



Prolactin levels in drug-naïve first episode nonaffective psychosis patients compared with healthy controls. Sex differences

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ABSTRACT

Recent studies have found hyperprolactinemia in first episode psychotic patients that had not previously received antipsychotic treatment (drug-naïve). Our goal was to learn whether there were differences in baseline prolactin concentrations between drug-naïve psychotic patients and healthy controls, as well as to study possible gender differences in the prolactin elevation. A cross-sectional study was conducted that included 61 drug-naïve psychosis patients and 45 healthy controls (aged between 14–55 years old). A blood sample was extracted between 8 and 10 a.m. Prolactin levels and TSH were determined. The Perceived Stress Scale (PSS) was conducted across the sample. This study showed significantly higher levels of prolactin in drug-naïve patients compared to healthy controls. These results were maintained after controlling prolactin levels for sex, age, THC consumption, baseline TSH, and PSS. A significant correlation between prolactin and PSS was not observed. Significant differences in prolactin levels between men and women were not observed. These results are clinically important because if elevated baseline prolactin levels are detected in these patients, it will be necessary to initiate neuroleptics that do not increase this hormone. There was no evidence that stress was related to an increase in prolactin at the onset of psychosis.

1. Introduction

Prolactin is an essential polypeptide that occurs in the lactotrophic cells of the anterior pituitary gland and is essentially regulated by hypothalamic dopamine inhibitory action.

The causes of hyperprolactinemia are several: physiological processes, prolactinomas, primary hypothyroidism, chronic renal failure, cirrhosis, and pharmacological effects (Tsigaropoulou et al., 2012). Therefore, it must be considered that hyperprolactinemia is a very common side effect of the medications used to treat schizophrenia (Petrikis et al., 2016). Hyperprolactinemia is often found in patients with chronic schizophrenia, which is the most frequent reason for the use of antipsychotic medication. However, some authors posit that there are indications that, in some cases, hyperprolactinemia may not

be due to antipsychotic medication, but rather to a pre-existing condition (Ittig et al., 2017; Riecher-Rössler et al., 2013). Riecher-Rössler has suggested that stress may induce hyperprolactinemia and that the dopaminergic increase that occurs in psychosis is, at least partially, a mechanism for regulating prolactin (Riecher-Rössler et al., 2013). It has also been hypothesized that both inflammation and deregulation in the serotonergic system could contribute to the hyperprolactinemia observed in first episode psychotic patients who have not previously received antipsychotic treatment (drug-naïve) (Petrikis et al., 2016).

There are numerous studies that have found levels of prolactin above the physiological limits in first episode drug-naïve psychotic patients, with prevalences of 33.3% (Aston et al., 2010), 39% (Riecher-Rössler et al., 2013), 35% (Ittig et al., 2017), and 11% (Lally et al., 2017). In a very recent meta-analysis (González-Blanco et al., 2016)

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involving a systematic review of studies that evaluated prolactin levels in drug-naïve psychotic patients with schizophrenia or related disorders compared to healthy controls, higher levels of prolactin were found in the patient group. It should be noted that this meta-analysis only included seven studies, so it is important to continue research in this area. There are few studies to evaluate other hormonal factors that could influence the levels of prolactin; therefore, (González Blanco et al., 2016) recommend that, in future studies evaluating the levels of prolactin in drug-naïve patients, it would be desirable to also examine cortisol, TSH, and ghrelin.

There are few studies evaluating the influence of gender on hyperprolactinemia in first episode drug-naïve psychotic patients. The recent meta-analysis of González Blanco et al. (2016) detected a significantly lower level of prolactin concentrations in first episode drug-naïve psychotic men than in women.

The goal of this study was to determine whether there were differences in baseline prolactin concentrations between first episode drug-naïve psychotic patients and healthy controls. Another aim was to study whether there was a relationship between perceived stress levels and prolactin levels, as well as to assess whether there could be gender differences in the elevation of prolactin.

2. Methods

2.1. Setting and recruitment

A cross-sectional study was performed which included 61 patients (38 females; 23 males) with a diagnosis of a first psychotic episode (non-affective psychosis), aged 14–55 years old, without previous antipsychotic treatment, and who were treated at the Mental Health care sector of Parc Sanitari Sant Joan de Déu/Child and Maternal Hospital of Sant Joan de Déu (Esplugues).

The patients were recruited from the acute psychiatric unit, the acute child and adolescent unit, and a community mental health service. The psychiatrist of the acute unit and the community mental health service was the one that identified the patients and referred them to the study. The information that patients were drug-naïve was reported by the patients themselves and their families, and reviewed in their medical history.

Forty-five healthy controls (20 females; 25 males), matched for sex and age, were recruited.

The criteria for patient inclusion were: Age between 14 and 55 years old. A first episode defined as the presence of one of the following symptoms: delusional ideas, hallucinations, disorganized language, catatonic or disorganized behaviour, and negative symptoms (alogia, aboulia, affective flattening) for at least one week and less than five years of development. Not having received previous antipsychotic treatment. Signing the informed consent for the study. Score in Young Mania Rating Scale (YMRS) \leq 20.

The inclusion criteria for the controls were: Age between 14 and 55 years old. No diagnosis of mental disorder. No family history of illness in the psychotic spectrum. Signing the informed consent for the study.

Exclusion criteria for all participants were the following: poorly controlled thyroid disease, alterations of the pituitary gland and ovaries, well-known pathology of the CNS (tumour, HIV, radiotherapy, etc.), concomitant treatment with cimetidine, metoclopramide, domperidone, famotidine, omeprazole, d-fenfluramine, methyl dopa, reserpine, calcium antagonists, cocaine, opioids (codeine and morphine), and anti-allergens, and antirheumatic treatment, renal (FG $<$ 50) or liver insufficiency (transaminase levels greater than three times the normal values), and intellectual disabilities (Premorbid IQ $<$ 70).

For women the exclusion criteria also included hormonal replacement treatment, fertility or oral contraceptive treatment, menopause (defined as FSH value greater than 20 mL/ml and more than one year of amenorrhea), and pregnancy or lactation at the time of the study.

This study was approved by the Research and Ethics Committee of

Sant Joan de Déu (Barcelona, Spain) and was carried out in accordance with the Helsinki Declaration.

2.2. Analytical determinations

In the study, blood analysis took place prior to the beginning of the antipsychotic treatment. In this analysis, prolactin, cortisol, and TSH were determined. Blood test was performed between 8 and 10 am. Before the extraction, participants were at rest for 30 min.

2.2.1. Prolactin measurement

The CMIA technology two-step ImmunoAssay “CHEMIFLEX” (Ref. Architect Prolactin 7K76, Abbott Laboratories, 65,205 Wiesbaden, Germany) was used to measure prolactin levels. The method has been standardized against the 3rd IRP WHO Reference Standard 84/500; hyperprolactinemia in this reference is defined as a value above the 97.5th percentile, that is $>$ 325 mU/l in men, $>$ 456 mU/l in women, and $>$ 466 mU/l in teenagers (aged 14–17 years old).

2.3. Instruments

The Perceived Stress Scale (Cohen et al., 1983) was used to measure the participants' appraisal of how stressful events in their lives were at the time of study recruitment.

BMI: the measurement of the body mass index was made by the nursing staff at the same time that the blood test was performed. BMI was calculated by dividing weight by height squared.

THC consumption: the consumption of THC was reported by the patient. It was measured if the patient had consumed THC in the prior three months.

2.4. Statistical analyses

Comparisons between groups were performed using a χ^2 test for categorical variables, and a Student's *t*-test for continuous and normally distributed variables. In addition, comparisons between groups (drug-naïve sample and healthy controls) were also made using linear regressions, controlling for potential confounding factors such as cannabis use, age, and TSH and Perceived Stress Scale scores.

In order to normalize prolactin levels according to sex and age (adults vs. teenagers), prolactin values were first log-transformed, and then normalized according to the reference levels in our population for each of the three defined groups (adult men, adult women, and teenagers).

Statistical significance was defined as $p <$ 0.05. All analyses were carried out using SPSS version 22.

3. Results

3.1. Sample description

The clinical and demographic characteristics of the individuals are shown in Table 1. The two groups studied did not have significant differences in age, gender, or body mass index (BMI) (Table 1). In the groups studied, the patients had a significantly higher consumption of tobacco and THC, as well as a higher score in the perceived stress scale (Table 1). In the control group significant levels of TSH (Table 1) were observed.

3.2. Hyperprolactinemia in antipsychotic drug-naïve patients and control subjects

In this study hyperprolactinemia was found in 56.7% of patients (59.5% of men and 52.5% of women) and in 20.5% of controls (12.5% of men and 30% of women) (Table 2).

When prolactin was analysed as a categorical variable

Table 1
Clinical and demographic characteristics of the patients and the controls.

	Patients (n = 61)	Control subjects (n = 45)	P value
Age (years)	24.61 (9.29)	27.62(9.96)	0.112
Male/female (% female)	38/23 (37.7%)	25/20 (44.4%)	0.309
IMC, mean (SD)	22.71(4.25)	24.23(4.83)	0.121
TSH, mean (SD)	1.47(0.95)	1.86(0.84)	0.031*
Cortisol, mean (SD)	433.66(156.36)	383.34(172.49)	0.135
Tobacco consumption,%	62.7%	25%	< 0.001**
THC consumption,%	45.8%	9.1%	< 0.001**
Perceived stress scale, mean (SD)	30.76(9.37)	18.57(7.82)	< 0.001**

* $p < 0.05$.

** $p < 0.001$.

(hyperprolactinemia: yes/no), significantly more hyperprolactinemia was found in patients vs. controls ($p = 0.000$). The same results were observed when prolactin was analysed as a continuous variable (prolactin normalized by age and sex) ($p = 0.010$) (Table 2).

In Table 2, the mean and SD of the normalized prolactin values according to group (patients/controls) and sex (male/female) can be seen.

3.3. Relationship between stress and prolactin

In the total sample there was no significant correlation between the Perceived Stress Scale and normalized prolactin ($r = 0.126, p = 0.218$). There was also no significant correlation in the patient subsample ($r = -0.165, p = 0.230$) or in the controls ($r = 0.297, p = 0.053$).

3.4. Effect of gender on prolactin levels

No significant differences were observed in prolactin levels between men and women. The same was true when prolactin was analysed as a categorical variable (hyperprolactinemia: yes / no) ($p = 0.580$) in the patients, ($p = 0.261$) and in the controls, or as a continuous variable ($p = 0.635$) in the patients and ($p = 0.341$) in the controls. Prolactin levels in patients and controls subdivided into men and women are shown in Fig. 1.

3.5. Evaluation of other factors that could affect prolactin

Linear regression analysis showed that the differences with respect to the level of baseline prolactin normalized by sex between the patient group and control group were still significant once corrected for age, THC consumption, baseline TSH level, and Perceived Stress Scale (Table 3).

4. Discussion

The main result of this study is that significantly higher levels of prolactin were found in patients with first episode psychosis that had not previously taken antipsychotic treatment compared to healthy controls (whether prolactin is evaluated as a continuous or categorical variable). These results were maintained after controlling the levels of prolactin for several variables (sex, age, THC consumption, baseline

Table 2
Hyperprolactinemia and normalized prolactin values in antipsychotic-naïve patients and control subjects.

	Patients Men	Women	Total	Controls Men	Women	Total
Proportion of patients with hyperprolactinemia, n (%)	22 (59.5)	12(52.2)	34(56.7)	3(12.5)	6(30)	9(20.5)
Prolactin normalized mean \pm SD	1.704 \pm 1.450	2.015 \pm 3.043	1.844 \pm 2.170	0.671 \pm 1.151	1.092 \pm 1.732	0.863 \pm 1.442

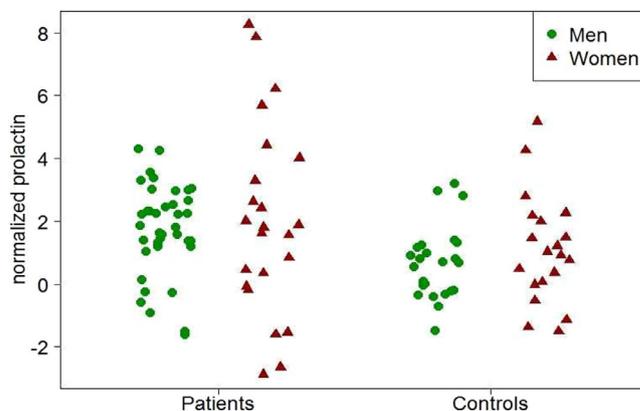


Fig. 1. Prolactin serum levels in first episode nonaffective psychosis patients and control subjects subdivided by sex.

Table 3
Regression of logarithmically normalized prolactin.

	Beta	t	Sig
Patient	0.316	2.385	0.965
THC consumption	0.047	0.425	0.672
Age	-0.117	-1.207	0.231
TSH	0.355	3.620	0.000
Perceived stress scale	0.013	0.110	0.913

Beta; standardized coefficient.

TSH, Perceived Stress Scale). In recent studies, higher levels of prolactin have also been found in first episode drug-naïve psychotic patients vs. controls (Albayrak et al., 2014; Garcia-Rizo et al., 2012; Petrikis et al., 2016). According to Labad et al. (2015) these findings are important because they underscore the fact that in a substantial proportion of individuals with psychotic disorders at early stages hyperprolactinemia is not secondary to D2-blockade by antipsychotics (Labad et al., 2015).

When the prevalence of hyperprolactinemia was evaluated in the patient sample, it was found in 56.7% of drug-naïve patients higher percentage than in previous studies such as (Lally et al., 2017) (11%), (Aston et al., 2010) (33.3%), (Ittig et al., 2017) (35%), and (Riecher-Rossler, 2013) (39%). It may be that this higher prevalence of hyperprolactinemia in our sample is due to the fact that most of our patients had required hospital admission, whereas in other studies the sample of patients was recruited from outpatient services.

There are multiple hypotheses that attempt to explain this increase in prolactin observed in patients with first episode psychosis, with little conclusive data.

It has been hypothesized that the increased stress experienced by patients with first episode psychosis could explain the increase in prolactin that is observed in these patients (Riecher-Rossler et al., 1993). Results that would argue in favour of this theory in our study include the significantly higher scores on the Perceived Stress Scale in patients vs. controls.

In the patient group, we did not observe a significant correlation between Perceived Stress Scale and baseline prolactin. These results match those of Lally et al. (2017), a study in which there was no association between the levels of prolactin and the Perceived Stress Scale

in drug-naïve patients (However, as the authors mention, caution must be taken in the interpretation of the results given the small number of cases).

It should be taken into account that in our study, when we analysed a hormonal stress marker (cortisol) we did not detect significant differences between patients and controls, as was observed in the studies of Garcia-Rizo et al. (2012) and Petrikis et al. (2016). These results run against the theory that the increase in prolactin was due to stress. Petrikis et al. (2016) concluded that it is conceivable that the high levels of prolactin in the group of patients compared to the controls is due to stress, although the serum levels of cortisol are were different in the two groups.

Riecher-Rössler et al. (2013) hypothesized that the increase in dopamine that occurs in psychosis could be a mechanism for down regulating the increase in prolactin produced by stress. According to Riecher-Rössler, this would mean that the tuberofundibular pathway of dopamine could be involved in the pathogenesis of psychosis and not just the mesolimbic or mesocortical pathways (Riecher-Rössler et al., 2013). Other authors hypothesize that inflammation could play a role in the elevation of prolactin (Petrikis et al., 2016; Song et al., 2014) or that prolactin hypersecretion may be part of a complex mechanism that could compensate for the reduced serotonergic activity (Petrikis et al., 2016; Pompili et al., 2012).

Regarding other variables evaluated, we found significant differences between the two groups with regard to tobacco consumption, with a higher consumption of tobacco in the patient group that was not detected in Garcia-Rizo et al. (2012) and Song et al. (2014). It is important to take this into account, given that several studies have shown that tobacco consumption influences the hormonal regulation of prolactin (Ohta et al., 2011; Xue et al., 2010). In our study we observed a significantly greater consumption of THC in patients vs. controls, although when we analysed THC as a possible confounding factor in the elevation of prolactin, this was not significant.

Another result of our study is that patients had significantly lower levels of TSH than controls. These results contrast with those of previous studies (Garcia-Rizo et al., 2012; Petrikis et al., 2016) which did not find differences in TSH levels between patients and controls. (Rao et al., 1990) concluded that the increase in dopaminergic activity affects the secretory functions of the pituitary gland and can lead to a reduction of TSH levels, which could explain the results found in our study.

With regard to the evaluation of gender differences, there were no significant differences found in prolactin levels between men and women, either in the patients or in the controls, which contrasts with the results of the meta-analysis of González-Blanco et al. (2016), in which male patients and controls had lower levels of prolactin than did women. At this point it is worth mentioning that in our study, when prolactin was evaluated as a continuous variable, it was normalized for age and gender. In previous studies higher levels of prolactin have been observed in women compared to men because the prolactin values were not normalized for gender.

It should be noted that our results must be interpreted in the context of certain limitations.

The size of the sample in our study was adequate to evaluate the differences between the patients and the controls, but perhaps it was too small to be able to identify differences of gender. Also, we only measured cortisol in the blood; perhaps there are other ways to better evaluate cortisol as a hormonal stress marker (curved cortisol, determination of cortisol in saliva, etc.).

A further limitation is that we do not know whether patients with first episode psychosis included in the study would be subsequently diagnosed with affective psychosis, which could condition the results of the baseline analysis. Moreover, virtually all the sample of patients had required hospital admission, which may also be a limitation.

We may conclude that in our study significantly higher levels of prolactin were found in patients vs. controls after controlling the

prolactin levels for several variables (sex, age, THC consumption, baseline TSH, Perceived Stress Scale). We consider these results to be relevant both theoretically and in practice. First, they provide data that may help us elucidate the ethiopathogenesis of first psychotic episodes. And second, they could improve the approach taken with these patients, because if high levels of prolactin are detected at baseline, antipsychotic drugs that do not increase this hormone should be introduced, as also suggested by another author (Riecher-Rössler et al., 2013). Hyperprolactinemia should be avoided, since we know that it may lead to reproductive problems (galactorrhea, menstrual irregularities, infertility, hirsutism, acne), sexual issues (dysfunction) (Rubio-Abadal et al., 2016), osteopenia, and osteoporosis (Stubbs, 2009), among others.

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Conflict of interest

All authors declare not to have any conflicts of interest that might be interpreted as influencing the content of the manuscript.

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Ahcart A, Alvarez M, Arranz B, Barneda V, Bogas JL, Bonilla R, Butjosa A, Casali T, Colomer B, Coromina M, Cuevas- Esteban J, Cunill R, Cuñat O, Del Cacho N, del Hoyo B, Delisau Y, Dolz M, Ferrer I, Foix A, Grases N, Iglesias-González M, Ledesma-Ipaguirre G, López- Ortiz C, Membrive P, Miñambres A, Muñoz-Samons D, Ochoa S, Pastrana N, Rodriguez MJ, Pelaez T, Saltó C, Sibelo S, Núñez C, Nuñez M, Pardo M, Redín J, Riera- Lopez de Aguilera I, Romans C, Rubio-Abadal E, Santos A, Sole L, Soler A, Teba S, Usall J, Vila- Badia R

References

- Albayrak, Y., Beyazyüz, M., Beyazyüz, E., Kuloğlu, M., 2014. Increased serum prolactin levels in drug-naïve first-episode male patients with schizophrenia. *Nord. J. Psychiatry* 68, 341–346.
- Aston, J., Rechsteiner, E., Bull, N., Borgwardt, S., Gschwandtner, U., Riecher-Rössler, A., 2010. Hyperprolactinaemia in early psychosis-not only due to antipsychotics. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 34, 1342–1344.
- Cohen, S., Kamarck, T., Mermelstein, R., 1983. A global measure of perceived stress. *J. Health Soc. Behav.* 24, 385–396.
- Garcia-Rizo, C., Fernandez-Egea, E., Oliveira, C., Justicia, A., Parellada, E., Bernardo, M., Kirkpatrick, B., 2012. Prolactin concentrations in newly diagnosed, antipsychotic-naïve patients with nonaffective psychosis. *Schizophr. Res.* 134, 16–19.
- González-Blanco, L., Greenhalgh, A.M.D., Garcia-Rizo, C., Fernandez-Egea, E., Miller, B.J., Kirkpatrick, B., 2016. Prolactin concentrations in antipsychotic-naïve patients with schizophrenia and related disorders: a meta-analysis. *Schizophr. Res.* 174, 156–160.
- Ittig, S., Studerus, E., Heitz, U., Menghini-Müller, S., Beck, K., Eglöf, L., Riecher-Rössler, A., 2017. Sex differences in prolactin levels in emerging psychosis: indication for enhanced stress reactivity in women. *Schizophr. Res.* 187, 111–116.
- Labad, J., Stojanovic- Pérez, A., Montalvo, I., Sole, M., Cabezas, A., Gutiérrez-Zotes, A., 2015. Stress biomarkers as predictors of transition to psychosis in at-risk mental states: roles for cortisol, prolactin and albumin. *J. Psychiatr. Res.* 60, 163–169.
- Lally, J., Ajnakina, O., Stubbs, B., Williams, H.R., Colizzi, M., Carra, E., Gaughran, F., 2017. Hyperprolactinaemia in first episode psychosis – a longitudinal assessment. *Schizophr. Res.* 189, 117–125.

- Ohta, C., Yasui-Furukori, N., Furukori, H., Tsuchimine, S., Saito, M., Nakagami, T., Kaneko, S., 2011. The effect of smoking status on the plasma concentration of prolactin already elevated by risperidone treatment in schizophrenia patients. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 573–576.
- Petrikis, P., Tigas, S., Tzallas, A.T., Archimandriti, D.T., Skapinakis, P., Mavreas, V., 2016. Prolactin levels in drug-naïve patients with schizophrenia and other psychotic disorders. *Int. J. Psychiatry Clin. Pract.* 20, 165–169.
- Pompili, M., Gibiino, S., Innamorati, M., Serafini, G., Casale, A., Del, De Risio, L., Girardi, P., 2012. Prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients. *Psychiatry Res.* 200, 389–394.
- Rao, M.L., Gross, G., Strebel, B., Bräunig, P., Huber, G., Klosterkötter, J., 1990. Serum amino acids, central monoamines, and hormones in drug-naïve, drug-free, and neuroleptic-treated schizophrenic patients and healthy subjects. *Psychiatry Res.* 34, 243–257.
- Riecher-Rössler, A., Rybakowski, J.K., Pflueger, M.O., Beyrau, R., Kahn, R.S., Malik, P., Fleischhacker, W.W., 2013. Hyperprolactinemia in antipsychotic-naïve patients with first-episode psychosis. *Psychol. Med.* 43, 2571–2582.
- Riecher-Rössler, A., Hafner, H., 1993. Schizophrenia and estrogens – is there an association? *Eur. Arch. Psychiatry Clin. Neurosci.* 242, 323–328.
- Rubio-Abadal, E., Del Cacho, N., Saenz-Navarrete, G., Arranz, B., Cambra, R.-M., Cuadras, D., PROLACT Group, 2016. How hyperprolactinemia affects sexual function in patients under antipsychotic treatment. *J. Clin. Psychopharmacol.* 36, 422–428.
- Song, X., Fan, X., Zhang, J., Zheng, H., Xue, L., Pang, L., Chen, X., Zhang, Wharrington, A., Ziedonis, D., Lv, L., 2014. Prolactin serum levels correlate with inflammatory status in drug-naïve first – episode schizophrenia. *World J. Biol. Psychiatry* 15, 546–552.
- Stubbs, B., 2009. Antipsychotic-induced hyperprolactinaemia in patients with schizophrenia: considerations in relation to bone mineral density. *J. Psychiatr. Ment. Health Nurs.* 16, 838–842.
- Tsigkaropoulou, E., Peppas, M., Zompola, C., Rizos, E., Xelioti, I., Chatziioannou, S., ..., Lykouras, L., 2012. Hypogonadism due to hyperprolactinemia and subsequent first episode of psychosis. *Gend. Med.* 9, 56–60.
- Xue, Y., Morris, M., Ni, L., Guthrie, S.K., Zubieta, J.-K., Gonzalez, K., Domino, E.F., 2010. Venous plasma nicotine correlates of hormonal effects of tobacco smoking. *Pharmacol. Biochem. Behav.* 95, 209–215.