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Longitudinal changes of telomere length and epigenetic age related to traumatic stress and post-traumatic stress disorder

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Summary Several studies have reported an association between traumatic stress and telomere length suggesting that traumatic stress has an impact on ageing at the cellular level. A newly derived tool provides an additional means to investigate cellular ageing by estimating epigenetic age based on DNA methylation profiles. We therefore hypothesise that in a longitudinal study of traumatic stress both indicators of cellular ageing will show increased ageing. We expect that particularly in individuals that developed symptoms of post-traumatic stress disorder (PTSD) increases in these ageing parameters would stand out.

From an existing longitudinal cohort study, ninety-six male soldiers were selected based on trauma exposure and the presence of symptoms of PTSD. All military personnel were deployed in a combat zone in Afghanistan and assessed before and 6 months after deployment. The Self-Rating Inventory for PTSD was used to measure the presence of PTSD symptoms, while exposure

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to combat trauma during deployment was measured with a 19-item deployment experiences checklist. These groups did not differ for age, gender, alcohol consumption, cigarette smoking, military rank, length, weight, or medication use. In DNA from whole blood telomere length was measured and DNA methylation levels were assessed using the Illumina 450K DNA methylation arrays. Epigenetic ageing was estimated using the DNAm age estimator procedure.
The association of trauma with telomere length was in the expected direction but not significant ($B = -10.2$, $p = 0.52$). However, contrary to our expectations, development of PTSD symptoms was associated with the reverse process, telomere lengthening ($B = 1.91$, $p = 0.018$). In concordance, trauma significantly accelerated epigenetic ageing ($B = 1.97$, $p = 0.032$) and similar to the findings in telomeres, development of PTSD symptoms was inversely associated with epigenetic ageing ($B = -0.10$, $p = 0.044$). Blood cell count, medication and premorbid early life trauma exposure did not confound the results.
Overall, in this longitudinal study of military personnel deployed to Afghanistan we show an acceleration of ageing by trauma. However, development of PTSD symptoms was associated with telomere lengthening and reversed epigenetic ageing. These findings warrant further study of a perhaps dysfunctional compensatory cellular ageing reversal in PTSD.

1. Introduction

In addition to a wealth of literature about the molecular sequelae of exposure to traumatic stress in humans, recent studies have identified telomere shortening as one of the alterations associated to traumatic stress, (for review see (Shalev et al., 2013)).

Telomeres are repeats of the nucleotides TTAGGG about 3–20 kB long at the end of chromosomes and have a function in protecting functional genetic code of the chromosomes against shortening due to duplication of DNA by DNA-polymerase that is part of normal cell division. Telomere length decreases with age, and the renewed interest in telomeres is partly due its association with longevity. Another age indicator that has recently been developed is the age estimator based of methylation of CpG sequences in the genome (Horvath et al., 2012; Horvath, 2013). DNA methylation is an epigenetic mechanism that plays a role in tissue type specification and is strongly related to ageing (Boks et al., 2009; Horvath et al., 2012). Recently Horvath (Horvath, 2013) identified 353 CpG loci that are routinely investigated in commercial available DNA methylation arrays that predict age with high accuracy. Interestingly, recent studies have firmly established that DNA methylation also plays a role in several diseases and is associated to environmental exposures and particularly traumatic stress (for reviews see [Vinkers, submitted]).

Considering that both telomere length and epigenetic age may be associated to trauma exposure, it is of interest to investigate this in a longitudinal design, which, in contrast to previous cross sectional studies, provide a higher level of evidence for a causal relationship. However, from the perspective of clinical utility, it is even more interesting to incorporate development of post-traumatic stress disorder (PTSD) symptoms as outcome in such an analysis in order to interpret the role of any trauma related changes in age-related parameters in disease aetiology of this psychiatric disorder. We hypothesised that both telomere shortening and accelerated epigenetic age would be positively associated with trauma exposure, and that development of PTSD symptoms would be associated with an even stronger acceleration of these ageing parameters.

2. Method

2.1. Subjects

We analysed longitudinal changes in a selected subgroup from a large, prospective cohort of 1032 Dutch military personnel deployed to Afghanistan, (see van Zuilen et al., 2011). Blood samples and standardised measures of Post-traumatic Stress Disorder (PTSD) symptoms were collected before and 6 months after deployment. The Self-Rating Inventory for PTSD (SRIP) was used to measure the presence of PTSD symptoms. The SRIP has a good reliability (Cronbach's alpha between 0.90 and 0.94) and validity (0.82 correlation to the Mississippi scale for combat-related PTSD) (Keane et al., 1988; Hovens et al., 2000). Exposure to combat trauma during deployment was assessed with a 19-item deployment experiences checklist as reported previously (van Zuilen et al., 2009). This assessment provides a range of self reported traumatic experiences that occur as part of deployment and include direct combat. From the entire cohort, 96 male participants were selected based on Dutch ethnicity, high or low levels of traumatic stress exposure and high and low levels of PTSD symptoms. This selection resulted in 64 participants with high combat trauma exposure (mean: 8.0 events ± 2.7) of which half had high levels PTSD symptoms at follow up (SRIP: 44.7 ± 8.7), and half low scores (24.9 ± 2.6), and 32 participants with low combat trauma exposure (mean: 0.4 events ± 0.5) and low levels of post-deployment PTSD symptoms at follow up (SRIP: 25.4 ± 3.7). These groups did not differ for age, gender, alcohol consumption, cigarette smoking, military rank, length, weight, or medication use. Traumatic experiences during childhood were assessed using the 27-item Dutch version of the self-report version of the Early Trauma Inventory (ETI) (Bremner et al., 2007). This questionnaire assesses exposure to potentially traumatic experiences before the age of 18 years (general trauma, physical abuse, emotional abuse and sexual abuse) (Hovens et al., 2002; Witteveen et al., 2006).

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