

Pro-inflammatory cytokine predicts reduced rejection of unfair financial offers

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Submitted: 2012-12-08 Accepted: 2013-01-17 Published online: 2013-02-25

Key words: **pro-inflammatory cytokine; interleukin (IL)-6; decision making; the Ultimatum Game (UG)**

Neuroendocrinol Lett 2013;34(1):47-51 PMID: 23524623 NEL340113A07 ©2013 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVES: This study aimed to examine one of biological correlates, pro-inflammatory cytokine, in rejection of unfair financial offers in the Ultimatum Game (UG), where the division of a sum of money is proposed and the player can accept or reject this offer.

METHODS: Nineteen participants played 20 trials of the UG as responders, and they were proposed unfair offers in a half of the trials. Baseline levels of several pro-inflammatory and anti-inflammatory cytokines, subjective happiness, and depression of them were measured.

RESULTS: Participants with higher levels of the pro-inflammatory cytokine, interleukin (IL)-6 rejected fewer unfair offers. This effect of IL-6 levels on decision-making was independent from other pro-inflammatory cytokines, anti-inflammatory cytokines, subjective happiness, and depression.

CONCLUSIONS: These results suggested that chronic higher levels of IL-6 might affect functions of neural regions related to decision making, and thus can modulate rejection of unfair offers.

INTRODUCTION

One of important topics in behavioral economics is to examine individuals' tendencies of responding to unfair allocation of resource in an economic game which is known as The Ultimatum Game (UG; Güth *et al.* 1982). The UG is a simple negotiation game where two players are given the opportunity to split a sum of money. One player (proposer) makes an offer as to how this money should be split between the two. The other player (responder) can either accept or reject this offer. If

it is accepted, the money is split as proposed, but if it is rejected, neither player receives anything. The standard economic solution to the UG for the responder is to accept any positive offer, even the smallest sum of money, on the reasonable grounds that any monetary amount is preferable to zero. However, in actuality, people normally reject unfair offers that are lower relative to those for their opponents; offers of less than 20–30% of the total have a greater than 50% chance of being rejected (Bolton & Zwick 1995; Güth *et al.* 1982). Behavioral and economic theories have argued

that such a rejection is done due to inequity aversion (Fehr & Gintis 2007) or to an emotional motivation of reputation maintenance (Yamagishi *et al.* 2009). We are specifically interested in biological mechanisms that determine such decision-making in the UG.

A neuroimaging study revealed that the anterior cingulate cortex (ACC) exhibited activation to unfair offers, and activity of the anterior insula positively correlated with rejection rates of the unfair offers (Sanfey *et al.* 2003). These results suggest that processing including conflict monitoring (ACC) and affectively negative responses with representation of physiological states (insula) might influence decision-making in the UG. Interestingly the association between insular activity and rejection was observed for unfair offers delivered by real persons but not for unfair offers done by a computer algorithm. This suggests that rejection of unfair offers is based on inter-personal emotions. Another lesion study indicated that damage of the orbitofrontal cortex (OFC) which is critical for emotion regulation was linked with increased rates of rejection (Koenigs & Tranel 2007), suggesting that rejection might be interpreted as failure of down-regulation of emotional impulsivity to provoking unfairness.

Here, we explored roles of peripherally circulating cytokines as a physiological factor that can potentially affect decision-making in the UG. Peripheral pro-inflammatory cytokines, which are immune signaling molecules that promote systemic inflammation, such as tumor necrosis factor (TNF)- α and interleukin (IL)-6, reach the brain via leaky regions in the blood-brain barrier, active transport molecules, and afferent nerve fibers (Raison *et al.* 2006; Dantzer *et al.* 2008). Brain regions related to the UG as described above, the anterior insula and ACC, are thought to be involved in afferent input of peripheral physiological states including cytokine signals (Craig 2002; Critchley 2005), which may play critical roles in decision-making (Damasio, 1994). Indeed, recent neuroimaging studies directly revealed that peripheral IL-6 increased by vaccination modulated activity of the anterior insula and ACC (Harrison *et al.* 2009). On the basis of those previous findings, we examined whether pro-inflammatory cytokines and anti-inflammatory cytokines that can regulate pro-inflammatory cytokines could affect decision-making in the UG. Additionally, we tested whether effects of cytokines on decision-making are mediated by chronic positive and negative affective states, subjective happiness and depression, which have been previously associated with levels of pro-inflammatory cytokines and inflammation (Steptoe *et al.*, 2008; Dantzer *et al.* 2008).

METHODS

Participants

Nineteen volunteers (right-handed male Japanese university undergraduates; age range, 18–20 years; mean age, 19.16 years, SD = 0.60) participated in the study.

All participants were healthy and were not taking any medications. The participants reported that they had no past history of psychiatric or neurological illness. None of them knew about the UG and other economic game tasks and theories. They gave written informed consent in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Nagoya University.

Affective states

Before the UG task, participants' happiness was measured by a subjective happiness scale (Lyubomirsky & Lepper 1999). This scale contains Likert-type 4 items with 7 points: validity and reliability of a Japanese version of this scale have been verified (Shimai *et al.* 2004). Additionally their levels of depression were measured by a validated Japanese version (Furukawa *et al.* 2008) of a psychological scale called K6 (Kessler *et al.* 2002). The K6 contains Likert-type 6 items with 5 points.

The Ultimatum game (UG)

Participants were required to act as responders to monetary offers for 10 different stake sizes that had been submitted by other male students who had acted as proposers in former sessions, while the proposers and the offers were actually set by the experimenter. They were instructed that if they accepted the offered amount, they would receive it; otherwise they would receive nothing. They were further told that both they and proposers would be paid the total amount of gain according to their decisions in overall sessions.

Participants played 20 games with 20 different proposers. There were 10 fair offers ranging at 40–50% of the stake and 10 unfair offers ranging at 10–27% of the stake. The stake itself ranged from 200 Japanese Yen (JPY; 100 JPY corresponded about to 1.20 USD) to 4000 JPY. Each participant received identical offers but the order of offers was randomized among participants. The offers were displayed on a PC monitor. After a 2-s stake size notification, an offer was presented for 6 s and participants could make their responses (acceptance or rejection) by pressing a button without time restriction. Debriefing after the experimental sessions revealed that none of the participants had doubts about the experimental manipulation and believed that offers had been given by real persons.

Measurement of cytokines

After the experimental sessions of the UG task, participants' blood samples were collected in serum-separator tubes and centrifuged at 4000 g for 20 min; the serum was separated and then stored at -80°C until analysis. Serum levels of pro-inflammatory cytokines such as IL-6, TNF α , and IFN- γ and anti-inflammatory cytokines such as IL-2, IL-4, and IL-10 were determined by a BD™ Cytometric Bead Array (Human Th1/Th2 Cytokine Kit II; BD Biosciences, San Diego, CA) according to the manufacturer's instructions.

Statistical analyses

Influences of concentrations of cytokines, subjective happiness, and depression on decision-making in the UG task were examined in the following three stages of analyses. First, correlations between concentration of each cytokine, scores of happiness and depression, and rejection rates of fair and unfair offers were calculated ($p < 0.05$). Considering influences of possible outliers, both Pearson's coefficient and Spearman's rank correlation coefficient which is more robust for outliers were calculated. Second, regression analyses were separately conducted for rejection rates of fair and unfair offers with concentrations of the cytokines and scores of happiness and depression as independent variables ($p < 0.05$). Third, mediations of happiness and depression in possible correlations between cytokines and decision-making were tested. Specifically, if at least one correlation between a cytokine and an index of decision-making, and also at least one correlation between happiness or depression and the same index of decision-making were significant, a mediation analysis was conducted by using the score of happiness or depression as a mediating variable ($p < 0.05$). If the correlation between the cytokine and decision-making was significantly reduced by adding scores of happiness or depression in the regression model and if the scores of happiness or depression significantly correlated both with the cytokine and with decision-making, happiness or depression was interpreted to mediate the association of the cytokine and decision-making.

RESULTS

Similar to previous studies including ours (Haselhuhn & Mellers 2005; van't Wout *et al.* 2006; Osumi & Ohira 2009), participants rejected 57.89% ($SD = 31.37\%$) of unfair offers on average. Naturally, this was greater than rejection of fair offers (2.11%, $SD = 6.31\%$), $t(18) = 8.41$, $p < 0.001$.

Lower rejection rates of unfair offers significantly correlated with higher concentrations of a pro-inflammatory cytokine: IL-6 both in Pearson's and Spearman's coefficients (Table 1, Figure 1). None of the other cytokines significantly correlated with decision-making. Also, none of anti-inflammatory cytokines significantly correlated with levels of IL-6 ($r(17) = -0.07$ – 0.25 , ns). Subjective happiness but not depression also showed a significant negative correlation with rejection rates of unfair offers. Happiness and depression did not correlate ($r(17) = -0.07$, ns). Not surprisingly, rejections of fair offers were not related to cytokine levels, subjective happiness, and depression because of very small rejection rates. Regression analyses further confirmed these results (Table 1): higher IL-6 levels were significantly related to lower rejection rates of unfair offers (adjusted $R^2 = 68$, $F(8,10) = 5.85$, $p < 0.01$) but not those of fair offers (adjusted $R^2 = 0.20$, $F(8,10) = 0.56$, ns), suggesting that baseline level of IL-6 determined deci-

sion-making for unfair offers independently from other pro-inflammatory and anti-inflammatory cytokines and subjective happiness. The regression analysis also revealed that depression was negatively related to rejection rate of unfair offers but not fair offers (Table 1). Finally, mediation analyses indicated that the associa-

Tab. 1. Relations among rejection rate of fair and unfair offers in Ultimatum Game and cytokines, happiness, and depression.

	Pearson's r		Spearman's ρ	
	Fair	Unfair	Fair	Unfair
IL-6	-0.37	-0.72**	-0.41	-0.68**
TNF- α	-0.28	-0.43	-0.22	-0.43
IFN- γ	0.09	0.13	0.02	0.17
IL-2	-0.21	0.01	-0.13	0.02
IL-4	0.26	0.19	0.28	0.19
IL-10	0.07	-0.23	0.09	-0.15
Happiness	-0.05	-0.52*	0.02	-0.48*
Depression	-0.40	-0.26	-0.36	-0.33

	Regression β	
	Fair	Unfair
IL-6	-0.44	-0.71**
TNF- α	0.01	0.07
IFN- γ	0.07	0.00
IL-2	-0.05	0.26
IL-4	0.49	0.34
IL-10	-0.24	-0.02
Happiness	0.34	-0.27
Depression	-0.43	-0.49*

Pearson's and Spearman's correlation coefficients and beta coefficients in regression analyses are shown. * $p < 0.05$; ** $p < 0.01$

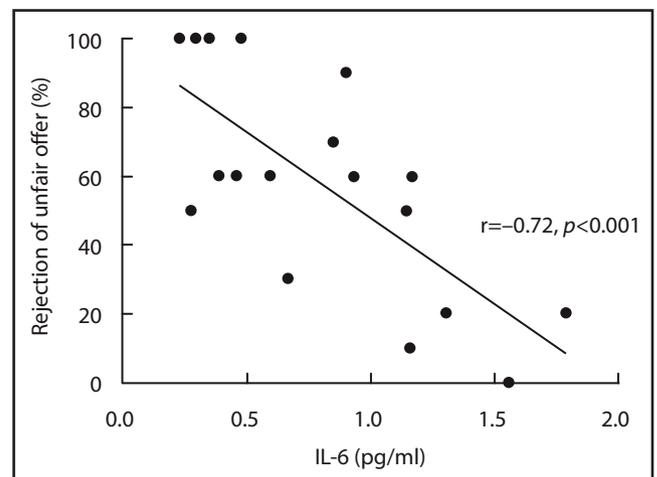


Fig. 1. Relation between concentration of IL-6 and rejection rate of unfair offers.

tion between concentrations of IL-6 and rejection rates was significantly reduced by adding neither scores of happiness nor scores of depression in the regression models, and that correlations between IL-6 and happiness and depression were not significant ($r(17) = 0.36$, ns; $r(17) = 0.00$, ns, respectively). Thus it was suggested that happiness and depression did not mediate the influence of IL-6 on rejection, and IL-6, happiness, and depression independently affected decision-making in the UG.

DISCUSSION

Our findings demonstrated a critical role of inflammation in accounting for individual differences of economic decision-making. Specifically, higher levels of the pro-inflammatory cytokine IL-6 were associated with lower rejection rates of unfair offers in the UG. There are numerous findings that pro-inflammatory cytokines including IL-6 can affect neural plasticity and neurogenesis, and thus can modulate higher-ordered cognitive functions such as learning and memory (for a review, Yirmiya & Goshen 2011). The present study expanded such previous findings to a domain of economic decision-making.

Modulation of decision-making shown in the present study was not considered as acute effects of IL-6 increased by infection or injury but more chronic dispositional effects of baseline levels of IL-6, because even the highest value of IL-6 in our samples was within the normal range and much smaller than values usually observed during infections. Thus, our findings suggest that chronically higher levels of IL-6 probably produce more cytokines such as IL-1 β in the brain, and in turn can affect structural and functional neural mechanisms underlying economic decision-making.

As described above, the degree of activation of the anterior insula correlated with higher rejection rates of the unfair offers (Sanfey *et al.* 2003), and acute increase of pro-inflammatory cytokines by vaccination enhanced activation of the anterior insula (Harrison *et al.* 2009). These findings seem to contradict to the present finding that higher IL-6 levels were linked with lower rejection rates of unfair offers. However, the term of activation in neuroimaging studies means reactivity of neural responses, specifically, a difference between neural activity during a task and that at baseline. Thus one possible interpretation for the ostensibly inconsistent findings might be that chronically higher levels of IL-6 could produce higher baseline activity of the anterior insula and lead to blunted neural reactivity to input of unfairness. Another possibility might be that IL-6 could chronically enhance activity of the OFC which regulates emotions (O'Connor *et al.* 2009) and inhibit emotional rejection of unfair offers. These neural mechanisms of effects of IL-6 on decision-making will be explored in future neuroimaging studies.

Our result that higher subjective happiness was significantly related to lower rejection rates of unfair offers seems inconsistent with a recent finding that individuals with trait positivity showed increased rejection rate of unfair offers (Dunn *et al.* 2010). Although approach emotions with positive affective tones such as pride and activeness have been associated with greater rejections as shown in the study by Dunn *et al.* (2010), positive emotions with less approach tendencies such as happiness might be rather linked with less rejections. This interpretation was in part supported by the linkage between higher depression, which is a negative emotion with less approach tendencies and reduced rejections of unfair offers revealed by the regression analysis in this study. This result is consistent with a previous report (Harlé *et al.* 2010). These findings suggest that non-approach emotions, regardless to their affective valence, might lead to lower levels of rejection of unfair offers in the UG. More importantly, our data indicate that effects of IL-6 on decision-making were not mediated by happiness and depression, suggesting that IL-6 might directly influence brain functions underlying economic decision-making and its effects might be independent from subjective affective states.

Dispositional higher concentration of testosterone (Burnham 2007), administration of testosterone (Zak *et al.* 2009) were previously associated with higher rejection rates of unfair offers. Because testosterone levels are negatively correlated with IL-6 levels (Martos-Moreno *et al.* 2006) and testosterone inhibited expression of IL-6 gene (Bellido *et al.* 1995), it seems reasonable that testosterone and IL-6 show opposite effects on decision-making in the UG. Reduced available cerebral serotonin caused by acute tryptophan depletion was also linked to more rejection of unfair offers (Crockett *et al.* 2008). Relationships between central serotonin and IL-6 are not fully understood, thus whether serotonin and IL-6 can affect decision-making in the UG either independently or in an interactive way should be examined in future. In addition, oxytocin was linked to generosity in proposers in the UG (Zak *et al.* 2007). It is interesting to examine effects of oxytocin on responders' decisions and interplays with pro-inflammatory cytokines because oxytocin has an anti-inflammation role (Gutkowska & Jankowski 2012).

Limitations in the present study should be recognized. First, the sample size was the minimum and thus the observed correlation between IL-6 and rejection of unfair offers might be due to outliers (Figure 1). Though significance of Spearman's rank correlation coefficient which is relatively robust for outliers in part supports validity of the correlation, the present findings must be tested using larger samples. Second, characteristics of the sample were restricted to young male Japanese people. The generalizability of the current findings should be further tested for sexes, different ages, and ethnicity. Third, relationships between IL-6 and other physiological mediators such as testosterone, serotonin,

and oxytocin, and interplays of those mediators to determine decision-making in the UG should be examined. Nonetheless, despite the limitations the present study preliminarily indicates that baseline levels of IL-6 are associated with reduced rejection rates of unfair financial offers.

ACKNOWLEDGEMENT

The present study was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (Research in a Proposed Research Area) 2010 (No. 4102-21119003) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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