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Metabolic state and value based decision-making in acute and recovered female patients with anorexia nervosa

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Methods

Clinical assessment

Exclusion criteria, comorbid psychiatric diagnoses and possible confounding variables were obtained using the expert form of the Structured Interview for Anorexia and Bulimia Nervosa (SIAB-EX; Fichter & Quadflieg 2001), medical records and our own semi-structured research interview. To ensure high diagnostic standards, only staff with a psychological or medical background was allowed to conduct the SIAB-EX assessment, after a diagnostic training had been completed successfully. The training included several steps to learn an adequate usage and evaluation of the interview, and was supervised by a qualified clinical psychologist. Only after reaching an acceptable inter-rater reliability, trainees were allowed to conduct the interview on their own.

The in-house semi-structured interview has been used continuously in our ongoing studies on AN (Ehrlich *et al.* 2015; Boehm *et al.* 2016; King *et al.* 2016; Bernardoni *et al.* 2017; Seidel *et al.* 2018) and helps to assess the following demographic and clinical data: socio-economic status, family history, detailed information on body weight, including highest and lowest lifetime-BMI and weight changes over the past six weeks, detailed information on menstrual cycle and contraceptives intake, current and past medical problems, current and past psychiatric or psychological treatments, current and past medication intake and nicotine use.

Finally we used BMI Standard Deviation Score (BMI-SDS) instead of BMI for statistical analysis providing an index of weight to height ratio that is corrected for age and gender (Kromeyer-Hauschild *et al.* n.d.; Hemmelmann *et al.* 2010).

Comorbidities

14 (14.9%) of acAN participants had associated psychiatric comorbidity (4 depressive disorders, 4 obsessive compulsive disorders, 2 anxiety disorders, 6 other disorders namely mutism, somatization disorder, social phobia and PTSD). 10 (27%) of recAN participants had associated psychiatric comorbidity at the time of treatment (6 depressive disorders, 1 obsessive compulsive disorders, 3 anxiety disorders, 4 other disorders namely panic disorder, insomnia and adjustment disorder.

Study Protocol

Following an overnight fast, blood was drawn into tubes containing EDTA (1.6 mg/ml) and aprotinin (270 KIU/ml) between 7:30 and 8 a.m. Subsequently participants underwent a one hour MRI scan including structural scans and a resting state fMRI run. Afterwards they had a standardized breakfast and immediately started the value-based decision-making battery (VBDM) at 9.30 a.m.

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Value-based decision-making (VBDM) Battery

The battery provides measures of impulsive decision making from four independent tasks: **delay discounting (DD), probability discounting of gains (PDG), probability discounting of losses (PDL), and a mixed gambles (MG)**. In all tasks, participants repeatedly had to decide for one of two offers presented simultaneously on a computer screen based on which is the more appealing to them (forced choice). In the DD task participants had to choose between a small immediate reward and a larger but later reward allowing to assess the rate of delay discounting. In PDG and PDL, the choice was between a sure gain or a sure loss and a larger but uncertain gain or loss, providing measures of probability discounting for wins and losses, respectively. In the MG task participants had to decide whether to accept or not a gamble in which they could win or lose money, which allowed to measure the degree of loss aversion.

Settings: Offers were randomly assigned to the left or to the right of the screen. There was no time limit to make a choice between the options presented in each trial. Outcomes of gambles were never presented during the experiment. However, subjects were informed that at the end, one trial per task would be selected randomly and according to their choice credited to their compensation. Task parameters were set as follows: For DD, delays were set to the values of 3, 7, 14, 31, 61, 180, and 365 days. Monetary rewards ranged from 0.30 to 10€. For PDG and PDL, possible probability values were set to 2/3, 1/2, 1/3, 1/4, and 1/5. Amounts ranged from 0.30 to 10€ in PDG and −0.30 to −10€ in PDL. For the MG task, amounts ranged from 1 to 40€ for gains and −5 to −20€ for losses. At the beginning of the MG task, subjects received 10€ “house money.” Task length for DD, PDG, and PDL was 30, for MG 40 trials. The experiments were presented using MATLAB Release 2010a (The MathWorks, Inc., Natick, MA.) and the Psychtoolbox 3.0.10 based on the Psychophysics Toolbox extensions (Brainard 1997; Pelli 1997).

Subjects with missing data due to technical issues were excluded from the analyses that required that specific data.

Choice parameters: The subjective value V of any monetary amount A in the number of days D has been modeled hyperbolically (Mazur 1987), and the degree of this devaluation is described by the discounting parameter k_{DD}:

$$V = \frac{A}{1 + k_{DD} * D}$$

High k values reflect steep discounting of delayed outcomes and, therefore, a tendency to favor immediate options, which is considered impulsive decision making. Hyperbolic discounting has also been used to compute the subjective value of probabilistic gains or losses, as a function of θ, “the odds against” the event of winning or losing (Rachlin *et al.* 1991; Green *et al.* 1999):

$$V = \frac{A}{1 + k_{PD} * \theta}$$

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so that in this case $k_{PD} = 1$ would reflect no discounting. Indeed, in that case, being p the probability for a win or loss, θ = (1-p)/p and k=1 would imply $V = A * p$. In this framework, going for the uncertain option is considered a risk seeking behavior, whether a loss or a win. While in the case of wins $k_{PDG} > 1$ leads to the depreciation of the uncertain reward and induces therefore a risk-averse behavior, in the case of losses $k_{PDL} > 1$ reduces the subjective value of the loss and is therefore linked to a risk-seeking behavior (Shead & Hodgins 2009). Previous studies have revealed a common decision bias to be risk averse for gains but risk seeking for losses (Kahneman & Tversky 1979) This introduces the concept of loss aversion, namely the tendency to weight the absolute value of losses higher than the absolute value of gains when comparing a loss and a gain directly with each other. In the MG task subject are presented with a 50/50% gamble of gaining one amount G or losing another amount L. The subjective value of the gamble can be estimated according to a simple linear model (Tom *et al.* 2007)

$V = \frac{1}{2}(G - \lambda L)$

so that λ>1 indicates some degree of loss aversion.

Bayesian estimation: To provide behavioral estimates of the discounting parameters, a trial-by-trial adaptive Bayesian approach for binary choice presentation was used (Pooseh *et al.* 2018). The main advantage of this approach is its isochronous adaptive nature. After each trial, the individual choice parameter is estimated and informs the options in the next trial, thus providing the most informative offers near the individual indifference point. This procedure allows for a very efficient inference of behavioral parameters. Behavioral parameter estimates across all sampled participants converged well and yielded stable final estimates of choice behavior (Figure S2).

So far the battery has been applied in studies of healthy participants (Deza Araujo *et al.* 2018; Neukam *et al.* 2018; Pooseh *et al.* 2018), in a clinical cohort (Bernhardt *et al.* 2017) and under a pharmacological intervention (Bernhardt *et al.* 2019).

Supplementary analyses

To test whether our results were driven by participants with psychiatric comorbidities, we repeated our analyses by excluding participants from the acAN and recAN groups with such conditions. The same effects and group differences were revealed as in our main analyses, namely an increased risk aversion in the recAN group as compared to HC and a preference for the delayed reward option in the acAN participants with high ghrelin concentrations. The results of these analyses are reported in Tables S1 and S2.

Similarly, while we have considered recovered participants that met our rather strict recovery criteria continuously during a time frame of 6 months, there is an ongoing debate regarding the definition of recovery of AN (Bachner-Melman *et al.* 2006; Couturier & Lock 2006; Bardone-Cone *et al.* 2007; Khalsa *et al.* 2017). To test the robustness of our findings of an increased risk aversion in the recAN group, we

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repeated our analysis by excluding recAN participants that had been recovered less than 12 months (n=2). The results were unchanged (see Table S3).

Supplemental Tables

Table S1 Group differences in decision-making parameters

Task	Group	Post-Hoc t	Age
DD	0.261	n/a	**0.006**
PDG	**0.010**	recAN>HC**	0.568
PDL	0.616	n/a	0.134
MG	0.709	n/a	0.704

P-values of F-tests derived from GLMs computed on a sample not including acAN and recAN participants with psychiatric comorbidities. The model includes group as factor and mean subtracted age as a covariate. The group effect was significant for PDG. A posthoc t-test (*t*=2.914, Estimate (SE) = 0.47(.16), *p* = 0.007; posthoc t-test, Bonferroni-corrected) revealed increased risk aversion for gains in recAN as compared to HC. Abbreviations: DD = delay discounting; MG = mixed gamble; PDG = probability discounting for gains; PDL = probability discounting for losses; Significance codes: ***<.001, **<.01, *<.05, Bonferroni corrected.

Table S2 Ghrelin effect on decision-making parameters

Task	Group	Age	ghrelin	ghrelin×group
DD	0.397	0.003	0.115	**0.019**
PDG	0.007	0.987	0.224	0.425
PDL	0.529	0.161	0.432	0.294
MG	0.502	0.605	0.299	0.083

P-values of F-tests derived from GLMs computed on a sample not including acAN and recAN participants with psychiatric comorbidities. The model includes group as factor, age and ghrelin as a covariate, and the group×ghrelin interaction. The group×ghrelin interaction was significant for DD. The linear coefficient relating ghrelin and k_{DD} was decreased in acAN when compared to HC resisting at the trend level when correcting for multiple testing (*t*(97) = -2.132, Estimate(SE) = -.0032(.0015), *p*

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= 0.066; posthoc t-test, Bonferroni-corrected). Abbreviations: DD = delay discounting; PDG = probability discounting for gains; PDL = probability discounting for losses; MG = mixed gamble.

Table S3 Group differences in decision-making parameters including only recAN participants recovered for more than 12 months

Task	Group	Post-Hoc t	Age
DD	0.344	n/a	**0.018**
PDG	**0.012**	recAN>HC**	0.898
PDL	0.393	n/a	0.188
MG	0.388	n/a	0.523

P-values of F-tests derived from GLMs computed on a sample excluding recAN participants recovered for less than 12 months. The model includes group as factor and mean subtracted age as a covariate. The group effect was significant for PDG. A posthoc t-test (t = 2.926, Estimate (SE) = .43(.15), p = 0.007; posthoc t-test, Bonferroni-corrected) revealed increased risk aversion for gains in recAN as compared to HC. Abbreviations: DD = delay discounting; MG = mixed gamble; PDG = probability discounting for gains; PDL = probability discounting for losses; Significance codes: ***<.001, **<.01, *<.05, Bonferroni corrected.

Supplemental Figures

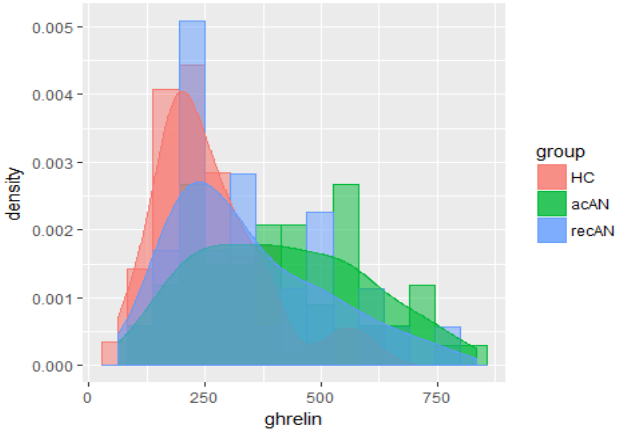

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Figure S1: Density plot showing distribution of ghrelin concentrations in the different groups in pg/ml.

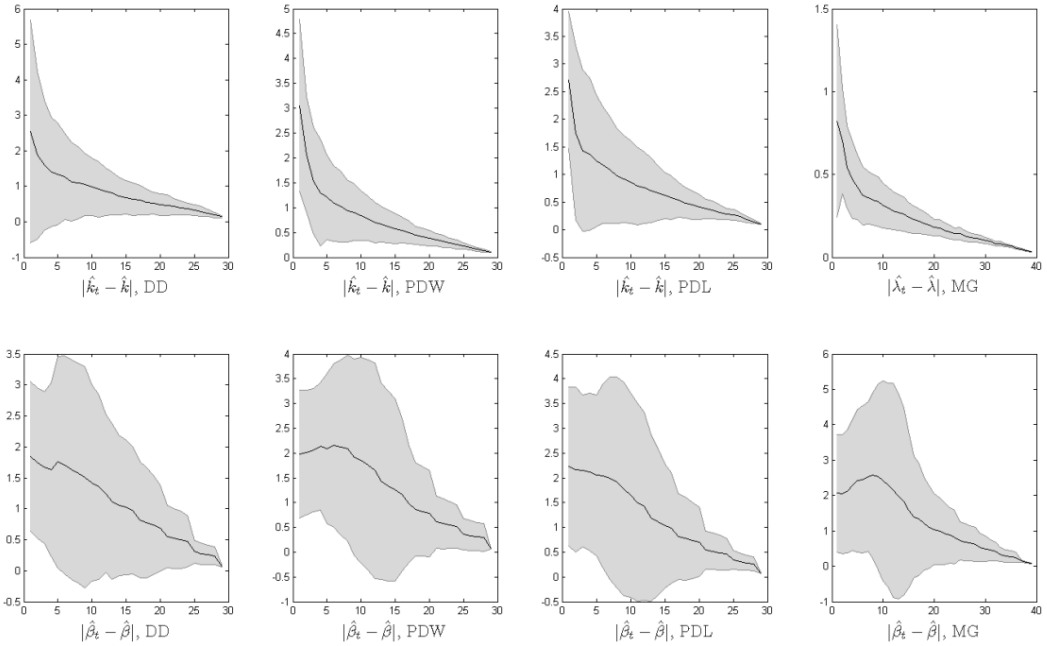

Figure S2: Convergence of parameter estimation in participant data. The average absolute differences between the estimation at each trial and the final estimation for all participants are shown trial by trial by black lines. The gray area depicts on standard deviation distance from the average. The decreasing pattern of the black lines is a sign of convergence and the same pattern for standard deviations shows that this is true for the whole group. The top row depicts $|\hat{k}_t - \hat{k}|$ for DD, PDG, and PDL and $|\hat{\lambda}_t - \hat{\lambda}|$ for MG; the bottom row shows $|\hat{\beta}_t - \hat{\beta}|$ for the same tasks.

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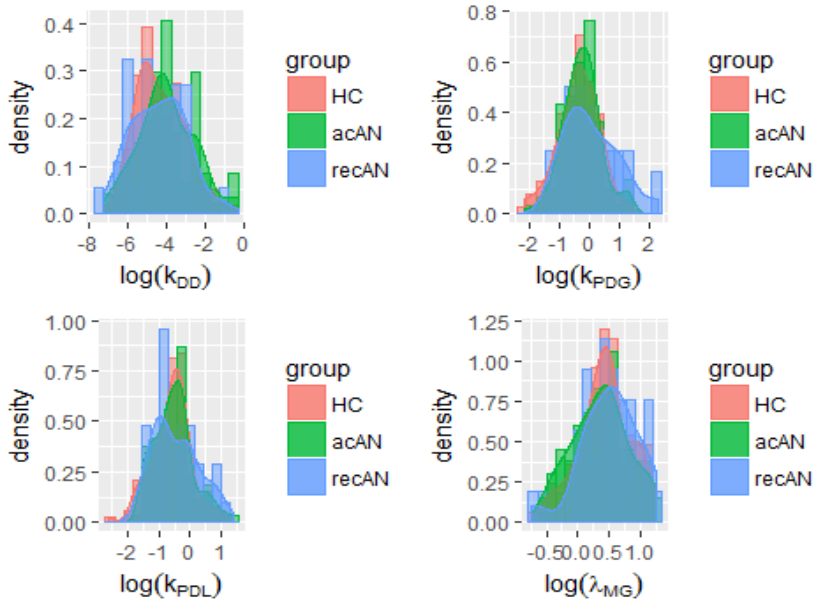

Figure S3: Density plot showing distribution of decision making parameters in the different groups. No significant violations from normality were detected.

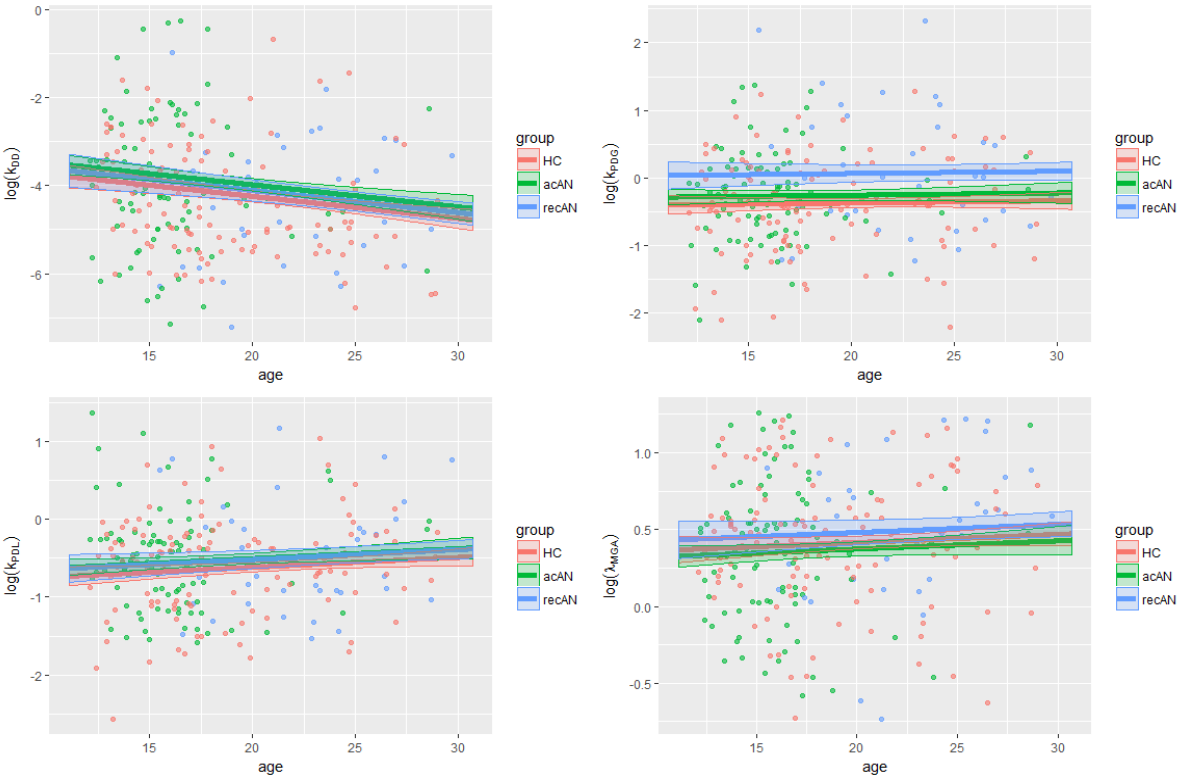

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Figure S4: Plots showing the associations between the estimated decision-making parameters and age, separate GLMs with group factor and age as covariate. Error bands represent 95% confidence levels.

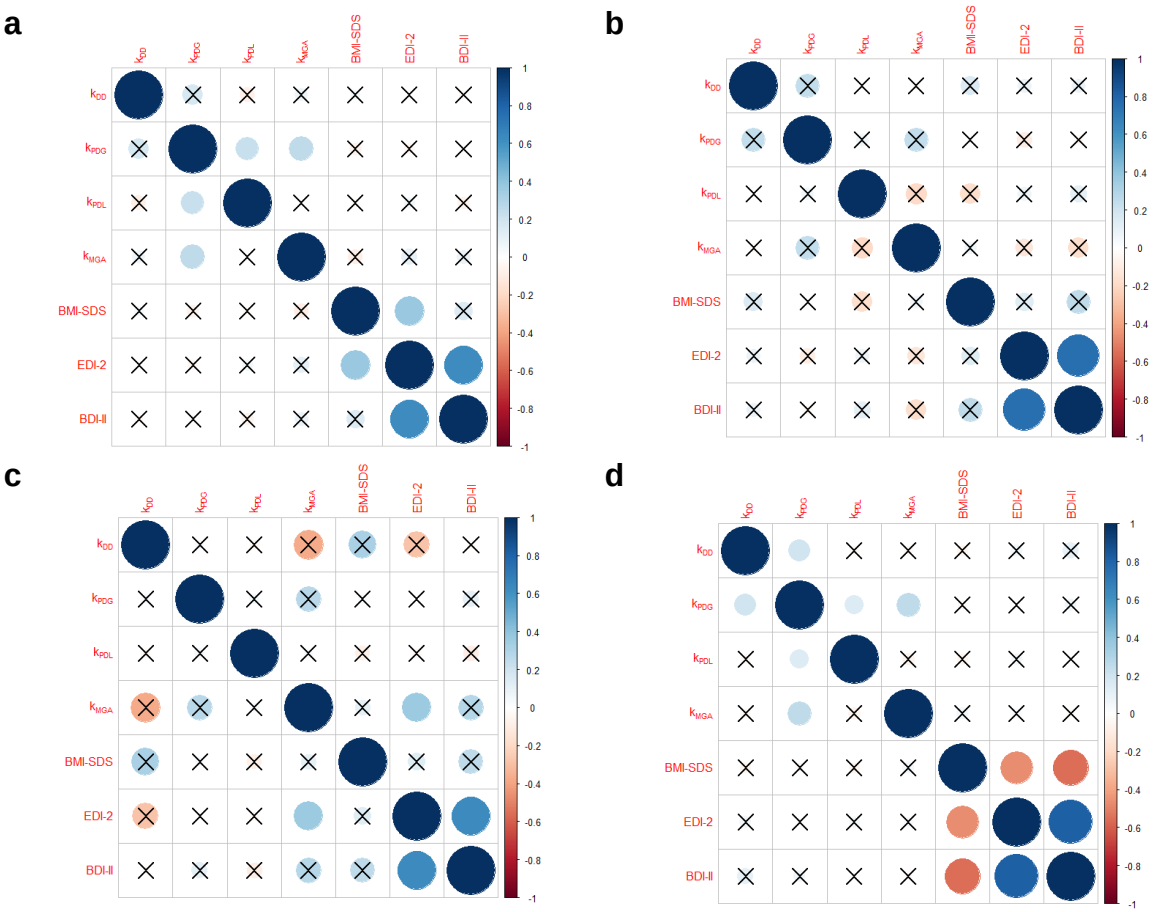

Figure S5: Correlations between clinical variables and discounting parameters in the **(a)** HC, **(b)** acAN, **(c)** recAN and the **(d)** entire sample. FDR corrected. Crosses indicate that the correlation is not significant.

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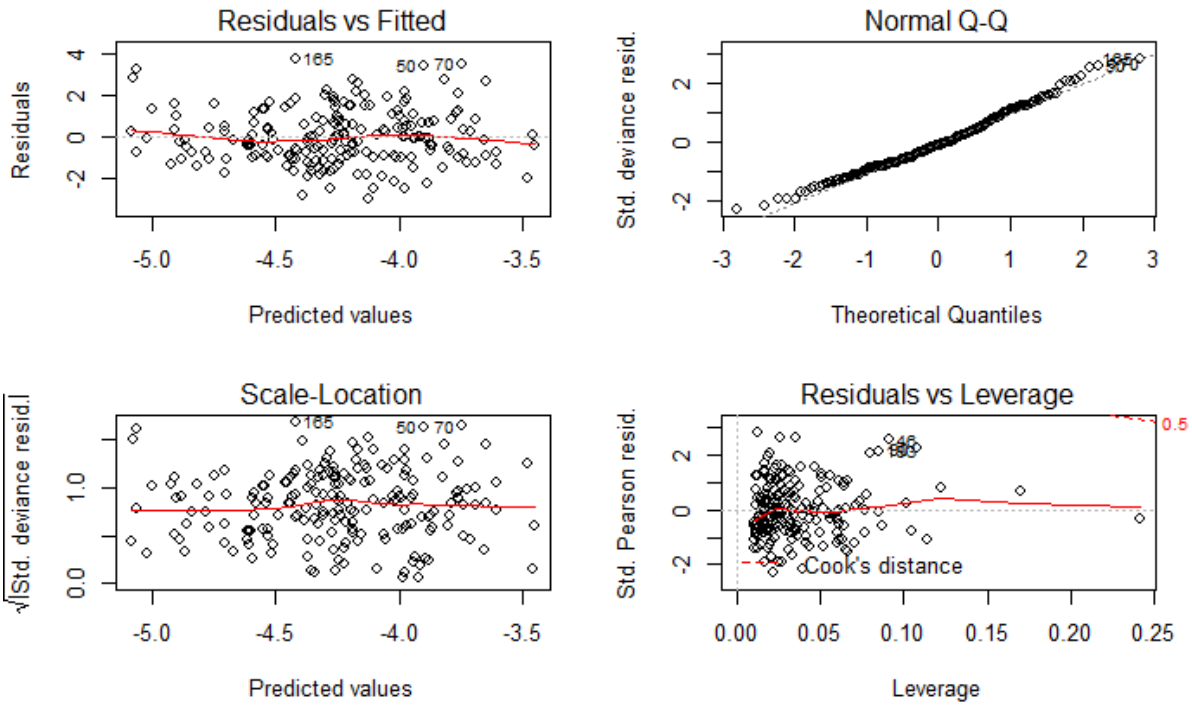

Figure S6: Q-Q and residual plots for the GLM with ghrelin as covariate.

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