



## Research paper

# Assessing the contributions of childhood maltreatment subtypes and depression case-control status on telomere length reveals a specific role of physical neglect

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## A B S T R A C T

**Background:** Studies have provided evidence that both childhood maltreatment and depressive disorders are associated with shortened telomere lengths. However, as childhood maltreatment is a risk factor for depression, it remains unclear whether this may be driving shortened telomere lengths observed amongst depressed patients. Furthermore, it's unclear if the effects of maltreatment on telomere length shortening are more pervasive amongst depressed patients relative to controls, and consequently whether biological ageing may contribute to depression's pathophysiology. The current study assesses the effects of childhood maltreatment, depression case/control status, and the interactive effect of both childhood maltreatment and depression case/control status on relative telomere length (RTL).

**Method:** DNA samples from 80 depressed subjects and 100 control subjects were utilized from a U.K. sample (ages 20–84), with childhood trauma questionnaire data available for all participants. RTL was quantified using quantitative polymerase chain reactions. Univariate linear regression analyses were used to assess the effects of depression status, childhood maltreatment and depression by childhood maltreatment interactions on RTL. The false discovery rate ( $q < 0.05$ ) was used for multiple testing correction.

**Results:** Analysis of depression case/control status showed no significant main effect on RTL. Four subtypes of childhood maltreatment also demonstrated no significant main effect on RTL, however a history of physical neglect did significantly predict shorter RTL in adulthood ( $F(1, 174)=7.559$ ,  $p=0.007$ ,  $q=0.042$ , Variance Explained=4.2%), which was independent of case/control status. RTL was further predicted by severity of physical neglect, with the greatest differences observed in older maltreated individuals ( $> 50$  years old). There were no significant depression case/control status by childhood maltreatment interactions.

**Limitations:** A relatively small sample limited our power to detect interaction effects, and we were unable to consider depression chronicity or recurrence.

**Conclusion:** Shortened RTL was specifically associated with childhood physical neglect, but not the other subtypes of maltreatment or depression case/control status. Our results suggest that the telomere-eroding effects of physical neglect may represent a biological mechanism important in increasing risk for ageing-related disorders. As physical neglect is more frequent amongst depressed cases generally, it may also represent a confounding factor driving previous associations between shorter RTL and depression case status.

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## 1. Introduction

Psychiatric disorders, such as depression, have been linked to a heightened risk of severe medical conditions as well as early naturally occurring mortality (Viron and Stern, 2010; O'Donovan et al., 2011; Penninx et al., 2013). Medical conditions that are particularly frequent amongst depressive disorder patients tend to be those associated with ageing, including, but not limited to, cardiovascular disease, stroke, obesity, and type II diabetes (Evans et al., 2005). This has raised the question as to whether depression could be associated with accelerated biological ageing, i.e., when the ageing at the cellular level exceeds that of which is expected by chronological age (Lindqvist et al., 2015).

Indeed, advanced biological ageing has been demonstrated at the molecular level amongst depressed patients relative to controls in some previous reports (Hartmann et al., 2010). Telomeres are capping structures of repeat DNA at the end of chromosomes which act as biomarkers for cellular ageing (Eitan et al., 2014). Although there have been mixed reports, most individually conducted studies have shown that depressed patients exhibit shortened telomere lengths in their blood cells relative to controls, which is indicative of biologically older cells (Hartmann et al., 2010; Simon et al., 2006; Garcia-Rizo et al., 2013; Elvsåshagen et al., 2011; Hoen et al., 2011; Lung et al., 2007; Verhoeven et al., 2014; Wikgren et al., 2012). This association has further been confirmed in recent meta-analyses (Schutte and Malouff, 2015; Ridout et al., 2016; Darrow et al., 2016; Lin et al., 2016). If this ageing effect is causal, shortened telomeres may represent a mechanism contributing to the pathophysiology of depressive disorders, or if it represents a consequence of having depression, ageing cells may moderate the increased risk of comorbid ageing-related disorders reported previously.

Interestingly, childhood maltreatment has also been associated with shortened telomere lengths in adulthood, and it acts as a significant risk factor for depressive disorders (Tyrka et al., 2010; Kananen et al., 2010; O'Donovan et al., 2011; Shalev et al., 2014). What remains relatively unclear is whether childhood maltreatment could be driving the differences in telomere length previously observed amongst depressed cases. Alternatively, there could be depression case/control by maltreatment interactions, which moderate telomere length. For instance, if telomere lengths were found to be shorter amongst maltreated individuals, but with an even greater shortening amongst those with a subsequent depression diagnosis, it may suggest that shortened telomeres (and potentially advanced biological ageing) is a causal mechanism relating to depression.

The current study investigated relative telomere length (RTL) in a sample of 180 UK subjects (80 depressive disorder cases, 100 control subjects). Through the inclusion of maltreatment data and depression case/control data in the same analysis we aimed to disentangle each factor's contribution to biological ageing and to detect disease by maltreatment interactions.

## 2. Methods

### 2.1. Participants and diagnosis

A cohort study design assessing both depressive disorder cases and controls was implemented to address the research questions. A total of 180 White subjects from the United Kingdom were included in the study; 77 males and 103 females with ages ranging between 20 and 84 years (mean age of 50 (15.65 S.D)). This consisted of 80 DNA samples obtained from subjects with a depressive disorder and 100 DNA samples obtained from control individuals, see Table 1. All of the control subjects and the majority of depressive disorder case samples were obtained from the South East London Community Health Study (SELCoH; Hatch et al., 2011, 2016; Brown et al., 2014). However, due to low numbers of depressive disorder cases, a further 25 case samples from the Depression Case Control Study (DeCC) were also included

(Gaysina et al., 2007). Inclusion of subject samples for the current study was based on: (i) availability of leukocyte DNA samples, (ii) participants being White and from the UK (due to population differences in TL), (iii) availability of information on depressive disorder case/control status and childhood maltreatment.

Control subjects were recruited as part of SELCoH and identified as having no current depressive disorder symptoms using the Clinical Interview Schedule-Revised (CIS-R) (Lewis et al., 1992), and no previous diagnoses of a depressive disorder, as assessed using a self-report questionnaire. Depressive disorder case status was characterised in SELCoH using the CIS-R, which uses an algorithm to approximate ICD-10 diagnoses (World Health Organisation, 1993). A subject was screened positive for a depressive disorder if they met diagnostic criteria for any of the following: mild depressive episode, mixed anxiety and depressive disorder, moderate/severe depressive episode. Although we considered 'depressive disorder' as a single group, for sensitivity analyses we did consider each of these groups separately. Depressive disorder diagnosis in DeCC was made using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN), as described previously, with all DeCC subjects representing major depressive disorder patients, i.e. those with moderate/severe depressive episodes (Wing et al., 1998; Gaysina et al., 2007).

Data regarding age, gender, depressive disorder disease status, and maltreatment status was obtained from all participants, and body mass index (BMI) data was available for 98% of subjects. For SELCoH subjects only, we also had information regarding smoking habits, antidepressant use, drug dependency, drug use, other medication use, and comorbid diseases, allowing us to perform sensitivity analyses to test for potential confounders.

### 2.2. Assessment of childhood maltreatment

The presence or absence of childhood maltreatment or maltreatment subtypes (emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect) was determined using the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003). Due to relatively small sample sizes and fewer instances of severe maltreatment, for our primary analyses, we dichotomised subjects into those with, or without, a history of childhood maltreatment. To achieve this, we first determined those with no history of maltreatment, and those with mild, moderate and severe maltreatment, as according to Bernstein et al., 2003. We then collapsed the mild/moderate/severe maltreatment groups into a single maltreatment category. For secondary analyses, where we do find a significant effect of a maltreatment subtype, we further consider the impact of severity (no/mild/moderate-severe maltreatment).

### 2.3. Ethics

The SELCoH study received approval from the King's College London research ethics committee, reference PNM/12/13-152. The DeCC study was approved by the Joint South London and Maudsley NHS Trust Institute of Psychiatry Research Ethics Committee. Informed written consent was obtained from all the participants at the time of sample collection.

### 2.4. DNA extraction and telomere assessment

10 mL of blood was collected from subjects in tubes containing EDTA (BD Vacutainer; BD, NJ, USA) and stored at  $-80^{\circ}\text{C}$ . DNA was then extracted using a standard in-house protocol described previously (Freeman et al., 2003) and stored at  $-80^{\circ}\text{C}$ . All samples had 260/280 ratios of between 1.7 and 1.9 as tested using the Nanodrop D1000 (Thermoscientific, Wilmington, DE, USA).

To assess the relative telomere length (RTL) of the 180 subject samples, two separate quantitative polymerase chain reactions (qPCRs)

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