Empathy and Oxidative Stress in Healthy Adults

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Abstract: Empathy is crucial for normal and effective social functioning, enabling comprehension and prediction of actions in social environments. Despite its importance for maintaining social relationships in human groups, the physiological correlates of empathy are not fully known. The aim of this study was to test whether empathy is related to oxidative stress level, that may result both from internal disturbances and influence of external adverse factors. Seventy-four healthy women (M age = 26.23, SD age = 2.88) and one hundred and one men (M age = 28.09, SD age = 3.03) took part in the study. Participants’ empathy was evaluated with self-assessment questionnaire—Empathy Quotient (EQ). Oxidative stress level was measured with serum 8-OH-dG, a product of oxidative DNA damage. The results showed that empathy is negatively related to oxidative stress level in men but not in women, when controlled for testosterone level. Revealed sex differences may be explained by men’s greater vulnerability to various adverse conditions and harmful factors. Men, compared to women, seem to be more susceptible to behavioral changes, induced by increased oxidative stress level. The study adds to growing evidence showing that many physiological mechanisms, other than hormonal factors, that may be also related with environmental harmful factors, are related to behavioral, affective and cognitive phenomena.

Keywords: 8-OH-dG; inter-individual comparison; physiology; sex differences; social behavior; testosterone

1. Introduction

Social relationships have played a crucial role in human evolution and still are the key contributor to individuals’ wellbeing [1,2]. Maintaining close and long-term social bonds requires understanding other people’s feelings, desires, thoughts and intentions. Although there are several definitions of empathy, in general, it is defined as the ability to understand and experience others’ feelings in relation to oneself, share affect and understand thinking and intentions of others [3]. As such, empathy is an essential part of normal and effective social interactions and functioning, enabling comprehension, as well as prediction of actions in social environment [3,4].

Many social behaviors are influenced by physiological factors [5,6]. Although empathy is crucial for the ability to maintain social relationships in human groups, the physiological correlates of empathy are not fully understood. So far, studies show that, among hormonal mechanisms, the most important factors are fetal [7] and adult testosterone levels [8]. Testosterone levels at both of these stages of ontogeny are negatively related to empathy level, which may explain sex differences in empathy that were observed in many studies. On average, men are less empathic compared to women [3]. Other studies showed shifts in empathy in menstrual cycle, linking empathy to progesterone level,
and the negative relationship between the two factors was observed mainly in the luteal phase [9]. Several studies have shown that oxytocin [10] and arginine vasopressin [11] also modulate empathy and induce prosocial behaviors.

There is growing evidence that a variety of behavioral, affective and cognitive phenomena are also driven by non-hormonal physiological mechanisms [12,13]. Recent studies suggest that oxidative stress level may also have a significant impact on nervous system functioning, and thus on human behavior [14,15]. Oxidative stress (OS) is a state of imbalance between reactive oxygen species and antioxidants levels. The production of energy via cellular respiration involves release of reactive oxygen species (ROS), oxygen-containing molecules, possessing an unpaired electron, which are thus highly unstable. Although ROS are by-products of a physiological process, they are toxic and rapidly react with lipids, proteins and nucleic acids, leading to cell damage [16]. In normal conditions, ROS are neutralized by antioxidants, converting them into stable, harmless molecules, but under pathophysiological conditions heightened ROS production exceeds the antioxidant capacity of a cell, yielding susceptibility to oxidative damage. Such pathophysiological conditions, that may induce oxidative stress, include not only intrinsic [17] but also extrinsic factors, such as exposure to psychological stress, smog and environmental pollution, linked with urban environment [18–21]. At low levels ROS are beneficial, as they are involved in pathogen elimination and cell signaling, but heightened oxidative stress is associated with premature aging of cells and can lead to tissue inflammation, damaged cell membranes, autoimmunity and cell death [16].

The nervous system is especially vulnerable to oxidative stress due to a few reasons. The human brain has higher energy requirements compared to other body tissues. Although the brain accounts for only a few percent of body weight, it is responsible for about 20% of basal oxygen consumption [22]. The brain has a limited antioxidant capacity as neurons do not produce glutathione (crucial antioxidant) [23]. Therefore, neurons are among the first cells to be affected by an increase in ROS production and shortage of antioxidants and are the most susceptible to oxidative stress. Studies confirm that increased oxidative stress level accompanies many neurodegenerative disorders, such as depression [24], anxiety [15,25], aggression disorders [14], and autism [26].

Oxidative stress not only underlies pathological processes and neurodegenerative disorders but its basal, steady state level seems to also be related to normal variation in some behavioral traits. For instance, heightened OS is observed in individuals with intermittent explosive disorder (characterized by explosive outbursts of anger and violence), and it is also related to a history of actual aggressive behavior in healthy people [14]. Many studies show that oxidative stress is one of the main, among previously explored, physiological correlates of autism and Asperger syndrome [26–28], neurological conditions related to decreased empathy and social malfunctioning, often defined as empathy deficit disorder [3]. Individuals with these conditions have profound difficulties with understanding others’ mental states and usually fail to comprehend deception, although they still describe themselves as being able to share others’ emotions [29]. As increased OS level is observed in pathological conditions related to empathy deficit disorders, it seems possible that variation in basal oxidative stress level may be also related to inter-individual differences in empathy level in healthy people.

The aim of this study was to investigate if oxidative stress level is linked to empathy in healthy adults. We hypothesized that OS is negatively related to empathy. As many research studies show that sex steroids may impact and/or mediate the relationship between non-hormonal factors and brain functioning [30], and testosterone level has been shown to be related to both oxidative stress [31] and empathy level [8], in the analyses, we controlled for testosterone level. Moreover, we tested the potential interaction between OS and testosterone to examine whether testosterone level differentiates the relationship between OS and empathy. We verified our research questions on men and women separately due to the reported, in previous research, sex differences in empathy and oxidative stress level [3,32].
2. Materials and Methods

2.1. Participants and General Procedure

Participants were recruited through information posted on social websites and in the local newspapers. Participation in the study was voluntary. Men and women were selected for participation if they met the following criteria: no diagnosed chronic diseases (diabetes, hypothyroidism, hormonal, autoimmune or metabolic disorders) and no current infections (see Section 2.4. General Health Evaluation). Additional criteria for women were regular menstrual cycles and no hormonal contraception. Women were recruited at the early follicular phase (between the 2nd and the 4th day). From the initial study group \(N = 231\), 37 men and 19 women were excluded due to smoking, high C-reactive protein (CRP) level (indicating ongoing systemic inflammation), abnormal testosterone level or drinking alcohol the day before blood analysis, resulting in the sample of 74 women \(M_{\text{age}} = 26.23, SD_{\text{age}} = 2.88\) and 101 men \(M_{\text{age}} = 28.09, SD_{\text{age}} = 3.03\). The study was approved by the Bioethics Commission at the Lower Silesian Chamber of Physicians and Dentists’ ethics committee. All participants read and signed the informed consent form.

The study protocol for each participant consisted of a fasting blood draw and answering the survey questions. The results of laboratory tests were paired with surveys, coded and anonymized for confidentiality reasons. Blood serum samples were collected in the morning hours (between 7:30 and 9:00 a.m.) by certified medical staff. The blood specimens were collected into serum vacutainer (BD Vacutainer®, Franklin Lakes, New Jersey, N.J., USA) and centrifuged for serum separation. Separated serum was portioned and frozen at \(-70\^\circ C\) until analysis. A general questionnaire was used to collect information on demographic data, health problems, education, stress, cigarette smoking and alcohol consumption (including alcohol consumption within last 24 h and binge drinking within last week). The study group consisted of an urban population, as most of the participants lived in the big city and suburbs \(N = 164\) or small city \(N = 5\), and only four in a village. A majority of the participants \(N = 161\) had a university degree. Place of living and education were not related to empathy, oxidative stress or testosterone levels \((p > 0.05)\).

2.2. Empathy Quotient (EQ)

Empathy level was evaluated with Empathy Quotient (EQ) [3]. EQ is a short, easy to use and to score, self-assessment questionnaire, developed to measure the cognitive and affective aspects of empathy in adults of normal intelligence. The EQ comprises 60 questions, broken down into two types: 40 questions tapping empathy (e.g., “I find it hard to know what to do in a social situation.” or “It doesn’t bother me too much if I am late meeting a friend.” or “When I was a child, I enjoyed cutting up worms to see what would happen.”) and 20 filler items (e.g., “I try to keep up with the current trends and fashions” or “I dream most nights.” or “I like to do things on the spur of the moment.”), included to distract participants from a constant focus on empathy [3]. On each empathy item a person can score 2 (indicating greater empathy), 1 or 0 (indicating no empathy), so the EQ has a maximum score of eighty and a minimum of zero. Reliability of the EQ was high, with the Cronbach’s alpha = 0.87.

2.3. 8-OH-dG (Oxidative Stress Marker) Measurements

8-hydroxy-2′-deoxyguanosine (8-OH-dG) is one of the predominant forms of free radical-induced oxidative lesions in nuclear and mitochondrial DNA, widely used as a biomarker of systemic oxidative stress [30]. 8-OH-dG level was measured in serum samples. Before the analyses, serum samples were filtrated using Ultra Filter (Amicon® Ultra 0.5mL Centrifugal Filters, Merck Millipore™, Burlington, MA, USA) to separate interfering substances. The filtration process was performed following the instructions, supplied with the Amicon® filter. The supernatant liquid was used to measure 8-OH-dG level. The quantitative detection of the 8-OH-dG in pre-filtered serum samples was evaluated with commercial ELISA kits (DEKOG200SE, DEMEDITEC®, Kiel, Germany), following the manual. After a
series of incubations (with samples, primary antibody, secondary antibodies and chromatic substrate) the absorbance at 450nm was measured by microplate reader (Asys UVM340, Biochrom®, Cambridge, UK). The standard curve was generated by plotting absorbance (Y axis) and concentration of standards (X axis). 8-OH-dG concentration was calculated in relation to the standard curve and expressed in ng/mL.

2.4. General Health Evaluation

Participants’ general health status was controlled based on physiological parameters, commonly used in clinical practice, including blood morphology with smear test and CRP level. All participants had blood morphological parameters within the normal range, or had one parameter slightly beyond or above the normal range of what, in clinical practice, is recognized as “healthy.” To control for possible asymptomatic infections, C-reactive protein (CRP) level, non-specific clinical inflammatory marker, was measured. CRP level was evaluated using commercial kit (catalog number DE740011, DEMEDITEC®, Kiel, Germany). Test procedure and calculation of the results were performed in accordance to the instructions supplied with the kit. Participants with CRP level above 10 pg/mL were excluded from the analyses, as such level may indicate increasing systemic inflammatory state, which may also result in higher oxidative stress.

2.5. Hormone Measurements

Serum free testosterone (fT) concentration was measured with enzyme-linked immunosorbent assay (ELISA) and commercial kit (catalogue number DE2924, DEMEDITEC®, Kiel Germany). Serum samples were assayed according to the manufacturer’s instructions. Both within and between assay variability were less than 10%, with the assay sensitivity of 0.06 pg/mL. The absorbance was measured using $\lambda = 450$ nm and microplate reader (Asys UVM340 Biochron®, Cambridge, UK). The standard curve was constructed by plotting the absorbance of each standard (vertical axis) against its concentration (horizontal axis). The concentration of fT in each sample was calculated in relation to the standard curve and expressed in pg/mL.

2.6. Statistical Analyses

The relationship between the variables was tested with correlation analyses, multiple regression and moderation analyses. Correlation analyses included Pearson’s correlation. Plasma 8-OH-dG levels were significantly skewed thus Box-Cox transformation was applied to the variable to obtain normal distribution. Data were first analyzed without any potential covariates and then with testosterone as a covariate. Regression analysis was used to investigate the possible moderation of testosterone on the effect of 8-OH-dG on empathy. For moderation analyses, the variables were centered in order to avoid high multicollinearity. $\alpha$ values $\leq 0.05$ denoted statistical significance.

3. Results

3.1. Descriptive Statistics

Women exhibited higher levels of empathy, compared to men. There was no sex difference in 8-OH-dG level. The mean testosterone levels were typical for men and women (Table 1).

|              | Men          | Women       | Difference |
|--------------|--------------|-------------|------------|
| Empathy Q    | 39.92 ± 11.33| 46.04 ± 9.48| $t (173) = -3.78, p < 0.001$ |
| 8-OH-dG      | 0.74 ± 0.58  | 0.62 ± 0.48 | $t (173) = 1.55, p = 0.12$   |
| Testosterone | 25.82 ± 9.59 | 1.79 ± 4.05 | $t (173) = 20.24, p < 0.001$ |
3.2. The Relationship between Empathy Quotient, 8-OH-dG and Testosterone Levels

The results of the simple correlation analyses showed that Empathy Quotient correlated negatively with 8-OH-dG in men but not in women. There was no relationship between testosterone and empathy or 8-OH-dG in men and women (Table 2).

Table 2. The correlation coefficients of the relationship between Empathy Quotient, 8-OH-dG and testosterone level in men (N = 101) and women (N = 74). The significant results are bolded.

|               | Empathy Quotient | 8-OH-dG |
|---------------|------------------|---------|
|               | Men              | Women   | Men      | Women   |
|               | r    | p       | r    | p       | r    | p       |
| 8-OH-dG       | −0.24 | 0.02   | −0.06 | 0.62   |
| Testosterone  | −0.04 | 0.74   | −0.11 | 0.36   | 0.08 | 0.44   |

The regression analysis model showed that both sex and 8-OH-dG level predicted empathy level (Model $F(2,172) = 9.72$, $R^2 = 0.10$, $p < 0.001$; 8-OH-dG: $\beta = −0.16$, $p = 0.02$; sex: $\beta = 0.26$, $p < 0.001$). In addition, when controlled for testosterone level, 8-OH-dG was negatively related to empathy ($\beta = −0.16$, $p = 0.03$) but testosterone was not related to empathy level ($\beta = −0.06$, $p = 0.66$). Further, we ran multiple regression analyses of the relationship between 8-OH-dG and empathy, controlled for testosterone level separately for men and women. The analyses revealed that 8-OH-dG is negatively related to empathy in men but not in women. There was no relationship between testosterone and empathy, regardless the sex (Table 3; Model 1).

A moderation analysis was also run, separately for men and women, to test if testosterone level may impact the relationship between oxidative stress and empathy. In men, only 8-OH-dG level was negatively related to empathy level, but not testosterone or interaction between 8-OH-dG and testosterone levels, thus the effect of OS on empathy was independent of testosterone concentration. In women, neither 8-OH-dG, testosterone, nor the interaction between the two variables were related to empathy level (Table 3; Model 2).

Table 3. The results of regression analyses of the relationship between empathy and 8-OH-dG, controlled for testosterone level for men (N = 101) and women (N = 74) separately. The significant results are bolded.

|       | Men               | Women              |
|-------|-------------------|--------------------|
|       | $\beta$ | SE  | t    | $p$ | $\beta$ | SE  | t    | $P$ |
| Model 1 | F(2,130) = 3.41, $R^2 = 0.04$, $p = 0.05$ | F(2,89) = 0.49, $R^2 = 0.02$, $p = 0.47$ |
| 8-OH-dG | −0.20 | 0.09 | −2.84 | 0.02 | 0.07 | 0.11 | 0.66 | 0.50 |
| Testosterone | −0.03 | 0.09 | −0.03 | 0.76 | −0.12 | 0.11 | −1.22 | 0.26 |
| Model 2 | F(3,97) = 2.68, $R^2 = 0.07$, $p = 0.05$ | F(3,70) = 3.66, $R^2 = 0.025$, $p = 0.02$ |
| 8-OH-dG | −3.41 | 1.26 | −2.71 | 0.008 | −0.06 | 1.60 | −0.04 | 0.97 |
| Testosterone | −0.01 | 0.11 | −0.07 | 0.95 | −0.90 | 0.86 | −1.04 | 0.30 |
| 8-OH-dG × Testosterone | −0.16 | 0.13 | −1.20 | 0.24 | 0.91 | 1.14 | 0.80 | 0.42 |

1 Interaction between 8-OH-dG and testosterone levels.

4. Discussion

So far, there have been only few research studies on the relationship between oxidative stress and behavior in healthy individuals, e.g., [14], and this is the first study to show the negative relationship between the level of systemic oxidative stress marker (8-OH-dG) and empathy. The results of this study confirmed our hypothesis for men but not for women, as we showed that empathy was negatively related to oxidative stress in men but not in women, also when controlled for testosterone level.
Sex differences in the relationship between OS and empathy, revealed in this study, may be explained by men’s lower resistance to various adverse conditions and harmful factors [33], which make them more vulnerable to genetic mutations or environmental insults, possibly including oxidative stress [32]. Previous research showed that male infants are more susceptible to OS and have higher levels of oxidative stress markers, compared to female infants [34]. Women also have greater antioxidant defenses, thus may be less prone to oxidative damage [35,36], which may explain the lack of the relationship between empathy and OS in women, who may be more effectively protected from harmful effects of OS, compared with men. Additionally, research studies show that inflammation in the cerebellum, measured with prostaglandins levels (also a biomarker of oxidative stress level) during a sensitive developmental window, impairs social behavior in males but not in females [37]. As reactive oxygen species are related to systemic inflammatory response and are generated by several cells involved in inflammatory reaction, it seems to confirm that men are more susceptible to behavioral changes, induced by increased oxidative stress level, compared to women.

The results of this study are consistent with the extreme male brain (EMB) theory of autism [3,38] and the research indicating an important role of oxidative stress in autism etiology [26–28]. According to EMB theory, the inter-individual variability in empathy is comprised between the two ends of the spectrum: “empathizing” (E) and “systemizing” (S). Empathizing, more characteristic of the female brain, is the drive to identify another’s mental state and to respond with an appropriate emotion to this. Systemizing, more characteristic of the male brain, is the drive to analyze a system in terms of its underlying lawful regularities and to construct systems using such lawful regularities [38]. As such, EMB theory predicts that autistic individuals show an exaggerated male profile, and autism spectrum conditions are perceived as empathy disorders. Although there is no clear gender difference in the identified risk genes, boys are at greater risk of developing Autism Spectrum Disorder (ASD) conditions (and healthy men also show lower empathy compared to healthy women), showing unexplained vulnerability of males to empathy deficits [3,38,39]. Studies also show that autistic children have lowered levels of antioxidants and increased OS level, which may contribute to the development and clinical manifestations of autism [37,40]. The results of this study showed that oxidative stress level is also related with variability of empathy level in healthy, non-autistic men.

As empathy is crucial for effective social functioning [3,4] the evidence for the relationship between OS level and empathy may be important for the research on human sociality and social interactions. Furthermore, as oxidative stress is one of the main proximal mechanisms responsible for the harmful effects of adverse factors related with urbanization, industrialization and western lifestyle [18–21,41], the results of our study show a potential physiological mechanism that may link these factors not only with human physical health, but also with behavioral alterations and social functioning. Also, the result may have potential important implications for work environments. For instance, previous research showed decreased empathy in medical interns during the resident program. As interns also suffer from psychological stress and sleep deprivation, the decrease in empathy may be a result of increased oxidative stress [42].

Finally, some limitations need to be addressed. One potential limitation of our study is that 8-OH-dG was only measured once. Single measures might be susceptible to temporal fluctuations, which might add noise to the data and limit the ability to detect the relationship between OS level and empathy. However, OS appears to possess substantial temporal stability, and individual differences in basal, steady-state OS levels emerge early in development [43] influencing physiological processes [44] and potentially an individual’s behavior. Also, factors that may potentially impact OS level, such as participants’ general health and actual infections, recent changes in lifestyle, alcohol use or smoking were thoroughly controlled in this study. Thus, we can presume that oxidative level, measured in this study, reflects basal inter-individual differences, related to empathy in men. Another limitation is related with the fact that empathy has a multidimensional nature, involving an affective component, which is the ability to experience and share the emotions of others, and a cognitive component, which is the ability to understand the emotions of others, thus measuring empathy is complicated. Empathy
Quotient, used in this research, is a one-dimensional measure of empathy and does not separate items into purely affective and cognitive categories. In most instances of empathy, the affective and cognitive components co-occur and cannot be easily disentangled [3]. Although most studies show the same pattern in gender differences, with women exhibiting higher affective and cognitive empathy [45], there is some evidence that sex steroids may have various impacts on affective and cognitive empathy in children, depending on an individual’s sex [46].

For future studies, it would be informative to replicate the results of this study using composite measures of the physiological indicators of oxidative stress level, including measurements of various products of oxidative damage and also antioxidants levels. Furthermore, it might be also interesting to investigate if oxidative stress level moderates both affective and cognitive components of empathy in men and women, using measurements of empathy other than EQ, capable of distinguishing its various components.

Thus, in conclusion, the results of our study showed that oxidative stress level predicts empathy in men, but not in women, which may have important implications for the studies on the physiological basis of human sociality and behavior. The results of our study support the previous results, showing that oxidative stress may be one of the key factors influencing functioning of the central nervous system [14,15], as it not only underlies neurological and behavioral disorders [14,15,24–26], but also may partly explain individual differences in behavioral traits, such as aggression [14] or empathy. The study adds to research showing that, other than hormonal (e.g., testosterone [7,8] or neurohormones [10,11]) factors, factors related to behavioral, affective and cognitive phenomena, should be included in attempts to explain human behavior [12,13]. As oxidative stress is related to sex steroids level [30,31] and this relationship may be bidirectional, studies concerning the relationship between sex steroids and human behaviors should not ignore the potential role of OS and oxidant levels.

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