient	Cluster	No. of Genes in Cluster[+]	Enrichment Score
Positive	Synaptic transmission	6	1.41
	Regulation of GTPase activity	4	1.19
	GTPase regulator activity	4	1.09
Negative	Disulfide bond	26	0.85
	EGF-like	3	0.85
	Membrane	39	0.83

[¶]Functional annotation clusters (FAC) were bioinformatically inferred using DAVID (see methods for more details).

[*]Assessed at the $p<0.01$ level.

[+]All genes are identified in terms of DAVID IDs; genes can appear in more than one cluster

Table 9

Functional annotation cluster[¶] analysis of genes showing significant[*] methylation × SEP interactions in PTS Symptom Severity

Interaction Coefficient	Cluster	No. of Genes in Cluster[+]	Enrichment Score
Positive	Plasma membrane	20	1.31
	Ion transport	8	0.95
	Neuron projection	6	0.83
Negative	Small GTPase regulator activity	4	1.16
	DNA binding	9	0.94
	Non-membrane bound organelle	6	0.15

[¶]Functional annotation clusters (FAC) were bioinformatically inferred using DAVID (see methods for more details).

[*]Assessed at the $p<0.01$ level.

[+]All genes are identified in terms of DAVID IDs; genes can appear in more than one cluster