THE EFFECT OF HEDONIC CAPACITY ON AFFECTIVE AND PHYSICAL SICKNESS RESPONSE

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Abstract

The presence of sickness in human individuals presents a significant healthcare burden. Understanding an individual's different sickness responses may help us to better manage sickness and its symptoms. Sickness induces changes in both physiology and affect. These behavioral ramifications have been extensively researched with the intravenous injection of the bacterial endotoxin E. coli lipopolysaccharide (LPS), which causes an acute inflammatory-induced sickness response. Previous research shows that positive affect is reduced during sickness while the physical sickness response increases. Hedonic capacity refers to a person's ability to experience pleasure and may explain differences among individuals' reactions of patterns and adaptations in the face of sickness. This could be due to the fact that lower levels of hedonic capacity indicate an already reduced to ability to experience pleasure that might be further diminished by the physiological and psychological changes associated with sickness. This study aimed to research the extent to which hedonic capacity affects affective and physical sickness response. It was hypothesized that individuals with a higher hedonic capacity experience less reduction in positive affect as well as smaller increases in physical sickness response during an inflammatory-induced sickness compared to individuals with lower hedonic capacity. This study was part of a larger cohort study. 110 healthy indivduals were screened and injected with LPS. Physical responses and state questionnaires were conducted. Multiple linear regression analyses were done. No significant relationships were observed between hedonic capacity and physical or affective sickness response. Additional neuropsychological research is recommended to investigate these results.

Keywords: Sickness behavior, Inflammation, Lipopolysaccharide, Hedonic capacity

THE EFFECT OF HEDONIC CAPACITY ON AFFECTIVE AND PHYSICAL SICKNESS RESPONSE

Everyone knows the feeling of being sick. The flu season, once again at its peak, ensures this. The estimated flu disease burden this season in the U.S. is estimated at 9,000,000 people (CDC, 2022). The presence of sickness in human individuals presents a significant healthcare burden since absence due to sickness introduces major costs for companies (HR Magazine, n.d.). Additionally, understanding individuals' different reactions to infectious agents is pertinent. For instance, some people cannot work when they catch the flu, while others do not experience any discomfort whatsoever. If we understand these individual differences better, it may help to better manage sickness and its symptoms. Furthermore, it is relevant to public policy making as well: Just recently leaders were engaged in discussions on how we should handle infected and possibly contagious but asymptomatic individuals, as in the case of the COVID-19 pandemic (Lasselin, 2021). Therefore, understanding sickness behavior as well as reduction in prevalence is needed in several facets of society.

When sickness arises, symptoms such as malaise, fatigue and pain emerge (Benson et al., 2017). Individuals become depressed and lethargic and show limited interest in their surroundings, as well as that they stop consuming food and water (Lasselin, 2021). The body's immune system responds by releasing pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-8 (IL-8) and anti-inflammatory cytokines such as interleukin-10 (IL-10), interleukin-1 (IL-1) and receptor antagonist (IL-1Ra) that assist in eliminating invading pathogens (Dantzer et al, 2008). These cytokines, along with other cells, trigger these physical and affective changes observed in sick individuals (Dooley et al., 2018; Schedlowski, 2014). This is referred to as affective sickness behavior. (Dantzer & Kelly, 2007). Additionally, it has been shown that there is a

difference in the immune response between male and female individuals. Specifically, Engler et al. (2016) found that men and women differ in inflammatory responses. Women have a substantially augmented pro-inflammatory sickness response relative to men (Engler et al., 2016).

The behavioral ramifications of being sick have been frequently investigated with assistance of inflammation-induced sickness. In such research, bacterial endotoxin called E. coli lipopolysaccharide (LPS), is administered that activates an acute immune response within the individual (Benson et al., 2017). Mechanisms of this immune-mediated sickness response are then monitored and researched. This immune response peaks in the first 2 to 6 hours after LPS administration (Fu et al., 2010) and then gradually returns to normal within a few hours (Lasselin, 2021). This relatively short immune response- and recovery permits researchers to investigate this in a relatively short period of time (Lasselin, 2021).

Using this method, inflammation has been shown to change neural reward processing (Capuron et al., 2012; Eisenberger et al., 2010; Harrison et al., 2015). Eisenberger et al. (2010) found a link between neural reward processing and anhedonia and Harrison et al. (2105) concluded that inflammation had a substantial effect on sensitivity to punishment in the reward process, compared to their control group.

Hedonic capacity is a person's ability to experience pleasure and derive enjoyment from various activities and stimuli. (Berridge & Kringelbach, 2015) and is closely linked to reward processing. It is involved in similar brain regions, such as the ventral striatum, prefrontal cortex and the mesolimbic dopamine system and influences reward processing by changing the brain's response to rewards (Höflich et al., 2019). A level of an individual's hedonic capacity can influence how rewards are processed and experienced. Individuals with high hedonic capacity typically show enhanced activation of these brain regions (Höflich et al., 2019). This reflects an amplified experience of pleasure and motivation. In Contrast,

individuals with low hedonic capacity may display reduced activation in these brain regions, which suggest a diminished experience of pleasure and reduced motivation to engage in such activities (Höflich et al., 2019). Thus, proper levels of hedonic capacity are vital for one's healthy psychological functioning and well-being (Berridge & Kringelbach, 2015).

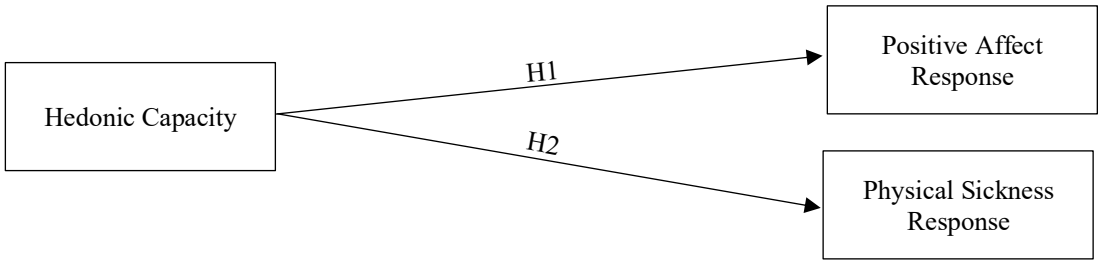
Previous research suggests that most pleasure comes from memory or anticipation (Rozin, 1999). Hedonic capacity has also been linked to Major Depressive disorder as well as Autism Spectrum disorder (ASD), happiness and motivation. (Gard et al., 2006). Gard et al. (2006) found correlations between the anticipatory pleasure scale and reward responsiveness. Though inflammation in relation to reward systems in the brain has been researched, the physical state of a sick body in relation to hedonic capacity remains limited.

Optimism and physical health, however, have been linked together. Optimism has been associated with lower risk of cardiovascular issues (Rozanski, Bavishi, Kubansky and Cohen; 2019). Likewise, Rasmussen et al. (2009) found that optimism is a significant predictor of positive physiological health outcomes. Reciprocally, hedonic capacity may explain differences among individuals' patters of reactions and adaptations in the face of sickness (Gustavsson, Jönsson, Linder and Weinryb, 2003) It could very well be that individuals with lower hedonic capacity may display more pronounced sickness behavior during sickness. This could be due to their already reduced to ability to experience pleasure, which may be further diminished by the physiological and psychological changes associated with sickness. Vice versa, individuals with higher hedonic capacity may experience a less pronounced sickness response.

This study aims to research the extent to which hedonic capacity affects affective and physical inflammatory sickness response to lipopolysaccharide (LPS). The following is hypothesized: individuals with higher hedonic capacity experience less reduction in positive affect during inflammatory induced sickness response as well as smaller increases of the

physical inflammatory sickness response to LPS. This will be assessed by measuring baseline hedonic capacity of individuals, as well as their affective and physical response to LPS at predetermined timepoints in one 8-hour session. Below a conceptual representation of the research question can be found.

Figure 1: *Conceptual representation of the research question.*



Note. A conceptual representation of the research question produced in Microsoft Word (2023).

H1: High hedonic capacity is related to less reduction of Positive Affect in response to LPS.

H2: High hedonic capacity is related to less increase of physical sickness response in response to LPS.

Methods

In this study, a subset of data from a larger cohort study was utilized. This original study was performed by Jansen et al. (2022) at the department of Intensive Care Medicine of Radboud UMC. For the current study only a subset of the dataset was used for analysis. This was the data obtained during the first day. The data subset is further elaborated in the following sections.

Participants

The protocol for this study was approved by the Local Ethics Committee (CMO Arnhem-Nijmegen; reference Nos. NL68166.091.18 and 2018-4983) and in accordance with the declaration of Helsinki. 110 participants were recruited. They were recruited on the basis of being between the ages 18 to 35 years old, having a healthy medical history, a proper

physical examination, and some additional routine laboratory tests, a 12-lead electrocardiogram that revealed no abnormalities and all participants signed an informed consent form. Smoking, use of any medication (contraceptives precluded), previous participation in experimental human endotoxemia, or signs of acute illness within 2 weeks prior to the start of the study were regarded as exclusion criteria. Participants were compensated with money for their participation (400 euros for two eight-hour sessions).

Study Design

In order to understand how hedonic capacity affects physical and affective inflammatory response to LPS, a prospective experimental cohort study was performed. A schematic overview of this study design is illustrated in Figure 2 and Appendix A and is discussed per component in further detail down below.

Prior to the experiment

Prior to the experiment, a screening was done, and at home (V0), baseline trait questionnaires were filled out. The collected data included demographic characteristics and medical parameters (both found in Appendix B) and a baseline trait questionnaire of the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) found in Appendix C..

Experimental Human Endotoxemia (IV LPS Administration)

Participants were instructed to abstain from alcohol and caffeine 24 hours prior to the experiment as well as to refrain from consuming food and drinks 12 hours prior to the experiment. On the day of the experiment itself, participants were admitted to Radboud University Medical Centre where a radial artery catheter (BD Infusion Therapy Systems, Sandy, UT, USA) and antebrachial venous cannula were placed intravenously into the participant. This allowed serial blood sampling, hemodynamic monitoring, and administration of fluids and LPS. In the 45 minutes prior to LPPS administration, hydration fluids (2,5% glucose/0.45% sodium chloride) were given a 2.5L-prehydration bolus to reduce

the of the risk of vasovagal collapse. Following that, it was continuously given at a rate of 150mL/h for the remaining duration of the experiment. Promptly after prehydration, a bodyweight-adjusted bolus dose of 1ng/kg LPS (Escherichia coli-derived, Type O0113, lot no.94332B1; List Biological Laboratories, Campbell, CA, USA) was administered. Blood samples were serially obtained to construct time-concentration curves of circuiting cytokines (Jansen et al., 2022). Temperature and cardiovascular monitoring (blood pressure and heart rate) and sickness symptoms (headache, muscle pain, back pain, nausea, shivers and vomiting were recorded throughout the whole experiment with intervals of 30 minutes. Additionally, Ethylenediaminetetraacetic acid (EDTA)-anticoagulated blood was collected 8 times (-=.5, 30, 60, 90, 120, 180, 240, and 360 minutes relative to LPS administration), immediately centrifuged (20000 g, 4 c, 10 min) after which the plasma was stored at -80C until analysis. Cytokines were determined using a simultaneous Luminex assay (Milliplex, Millipore, Billerica, MA, USA) in a single batch.

Measures

Hedonic capacity

To measure hedonic capacity, the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) (found in Appendix C.) was used. It is a commonly used self-report measure specifically designed to measure anticipatory and consummatory pleasure. The questionnaire consisted of 18 items, and every item could be answered with a Likert scale that ranges from 1 (not at all right for me) to 6 (completely right for me). 10 items measured anticipatory pleasure (AC), while the other 9 items gave an indication of consummatory pleasure (CP). The TEPS (Gard et al., 2006) was considered a trait measure in this study and was measured prior to the start of the experiment.

Affective sickness response

Affective sickness response was measured using the Positive Negative Affect Scale (PANAS; Watson, Clark & Tellegen, 1988). This self-report questionnaire (found in Appendix D.) is designed to measure 2 dimensions of emotional experience: Positive Affect and Negative Affect. The answer to each item was quantified with the use of a 5-point Likert scale. For this study only the Positive Affect subscale was incorporated. The PANAS (Watson, Clark & Tellegen, 1988) was considered a state measure in this study, meaning that it was measured at the start of the experiment (V1T0), as well as throughout the duration of the hospitalization at six different timepoints. Positive Affect response to LPS was measured as the difference between the sum score of the Positive Affect dimension at 2 hours after LPS administration (V1T2) versus Positive Affect at baseline (V1T0).

Physical sickness response

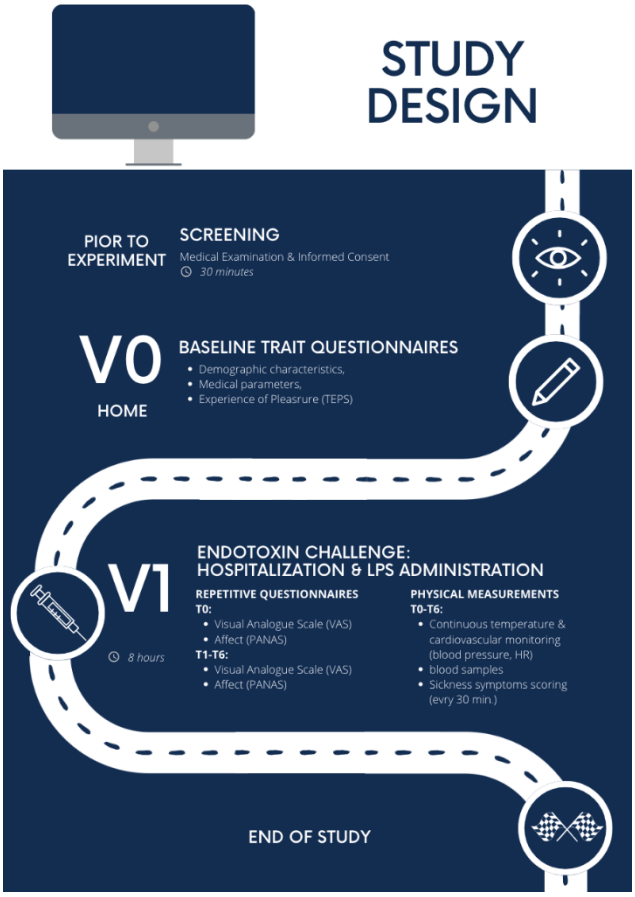
Physical sickness response was measured with the use of two indicators. Firstly, by monitoring concentrates of the pro-inflammatory cytokines, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interleukin-8 (IL-8). Secondly, the physical sickness symptoms were quantified by the Visual Analogue Scale (VAS; Hayes & Patterson, 1921). This scale consisted of 10 statements on which participants had to slide an indicator from left to right to indicated which item corresponded to their physical sickness symptoms. Both variables were considered state measures. The pro-inflammatory cytokines were recorded at the start of the experiment (V1T0), as well as throughout the duration of the visit at 2 hours and 6 hours after LPS administration (V1T0, V1T2, V1T6). These measurement timepoints are identical for the Visual Analogue Scale (VAS; Hayes & Patterson, 1921) (found in Appendix E.).

One indicator of physical sickness response to LPS was measured as the difference between the composite score of the pro-inflammatory cytokines (TNF-α, IL-6 and IL-8)

2 hours after LPS administration (V1T2) versus the composite score of the pro-inflammatory cytokines at baseline (V1T0).

The other indicator of physical sickness response to LPS was measured as the difference between the sum score of the Visual Analogue Scale (VAS; Hayes & Patterson, 1921) 2 hours after LPS administration (V1T2) and the sum score of VAS scores (Hayes & Patterson, 1921) at baseline (V1T0).

Figure 2: *Infographic of study design.*



Note. A Flow chart of the study design produced in Canva (2023). V0 = measurements taken at home; V1 = measurements taken during the hospitalization; T1, T2, T3, T5 and T6 denote the timepoints in hours relative to LPS administration.

Statistical Analysis

The collected raw data was merged using RStudio (RStudio Team, 2020). Cases with missing and incomplete information were excluded. The data was checked for the assumptions of the multiple linear regression analysis. Linearity was visually inspected using normal P-P plots and homoskedacity and independence of errors were visually inspected with scatterplots as well as checked for in residuals statistics as well as in a scatterplot of residuals against predicted values. Normality was visually inspected using histograms and Quantile-Quantile plots and independence of independent variables was checked using the correlations output. The data did not violate any of these assumptions. Data was transformed into z-scores as well as Log10 scores. After careful consideration, the cases with extreme values, defined as values with deviations larger than 3 standard deviations, were kept in the dataset for further analysis.

A power analysis was conducted using G*Power version 3.1.9.7 (Faul et al., 2007) to determine the minimum sample size required to test the study hypothesis.

Repeated measures ANOVAs were done to assess the effect of LPS administration on Positive Affect (Watson, Clark & Tellegen, 1988), scores on the VAS (Hayes & Patterson, 1921) and the concentrations of the composite score of pro-inflammatory cytokines.

To analyze a possible relationship between hedonic capacity and affective as well as physical inflammatory sickness response to LPS, several descriptive statistics were analyzed and visualized. These included the differences in the sum scores on Positive Affect of the PANAS (Watson, Clark & Tellegen, 1988), the VAS (Hayes & Patterson, 1921) and the composite score of the pro-inflammatory cytokines at 2 hours (V1T2) versus baseline (V1T0) post LPS administration as well as the directions of these differences. Analysis between baseline (V1T0) and 2 hours (V1T2) post LPS administration was selected because it aligned with a peak production of the composite scores of the pro-inflammatory cytokines.

Additionally, three multiple linear regression analyses were conducted. Measurement scores of hedonic capacity were put in three multiple linear regression analyses to discover its possible relation to affective and physical sickness response, including gender as covariate. This was done because men and women have shown to respond differently to LPS (Engler et al., 2016). The transformed sum score data gathered with the TEPS (Gard et al., 2006) and a dummy variable of gender were used as independent variables and the difference score of the PANAS (Watson, Clark & Tellegen, 1988) at 2 hours (V1T2) versus baseline (V1T0), the difference score of the composite score of the pro-inflammatory cytokines (TNF-α, IL-6 and IL-8) at 2 hours (V1T2) versus baseline (V1T0) and the difference score of the VAS (Hayes & Patterson, 1921) scores at 2 hours (V1T2) versus baseline (V1T0) were used as dependent variables in these multiple linear regression analyses. Statistical analyses were two-sided, with a degree of significance set at $\alpha < .05$ and performed using IBM SPSS Statistics 27 (IBM Corp., 2020) and a 95% confidence interval.

Results

To test whether hedonic capacity reduced the physical and affective inflammatory-induced sickness behavior in participants, the following steps were undertaken.

Preparing the Data

Before any further computations were conducted, the raw dataset of 110 participants ($n = 110$) were merged using statistical analysis software RStudio (RStudio Team, 2020) and scanned for missing values and outliers. Cases with missing values were excluded. The data of 3 participants was excluded due to wrong LPS dose administration. During this process, a total number of 18 participants (16.36%) were excluded from the dataset. After careful consideration, outliers defined as cases that contained data with standard deviations larger

than 3, were kept in the analysis. Post-hoc exclusion of this extreme data did not change the main results. The data of a sample of 92 participants (n = 92) was used for further analysis.

The power analysis that was performed indicated that the required sample size to achieve 80% power for detecting a medium effect at a significance criterion of $\alpha = .05$ was n = 89 for a multiple regression analysis. Thus, the sample size of n = 92 used in further analysis was adequate to test the study hypothesis.

The repeated measures ANOVAs conducted to assess the effect of the LPS manipulation indicated the following: The means of the composite score of pro-inflammatory cytokine concentrates were found to be statistically significant ($F (2, 1.011) = 194.417$, $p = < 0.01$) computed using $\alpha = .05$. The means of the sum scores of the VAS (Hayes & Patterson, 1921) were found to be statistically significant ($F (2, 1.908) = 15.320$, $p = < 0.01$) computed using $\alpha = .05$. The means of the sum scores of Positive Affect measured with the PANAS (Watson, Clark & Tellegen, 1988) were found to be statistically significant ($F (2, 1.849) = 26.511$, $p = < 0.01$) computed using $\alpha = .05$.

Descriptive Analyses

Data from 92 participants were analyzed. Gender was equally distributed in the sample (n = 41 for men; n = 41 for women). This is visualized in Figure 3. Ages ranged from 18 up to 33 years old (M = 23.11; SD = 2.64). Length ranged from 1.60 m to 1.97 m (M = 1.76; SD = .09). Body weight among the participants ranged from 47.0 kg to 11.2 kg (M = 74.63; SD = 12.37) with a BMI ranging from 12.72 to 31.90 kg/m^2 (M = 23.92; SD = 3.09). A summary of the demographic characteristics is displayed in Table 1. An over of the distribution of gender and age across the sample are visualized in Figure 3.

The overall score on the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) was on average 83.60 (M = 83.60; SD = 9.72). An overview of the distribution of the

sum scores on the TEPS (Gard et al., 2006) across the sample are visualized in Figure 4. A boxplot visualization of the scores on Temporal Experience of Pleasure Scale (Gard et al., 2006) across the sample is illustrated in Figure 5.

The scores on the Positive Affect dimension of the PANAS (Watson, Clark & Tellegen, 1988) decreased from a mean score of 18 at baseline (V1T0) to a mean score of 13 at 2 hours (V1T0), indicating a decrease of 27.78%. The scores at baseline (V1T0), 2 hours (V1T2) and 6 hours (V1T6) post LPS administration are illustrated in Figure 6.

The sum scores of the Visual Analogue Scale (VAS; Hayes & Patterson, 1921) decreased from a mean sum score of 10 at baseline (V1T0) to a mean sum score of 8 at 2 hours (V1T0), indicating a decrease of 20%. The scores at baseline (V1T0), 2 hours (V1T2) and 6 hours (V1T6) post LPS administration are illustrated in Figure 7.

The composite scores of the pro-inflammatory cytokines TNF-α, IL-6 and IL-8 increased from a mean sum score of 35.28 pg/mL at baseline (V1T0) to a mean sum score of 611.08 pg/mL at 2 hours (V1T2), indicating an increase of 1631.12%. The scores at baseline (V1T0), 2 hours (V1T2) and 6 hours (V1T6) post LPS administration are illustrated in Figure 8 and 9.

Table 1

Demographic and clinical descriptive statistics.

Variables	Mean n = 92	Variance	SD	Minimum	Maximum
Gender					
Men	41				
Women	41				
Age (years)	23.11	6.96	2.64	18	33
Length (m)	1.76	.01	.09	1.60	1.97

Weight (kg)	74.63	152.91	12.37	47.0	111.2
BMI (kg/m^2)	23.92	9.52	3.09	17.72	31.90
TEPS	83.60	84.09	9.17	57	101

Note. Age is indicated in years. Length is indicated in meters; Weight is indicated in kilograms; Body Mass Index (BMI) is indicated as a person's weight in kilograms divided by the square of height in meters (Kg/m^2)). TEPS denotes the sum scores obtained on the Temporal Experience of Pleasure scale Gard et al., 2006).

Figure 3

Demographic Characteristics of Participants.

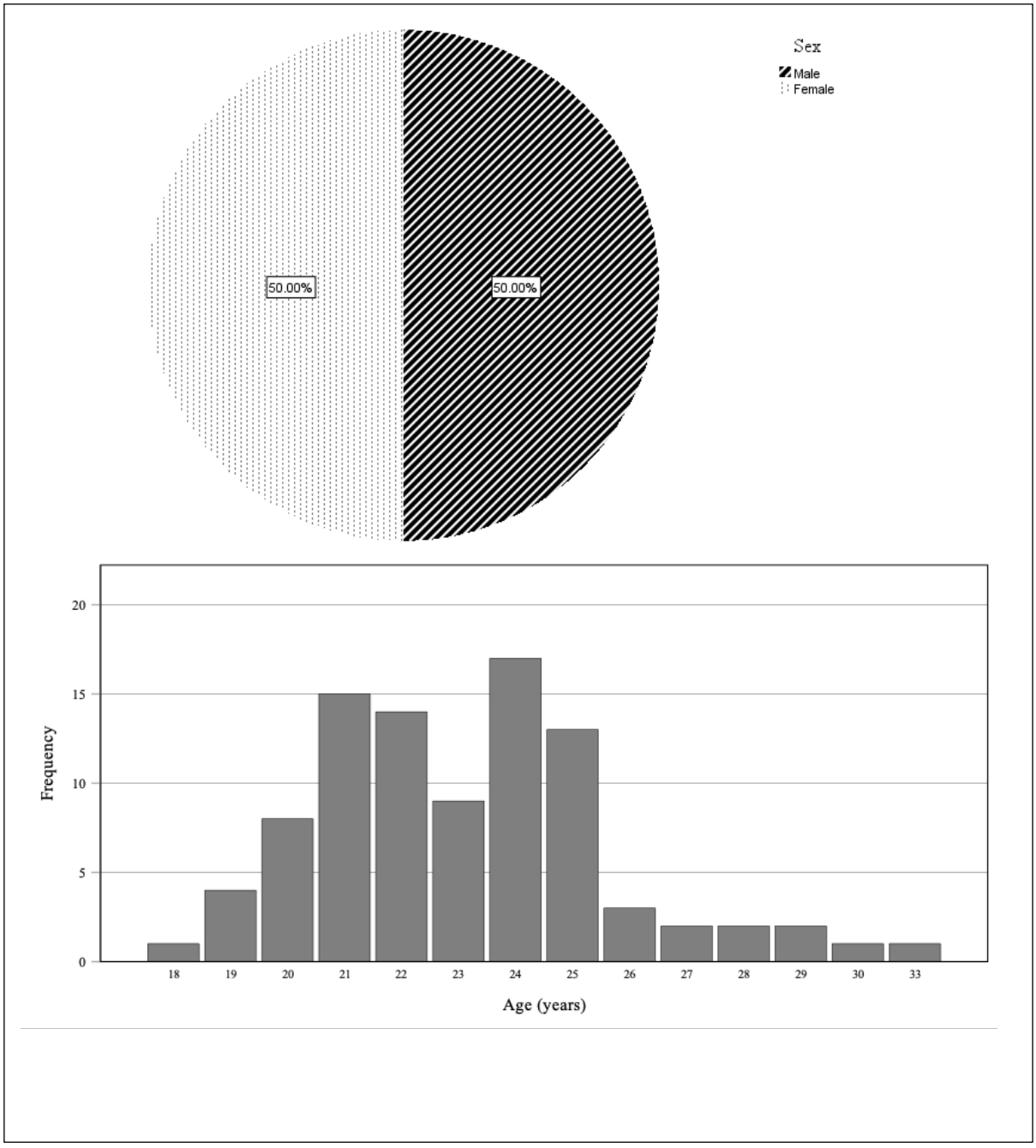


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Figure 4

Frequencies of the sum score on the Temporal Experience of Pleasure Scale (Gard et al., 2006).

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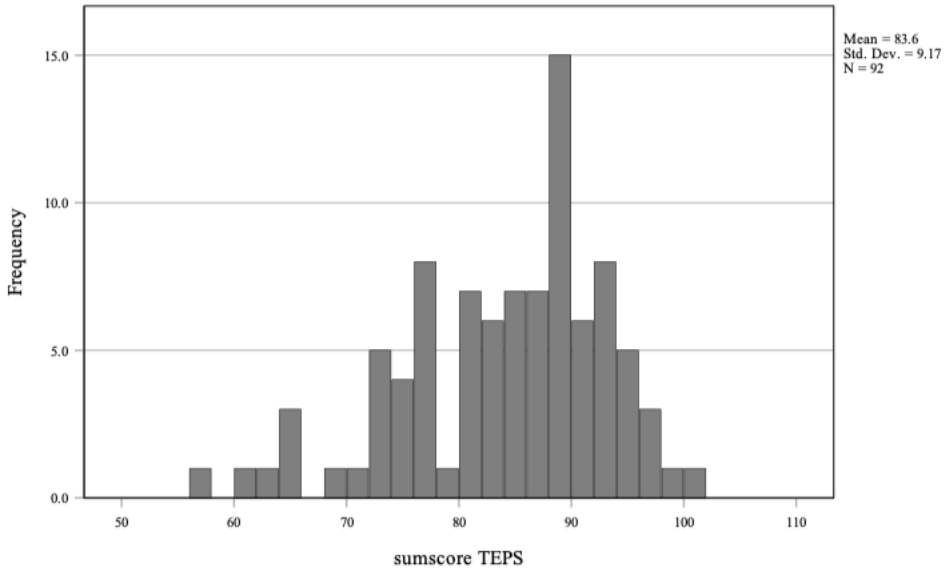


Note. Sumscore TEPS is visualized as the sum scores on the Temporal Experience of Pleasure Scale (Gard et al., 2006). Frequencies denotes the number of participants that scored on the TEPS (Gard et al., 2006).

Figure 5

A Boxplot Visualization of Participants' Total Scoring on the Temporal Experience of Pleasure Scale (TEPS; Gard et al., 2006) divided by Gender.

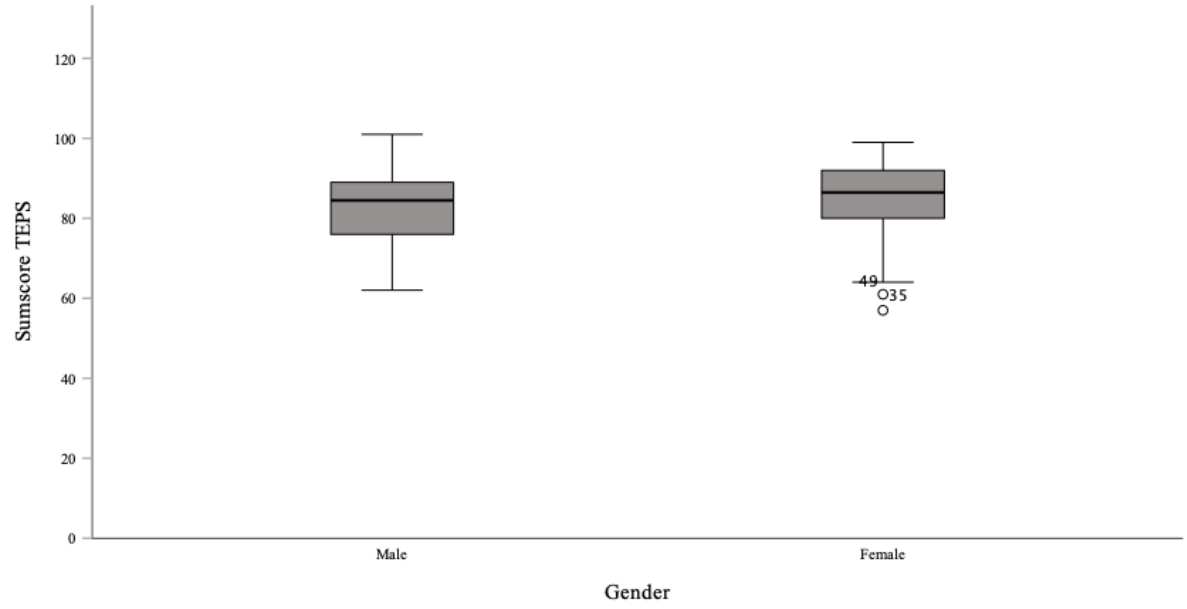
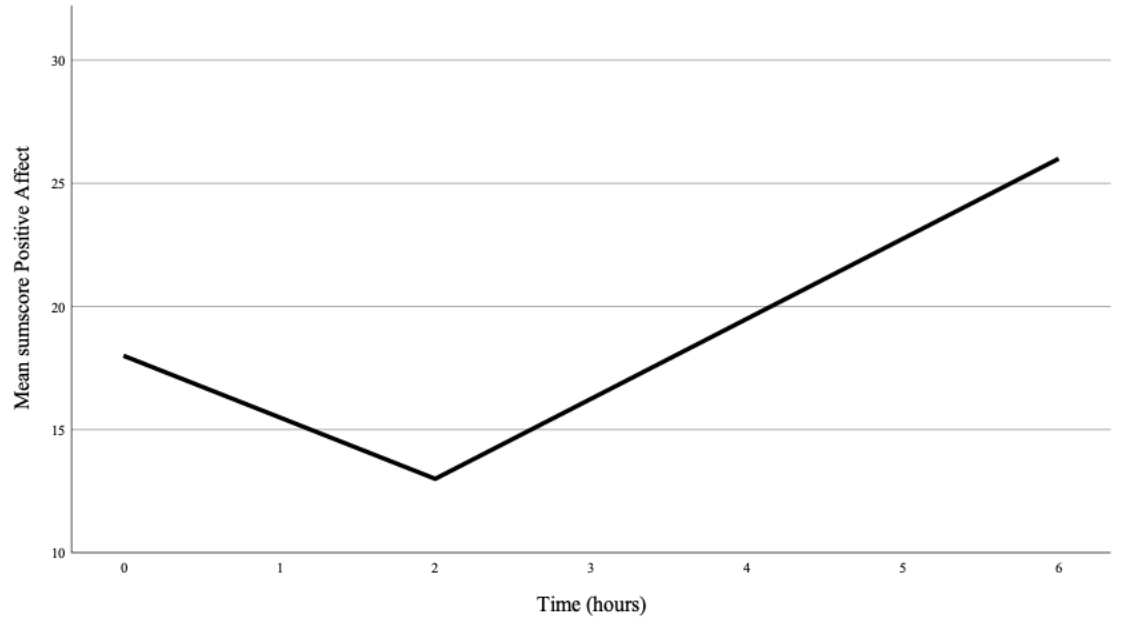


Figure 6

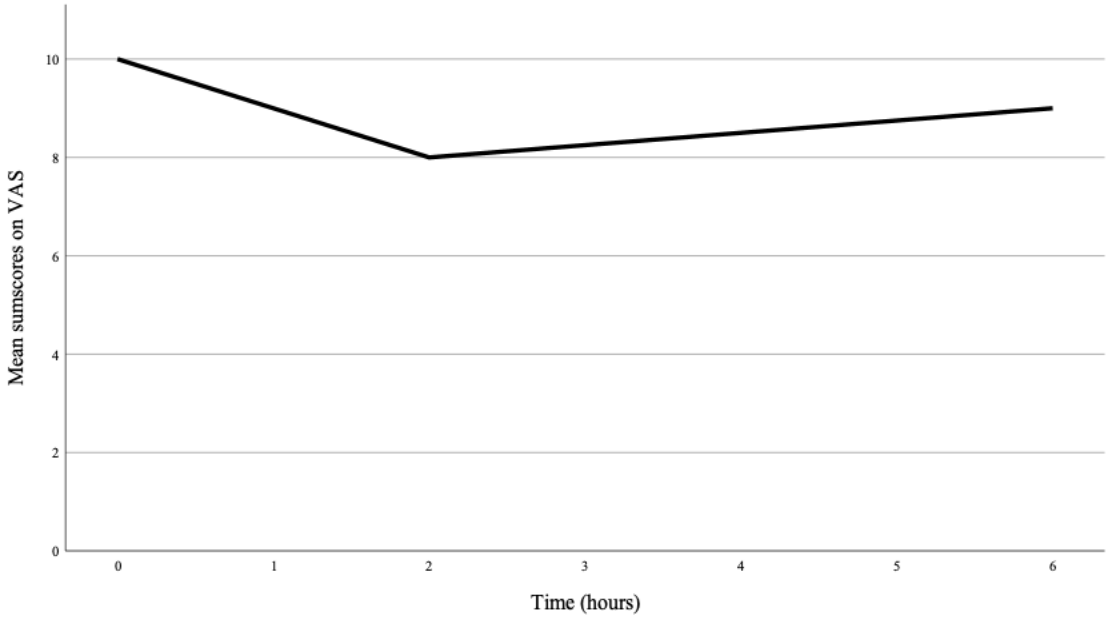
Mean sum scores on the Positive Affect dimension of the Positive Affect Negative Affect Scale (PANAS; Watson, Clark & Tellegen, 1988) across time.



Note. Mean sum scores on the Positive Affect denotes the mean sum scores on the Positive Affect dimension of the PANAS (Watson, Clark & Tellegen, 1988 measured at baseline (V1T0), 2 hours (V1T2) and 6 hours (V1T6) relative to LPS administration.

Figure 7

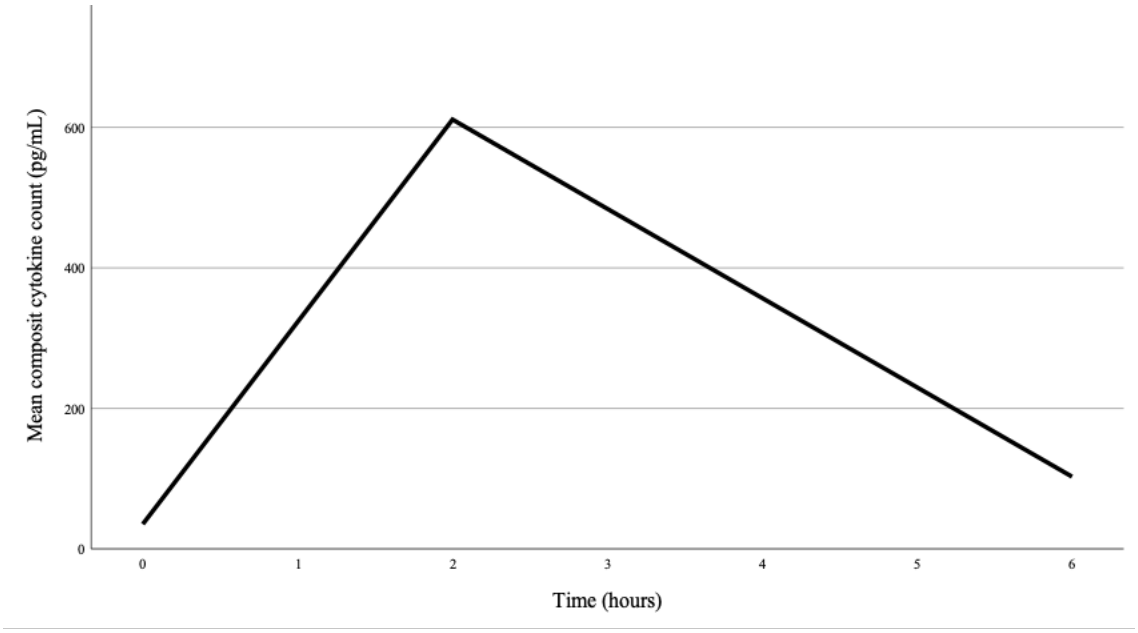
Mean sum scores on the Visual Analogue Scale (Hayes & Patterson, 1921) across time.



Note. Mean sum scores on VAS denotes the mean sum scores on the VAS measured at baseline (V1T0), 2 hours (V1T2) and 6 hours (V1T6) relative to LPS administration.

Figure 8

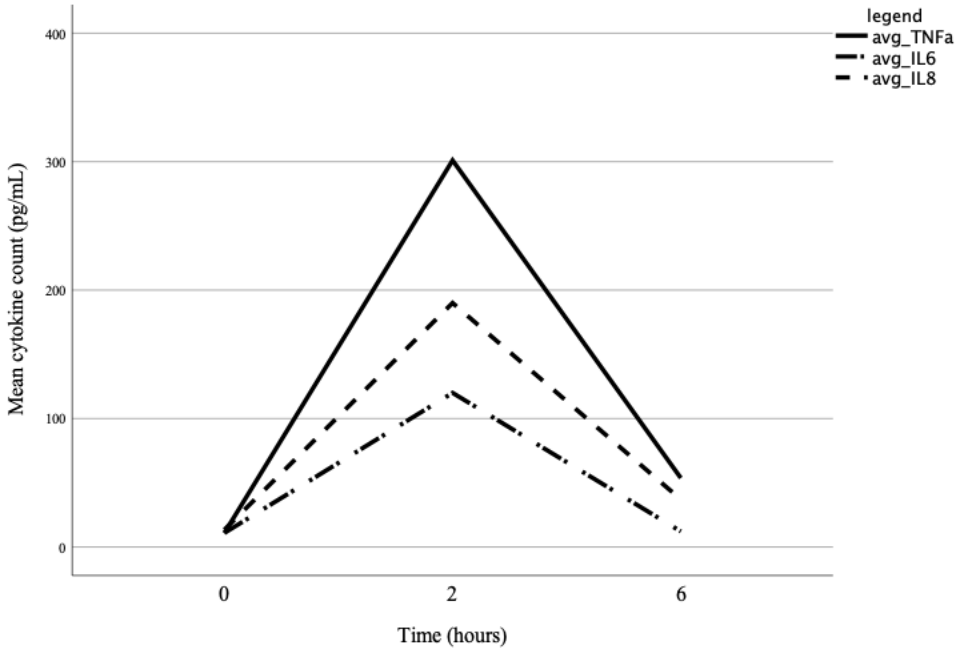
Mean composite scores of the pro-inflammatory cytokines across time.



Note. Mean cytokine count in picograms per milliliter (pg/mL) denotes the mean composite scores of the pro-inflammatory cytokines TNF-α, IL-6 and IL-8 measured at baseline (V1T0), 2 hours (V1T2) and 6 hours (V1T6) relative to LPS administration.

Figure 9

Mean cytokine count of the pro-inflammatory cytokines TNF-α, IL-6 and IL-8 across time.



Note. Mean cytokine count in picograms per milliliter (pg/mL) denotes the mean concentrate of each pro-inflammatory cytokine (TNF-α, IL-6 and IL-8) measured at baseline (V1T0), 2 hours (V1T2) and 6 hours (V1T6) relative to LPS administration.

Statistical analysis

To understand whether hedonic capacity had an effect on the affective and physical sickness response, simple and multiple linear regression analyses were conducted.

A linear regression analysis showed that sum scores on the TEPS (Gard et al., 2006) tended to predict less reduction of the difference scores on the Positive Affect dimension of the PANAS (Watson, Clark & Tellegen, 1988) between baseline (V1T0) and two hours (V1T2) post LPS administration (β = -.205, SE = .103, t = -1.98, p = .051). Sum scores on the TEPS (Gard et al., 2006) accounted for 4.2% of variance in Positive Affect scores (R^2 = .042, F (1,90) = 3.928. p = .051, 95% CI [-0.409,0.000]) Individuals with higher sum scores on TEPS tended to show non-significant smaller decreases in Positive Affect after LPS administration.

Another linear regression analysis showed that sum scores on the TEPS (Gard et al., 2006) did not significantly predict less reduction of the difference scores on the VAS (Hayes & Patterson, 1921) between baseline (V1T0) and two hours (V1T0) post LPS administration ($\beta = .089$, SE = .105, t = .847, $p = .399$). Sum scores on the TEPS (Gard et al., 2006) accounted for <1% of variance in VAS scores ($R^2 = .008$, F (1, 90) = .718, $p = .399$, 95% CI [-0.120,0.298]). Individuals with higher sum scores on the TEPS showed insignificant, larger increases in physical sickness response measured by the VAS (Hayes & Patterson, 1921) after LPS administration.

A third linear regression analysis showed that sum scores on the TEPS (Gard et al., 2006) did not significantly predict less reduction of the difference scores in pro-inflammatory cytokine concentrates between baseline (V1T0) and two hours (V1T0) post LPS administration ($\beta = .138$, SE = .104, t = 1.326, $p = .188$). Sum scores on the TEPS (Gard et al., 2006) accounted for 1.9% of variance in pro-inflammatory cytokine concentrates ($R^2 = .019$, F (1, 90) = 1.757, $p = .188$, 95% CI [-0.069,0.346]). Individuals with higher sum scores on the TEPS showed insignificant, larger increases in physical sickness response as measured by the composite scores of pro-inflammatory cytokine concentrates after LPS administration.

A summary of the linear regression analyses conducted can be found in table 2.

Table 2

A linear regression analyses summary for sum sores on the TEPS on the difference in the scores on the Positive Affect dimension of the PANAS, the difference in VAS scores and the difference in the composite scores of pro-inflammatory cytokines at 2 hours (V1T2) versus baseline (V1T0).

TEPS	*SE*	95% CI		β	t	*p*
		LL	*UL*			
PANAS dV1T2-V1T0	.103	-.409	.000	-.205	-1.982	.051
VAS dV1T2-V1T0	.105	-.120	.298	.089	.847	.399
Comp. cytokinecon. dTV12-V1T0	.104	-.069	.346	.138	1.326	.188

Note. PANAS dV1T2-V1T0 denotes difference score on Positive Affect; VAS dV1T2-V1T0 denotes difference score on the VAS; Comp. cytokinecon. dTV12-V1T0 denotes the difference in composite scores of pro-inflammatory cytokine concentrates All variable differences are defined as 2 hours (V1T2) versus baseline (V1T0). CI = Confidence Interval for β;

When controlled for gender, a multiple linear regression analysis showed that sum scores on the TEPS (Gard et al., 2006) tended to predict less reduction of the difference scores on the Positive Affect dimension of the PANAS (Watson, Clark & Tellegen, 1988) between baseline (V1T0) and two hours (V1T2) post LPS administration (β = -.192, SE = .104, t = 1.855, p = .067). Sum scores on the TEPS (Gard et al., 2006) accounted for 5.4% of variance in Positive Affect scores (R^2 = .054, F (2,89) = 2.547. p = .084, 95% CI [-0.398,0.014]) Individuals with higher sum scores on TEPS tended to show non-significant smaller decreases in Positive Affect after LPS administration when controlled for gender.

When controlled for gender, a second multiple linear regression analysis showed that sum scores on the TEPS (Gard et al., 2006) did not significantly predict less reduction of the difference scores on the VAS (Hayes & Patterson, 1921) between baseline (V1T0) and two hours (V1T0) post LPS administration (β = .080, SE = .106, t = .753, p = .454). Sum scores on the TEPS (Gard et al., 2006) accounted for 1.5% of variance in VAS scores R^2 = .015, F (2, 89) = .685, p = .507, 95% CI [-0.131,0.290]) Individuals with higher sum scores on the

TEPS showed insignificant, larger increases in physical sickness response measured by the VAS (Hayes & Patterson, 1921) after LPS administration when controlled for gender.

When controlled for gender, a third multiple linear regression analysis showed that sum scores on the TEPS (Gard et al., 2006) did not significantly predict less reduction of the difference scores in pro-inflammatory cytokine concentrates between baseline (V1T0) and two hours (V1T0) post LPS administration (β = .111, SE = .102, t = 1.089, p = .279). Sum scores on the TEPS (Gard et al., 2006) accounted for 8% of variance in pro-inflammatory cytokine concentrates (R^2 = .081, F (2, 89) = 3.898, p = .024, 95% CI [-0.092,0.315]). Individuals with higher sum scores on the TEPS showed insignificant, larger increases in physical sickness response as measured by the composite scores of pro-inflammatory cytokine concentrates after LPS administration when controlled for gender.

A summary of the multiple linear regression analyses conducted can be found in table 3.

Table 3

A multiple linear regression analyses summary for sum sores on the TEPS on the difference in the scores on the Positive Affect dimension of the PANAS, the difference in VAS scores and the difference in the composite scores of pro-inflammatory cytokines at 2 hours (V1T2) versus baseline (V1T0) when controlled for gender.

TEPS	*SE*	95% CI		β	t	*p*
		LL	*UL*			
PANAS dV1T2-V1T0	-.104	-.398,	.014	-.192	1.855	.067
VAS dV1T2-V1T0	.106	-.131	.290	.080	.753	.454
Comp. cytokinecon. dTV12-V1T0	.102	-.092	.315	.111	1.089	.279

Note. PANAS dV1T2-V1T0 denotes difference score on Positive Affect; VAS dV1T2-V1T0 denotes difference score on the VAS; Comp. cytokinecon. dTV12-V1T0 denotes the

difference in composite scores of pro-inflammatory cytokine concentrates All variable differences are defined as 2 hours (V1T2) versus baseline (V1T0).

CI = Confidence Interval for β;

Discussion

This study is one of the first ones to investigate the relationship between hedonic capacity and affective and physical sickness response to LPS. A borderline negative, non-significant relationship between hedonic capacity and Positive Affect indicates that individuals with higher scores on the TEPS (Guard et al., 2006) tended to show less reduction in Positive Affect during the response to LPS. Controlling for gender did not give any substantial differences in results. These findings, although non-significant, tend to be in line with the first hypothesis. The insignificant, positive relationship found between hedonic capacity and physical sickness response measured by the VAS (Hayes & Patterson, 1921) and the composite score concentrates of TNF-α, IL-6 and IL-8 indicated higher scores on hedonic capacity were related with larger increases in physical sickness response. The hypothesis that higher hedonic capacity is related to less reduction of Positive Affect in response to LPS can be rejected. The hypothesis that higher hedonic capacity is related to less reduction of the physical sickness response to LPS can be rejected as well.

These results are not completely unexpected. The negative relation between LPS and the physical sickness response to LPS was aleady established by Dantzer & Kelly, 2007

The however insignificant, negative relationship found between hedonic capacity and Positive Affect during an inflammatory-induced sickness response

is closer in line with previous literature of inflammation-induced sickness behavior in relation to major depressive disorder (Lasselin, 2021) and could support future research on this.

An explanation for insignificance between the relationship of hedonic capacity on physical sickness response could indicate a lack of true effect. It is possible that the relationship investigated in this study simply does not exist. The absence of a significant effect suggest that the predictor variable examined may not have had a substantial impact on the affective and physical sickness response. Another explanation for the insignificance found in this study might be that the timing of the sickness response as measured 2 hours after LPS administration is not the correct timepoint to measure difference of affective and physical sickness response. The lack of difference in outcomes when including gender as a covariate is in contrast with what Engler et. Al (2016) found, as well as in contrast with what Weinryb et al. (2003) found, that hedonic capacity might explain differences among individuals' patters of reactions and adaptations in the face of sickness.

Future research could implement, in addition to applying a holm-Bonferroni correction, analyze data obtained at other timepoints, such as the oral responses given every 30 minutes in the larger study done by Jansen et al. (2022). Another way to account for different timepoint measures might be to apply a multilevel regression model. This way within subject correlations could be taken into consideration. Additionally, unequal time intervals could be managed and incorporated within the analysis (e.g., the oral questionnaire on physical sickness symptoms administered every 30 minutes. Additionally, an LPS study might lack ecological validity. This could have implications for generalization of the results to everyday life.

Avenues for future research include further building on the investigation of the relationship between hedonic capacity and major depressive disorder. Another addition would be measuring positive mindset in relation to physical health and affective health to further build upon the research done by Rasmussen et al. (2009). For example, instead of testing if hedonic capacity might moderate the reduction in positive Affect during

inflammation, the life satisfaction Scale could be used. This study contributed to the understanding of sickness behavior, and therefore could give guidance in navigating public policy and other several different facets of society.

In sum, the current study investigated the effect of hedonic capacity on affective and physical sickness response induced by LPS and found that there was a negative trend, but insignificant relationship between hedonic capacity and Positive Affect during inflammatory induced sickness response to LPS. No significant relationships were found between hedonic capacity and the physical sickness response to LPS. Results of the current study contribute to the existing literature by expanding the understanding of the complex relationship between hedonic capacity and the affective and physical sickness response induced by LPS. More research is needed to investigate possible missed relations in different timepoints as well as more clarity on whether the exists.

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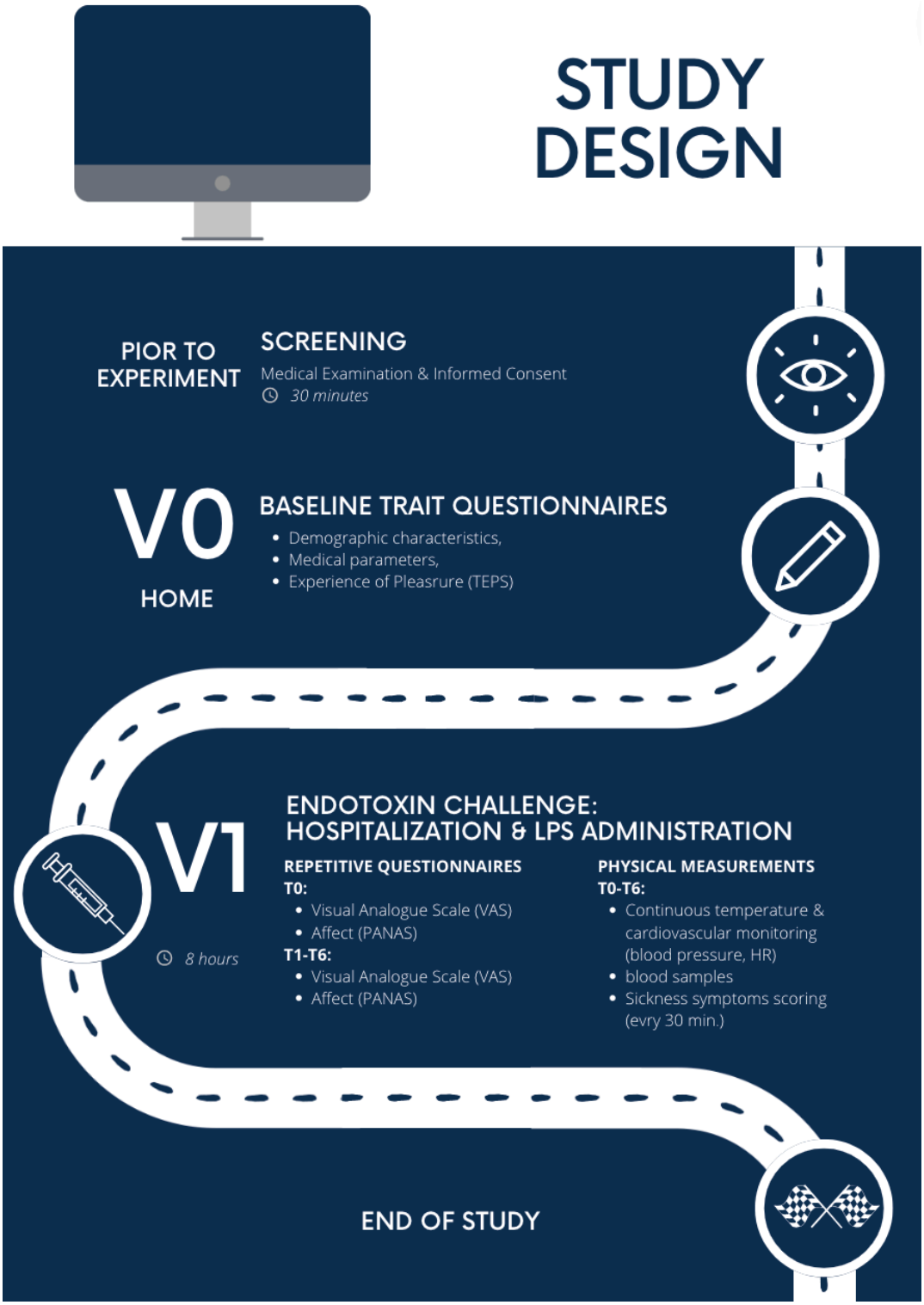
Appendix A.

Study design infographic



Appendix B.

Demographic characteristics and medical parameters

Are you interested in learning new things?

What is your gender?

What is the level of your English?

What is your current marital status? (Please choose the option that best describes your current situation)

What is the highest diploma that you have obtained so far?

What kind of work/study are you currently doing?

What is your ethnic background?

Were you born in the Netherlands?

In which country were you born?

Have you always lived in the Netherlands to date?

In which countries have you lived and when was this?

How would you describe the area where you currently live?

How would you describe the area where you lived in your youth?

During your childhood, how often did you come into contact with farm animals (pigs, cows, sheep, goats, horses, chickens, etc.)?

Do you currently have pets living with you in your home (cats, dogs, hamsters, guinea pigs, etc.)?

Have you been outside of Europe in the last 10 years?

Which continents outside of Europe have you been to?

Are you left or right handed?

Do you have any children?

How many children do you have and how old are they?

What do you think about your health in general?

How often have you used drugs or narcotics in the past year (on average)?

Which drugs do you use or have you used in the last 3 months?

Which contraceptive method do you use?

Do you have a regular menstrual cycle?

What was the first day of your last menstruation?

In the past 3 months, how often have you had abdominal pain?

Did you suffer from abdominal pain only during menstruation?

In the past 3 months, how often have you experienced nausea ?

In the past 3 months, how often have you suffered from very thin or watery stools?

Are there any close relatives (1st degree: father, mother, brothers and sisters; 2nd degree: grandparents; 3rd degree: uncles, aunts, cousins) of you that suffer from an inflammatory bowel disease (Crohn's disease, Ulcerative colitis, appendicitis)?

Have you used antibiotics in the past 10 years?

Have you used antibiotics in the last 6 months?

Do you often use probiotics (activia, yakult, active bifidus, etc.)

Do you have allergies?

What are you allergic to (multiple options possible)?

You have one or multiple other allergies, namely to

Have you ever had a tick bite?

Have you had a circle on your skin (erythema migrans)?

Have you ever been treated with antibiotics for Lyme disease?

In what year?

Do you often have a headache?

Do you often have muscle pain?

Do you often have concentration problems?

Have you ever had fungal infections in the past?

What kind of fungal infections did you suffer from?

Have you had an episode with cold symptoms in the last 6 months?

How many days did you have a cold in the last 6 months?

Have you ever had malaria?

Have you ever participated in a malaria study?

How would you classify your dietary pattern (more options possible)?

How often do you eat meat? This can be any type of meat.

What kind of meat do you eat (more than one option possible)?

How often do you eat fish? This can be any type of fish.

What kind of fish do you mainly eat (more than one option possible)?

How often do you eat the recommended daily consumption of 2 (or more) pieces of fruit?

This may be either fresh fruit, frozen or canned.

How often do you eat vegetables?

How often do you eat beans, peas, cabbages (cauliflower, savoy cabbage, white cabbage,

etc.) broccoli and other fiber-containing vegetables?

How often do you drink sugar-containing drinks? (cold: Coca Cola, Sprite, Fanta, Ice-tea,

Nestea, energy drinks such as Red Bull, etc.) (hot: cappuccino, coffee with sugar, lattes, ...)

How many sugar-containing drinks do you drink on average:

How many units of alcohol do you drink on average per week?

How much chocolate do you eat per month?

What kind of chocolate do you mainly eat?

How much milk do you drink per week?

Do you consume light drinks (containing aspartame)?

How many light drinks do you consume per week?

Is your diet gluten free?

Do you drink caffeine-containing drinks (eg coffee, cola, energy drinks)?

How many caffeine-containing drinks do you drink on average per week?

How often do you practice sports?

Do you have a lot of exercise during the day?

What is your favorite color?

What is your favorite style of music?

What is your political preference?

What is your favorite football club?

What is your (original) hair color?

What is the color of your eyes (choose the most dominant)?

What was the average grade with which you completed your secondary school (average of all subjects on a scale of 0-10, 6 is the minimum to get a degree)?

Do you prefer coffee or tea?

Do you prefer sweet or savory food?

Please read each statement carefully. Select the appropriate option that best fits your feeling or behavior in general.

Does anything interest you?

Are you concerned about your health?

Do you put much effort into things?

Are you always looking for something to do?

Do you have plans and goals for the future?

Do you have motivation?

Do you have the energy for daily activities?

Does someone have to tell you what to do each day?

Are you indifferent to things?

Are you unconcerned with many things?

Do you need a push to get started on things?

Are you neither happy nor sad, just in between?

Would you consider yourself apathetic?

Appendix C.

Temporal Experience of Pleasure Scale Gard et al., 2006)

TEPS

AANWIJZINGEN: Lees a.u.b. elke bewering zorgvuldig en geef aan hoe juist de bewering voor u, in het algemeen gezien, is. Geef a.u.b. op alle items een antwoord. Mocht het zo zijn dat u nog nooit zo een ervaring beleefd hebt, denk dan aan uw meest vergelijkbare ervaring. Laat geen bewering blanco. Kies slechts één antwoord voor elke bewering. Maakt u zich geen zorgen over het wel of niet consistent zijn in u antwoorden. Kies altijd een van de volgende 6 antwoordopties en OMCIRKEL uw antwoord aan de rechter kant van de bewering.

1 Helemaal onjuist voor mij	2 Gemiddeld onjuist voor mij	3 Een beetje onjuist voor mij	4 Een beetje juist voor mij	5 Gemiddeld juist voor mij	6 Helemaal juist voor mij

1. Als ik hoor dat er een nieuwe film uitkomt waar mijn favoriete acteur in speelt, dan moet ik er meteen naar toe.	1	2	3	4	5	6	10. De avond voor vertrek op vakantie kan ik nauwelijks slapen.	1	2	3	4	5	6
2. Ik vind het heerlijk om frisse lucht op te snuiven als ik buiten loop.	1	2	3	4	5	6	11. Als ik onderweg ben naar een pretpark, kan ik niet wachten tot ik in de achtbaan zit.	1	2	3	4	5	6
3. Ik ben dol op de geur van pas gemaaid gras.	1	2	3	4	5	6	12. Ik vind het heerlijk om eens uitgebreid te gapen.	1	2	3	4	5	6
4. Er zijn heel veel dingen in mijn leven waar ik naar uitkijk.	1	2	3	4	5	6	13. Ik kijk niet erg uit naar dingen als uit eten gaan.	1	2	3	4	5	6
5. Ik vind het heerlijk als mensen met mijn haar spelen.	1	2	3	4	5	6	14. Ik ben dol op het geluid van de regen op het raam als ik lekker warm in bed lig.	1	2	3	4	5	6
6. Uitkijken naar een aangename gebeurtenis is al aangenaam op zich.	1	2	3	4	5	6	15. Als ik denk aan mijn lievelingseten, kan ik het bijna proeven.	1	2	3	4	5	6
7. Een kop warme koffie of thee op een koude ochtend vind ik een echte traktatie.	1	2	3	4	5	6	16. Als ik iets bestel in een restaurant, dan stel ik me voor hoe lekker het zal zijn.	1	2	3	4	5	6
8. Als ik aan iets lekkers denk, zoals een chocolate chip cookie, dan móet ik er gewoon een eten.	1	2	3	4	5	6	17. Het geluid van een knapperend haardvuur vind ik heel ontspannend.	1	2	3	4	5	6
9. Ik kan echt genieten van de schoonheid van een vers pak sneeuw.	1	2	3	4	5	6	18. Als er iets spannends staat te gebeuren in mijn leven, dan kijk ik daar erg naar uit.	1	2	3	4	5	6

Temporal Experience of Pleasure Scale (TEPS) – Item key and other information
David E. Gard, Marja Germans Gard, Ann M. Kring, & Oliver P. John (2006). Anticipatory and consummatory components of the experience of pleasure: A scale development study. *Journal of Research in Personality, 40*, 1086-1102.

Dutch Version by Nicole Geschwind, Marieke Wichers, Jim van Os, and Frenk Peeters (2007).

The TEPS was translated into Dutch and backtranslated to English by an official translation agency using the mother tongue principle. We ensured that the Dutch items conveyed the anticipatory or consummatory component of reward in an appropriate way and requested changes from the translation agency where necessary. The final version's backtranslation was approved by David E Gard.

1 Helemaal onjuist voor mij	2 Gemiddeld onjuist voor mij	3 Een beetje onjuist voor mij	4 Een beetje juist voor mij	5 Gemiddeld juist voor mij	6 Helemaal juist voor mij

1. Als ik hoor dat er een nieuwe film uitkomt waar mijn favoriete acteur in speelt, dan moet ik er meteen naar toe. **(Anticipatory)**	1	2	3	4	5	6	10. De avond voor vertrek op vakantie kan ik nauwelijks slapen. **(Anticipatory)**	1	2	3	4	5	6
2. Ik vind het heerlijk om frisse lucht op te snuiven als ik buiten loop. **(Consummatory)**	1	2	3	4	5	6	11. Als ik onderweg ben naar een pretpark, kan ik niet wachten tot ik in de achtbaan zit. **(Anticipatory)**	1	2	3	4	5	6
3. Ik ben dol op de geur van pas gemaaid gras. **(Consummatory)**	1	2	3	4	5	6	12. Ik vind het heerlijk om eens uitgebreid te gapen. **(Consummatory)**	1	2	3	4	5	6
4. Er zijn heel veel dingen in mijn leven waar ik naar uitkijk. **(Anticipatory)**	1	2	3	4	5	6	13. Ik kijk niet erg uit naar dingen als uit eten gaan. **(Anticipatory, reverse coded)**	1	2	3	4	5	6
5. Ik vind het heerlijk als mensen met mijn haar spelen. **(Consummatory)**	1	2	3	4	5	6	14. Ik ben dol op het geluid van de regen op het raam als ik lekker warm in bed lig. **(Consummatory)**	1	2	3	4	5	6
6. Uitkijken naar een aangename gebeurtenis is al aangenaam op zich. **(Anticipatory)**	1	2	3	4	5	6	15. Als ik denk aan mijn lievelingseten, kan ik het bijna proeven. **(Anticipatory)**	1	2	3	4	5	6
7. Een kop warme koffie of thee op een koude ochtend vind ik een echte traktatie. **(Consummatory)**	1	2	3	4	5	6	16. Als ik iets bestel in een restaurant, dan stel ik me voor hoe lekker het zal zijn. **(Anticipatory)**	1	2	3	4	5	6
8. Als ik aan iets lekkers denk, zoals een chocolate chip cookie, dan móet ik er gewoon een eten. **(Anticipatory)**	1	2	3	4	5	6	17. Het geluid van een knapperend haardvuur vind ik heel ontspannend. **(Consummatory)**	1	2	3	4	5	6
9. Ik kan echt genieten van de schoonheid van een vers pak sneeuw. **(Consummatory)**	1	2	3	4	5	6	18. Als er iets spannends staat te gebeuren in mijn leven, dan kijk ik daar erg naar uit. **(Anticipatory)**	1	2	3	4	5	6

Appendix D.

Positive Affect Negative Affect Scale

THE OHIO STATE UNIVERSITY

Positive and Negative Affect Schedule (PANAS-SF)

Indicate the extent you have felt this way over the past week.		Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
PANAS 1	Interested	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 2	Distressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 3	Excited	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 4	Upset	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 5	Strong	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 6	Guilty	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 7	Scared	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 8	Hostile	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 9	Enthusiastic	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 10	Proud	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 11	Irritable	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 12	Alert	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 13	Ashamed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 14	Inspired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 15	Nervous	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 16	Determined	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 17	Attentive	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 18	Jittery	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 19	Active	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PANAS 20	Afraid	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Scoring:

Positive Affect Score: Add the scores on items 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19. Scores can range from 10 – 50, with higher scores representing higher levels of positive affect.
Mean Scores: 33.3 (SD±7.2)

Negative Affect Score: Add the scores on items 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. Scores can range from 10 – 50, with lower scores representing lower levels of negative affect.
Mean Score: 17.4 (SD ± 6.2)

Your scores on the PANAS: Positive: ____ Negative: ____

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *Journal of personality and social psychology*, *54*(6), 1063.

Appendix E.

Visual Analogue Scale

--- How do you feel RIGHT NOW? ---

1. No headache/Strong headache
2. No muscle ache/Strong muscle ache
3. No dry mouth/ very dry mouth
4. Not dizzy/Very dizzy
5. No stomach ache/ Strong stomach ache
6. No joint aches/ Strong joint aches
7. No sore throat/very sore throat
8. No difficulty breathing/A lot of difficulty breathing
9. No chest pain/Strong chest pain
10. No eye problems/ Lots of eye problems