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Research article

Two profiles in the recovery of reward devaluation in rats: Latent class growth analysis

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ABSTRACT

Consummatory successive negative contrast (cSNC) occurs when animals exposed to an unexpected downshift from a high palatable reward (e.g., 32% sucrose solution) to a less preferred one (e.g., 4% sucrose solution) show an abrupt and transient suppression of the consummatory response, compared with control animals that always had access to the less preferred one. This phenomenon constitutes an animal model of stress produced by frustrative events. To obtain information about individual differences regarding cSNC, we used Latent Class Growth Analysis (LCGA) to analyze a sample of 53 animals exposed to an incentive downshift. We found two profiles of animals, both showing the suppression of the consummatory response but diverging in the speed of the recovery. Our results are consistent with previous literature showing individual differences in cSNC and do not support the existence of a third profile.

1. Introduction

Mood disorders are pervasive in our society and studying them requires several research strategies. Studies with animal models help us to disentangle cause-effect relationships, since we can modify different environment or genetic conditions to produce depression or anxiety-like behaviors. For instance, affecting the conditions under which animals receive a reward appears to be related to these kinds of behaviors. Establishing individual differences in the way animals respond to these conditions might help us to understand the individual differences that we find in humans. One of the conditions that we want to explore is reward loss.

Reward loss refers to situations in which animals receive an unexpected reward reduction or omission. These situations appear to be aversive and stressful [1]. cSNC is one of the phenomena most commonly studied that happens as a consequence of a reward loss. cSNC occurs when animals exposed to an unexpected downshift from a high palatable reward (e.g., 32% sucrose solution) to a less preferred one (e.g., 4% sucrose solution) show an abrupt and transient suppression of the consummatory response, as compared to control animals that had always access to the less preferred one [2]. Animals experience an aversive emotional state when they find a negative discrepancy between the expected and the obtained reward. cSNC is a consequence of this particular state, also called frustration, and is closely related to fear and anxiety [1,2]. Amsel stated that the first reaction to the downshifted incentive is an unconditioned response that takes place in the first session (primary frustration), while a second reaction, a conditioned response, is present in subsequent sessions (secondary frustration) [1]. Consistent with this statement, the administration of benzodiacepines reduces the size of cSNC [3,4]; the increased hypothalamic-pituitary-adrenal activation level correlates with stronger suppression of the consummatory responses [5,6]; and lesions in the lateral amygdala attenuate these responses, while lesions in the corticomedial and central amygdaloidal nuclei eliminate them [7].

Most studies have addressed this topic based on the analysis of mean-level responses. However, the animals' responses to a reward devaluation event reflect a range of individual differences that indicate the lack of an homogenous response. Selective breeding studies also suggest important individual differences [8,9]. Several additional studies have indicated that anxiety-related behaviors such as high avoidance are susceptible to be genetically selected as a trait, suggesting important variations across individuals [10–12]. As previously stated, selective breeding is important to understand individual differences; however, since they are artificial, variations may be magnified and may

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not reflect natural variations in a particular behavior.

Another way of evaluating the individual differences consists of examining the correlations between the cSNC measures and several tests of emotional behaviors. For instance, Flaherty et al. found that the rats' first reaction to reward devaluation correlated with the entry frequency to an open arm in an elevated plus maze and the latency to emerge in an emergence test [13]. Nevertheless, other studies have attempted to replicate these correlations, but they have found contradictory and inconsistent results [14,15]. In fact, there are documented difficulties in finding inter-correlations in the measurements of different tests that evaluate stress and anxiety in rodents [16]. This suggests that simple correlational approaches have serious limitations to address the individual differences expressed in a particular situation.

Recently Papini et al. identified several profiles of cSNC in rats using a more complex approach [17]. Specifically, the authors analyzed through latent growth mixture modeling (GMM) the data from 21 experiments in both male and female Long Evans and Wistar rats, and found three profiles: animals without expression of negative contrast, animals showing negative contrast but no recovery, and animals expressing both negative contrast and recovery of the consummatory response. GMM is a statistical technique derived from Structural Equation Modeling. It identifies unobserved classes or profiles across a pool of observations across time. Each profile has its own longitudinal change with a particular slope (indicative of the increasing or decreasing of the measurements across time) and intercept (indicative of the magnitude of the measurement of the initial responses). Under GMM each profile has its own estimate of mean and variance [18].

The fact that a previous study used GMM to identify different profiles of cSNC response poses specific problems. First, GMM does not work well with small samples [19,20]; second, although the authors try to homogenize those responses by comparing experimental with control ones, several important variations (sex of the animals, strains, and experiments) made the analysis even more difficult. As a consequence, entropy, an important index of a good classification, was less than 0.8; one of the profiles (i.e., animals without expression of negative contrast) comprised less than 10% of the animals, which made the existence of the profile less likely to be correctly identified [21]. Finally, the profile of rats that comprised less than 10% of the animals (rats with no contrast) had a very distinctive and lower consummatory response during the entire experiment. We believe that this does not reflect an absence of cSNC, but a low response to any reward.

When the sample size is relatively small, a useful alternative statistical technique is Latent Class Growth Analysis (LCGA), which is also derived from SEM; and like GLM, each identified profile has a particular slope and intercept. The distinctive characteristic is that the variance in each profile is fixed at zero. This requirement allows the sample size to be relatively small [22].

The purpose of this study was to identify the number of profiles of cSNC, but by using a more conservative approach and a more homogenous sample of rats. In this regard, the all-male Wistar rats underwent the same training protocol (four different groups, each at a different time). We used the LCGA to conduct the statistical analysis; this kind of technique is particularly relevant for analyzing longitudinal analysis in small samples.

2. Method

2.1. Subjects and apparatus

The subjects were 83 male Wistar rats bred at the Medical Research Institute vivarium (Universidad de Buenos Aires), coming from four different experiments as controls, and housed individually when they had reached the age of approximately 90 days. At this moment they began food restriction until they were 81% to 85% of their *ad libitum* body weight (250–506 g). For their housing conditions, the 12 h light-dark cycle (on 07:00) and the temperature (21–22 °C) had a controlled variation. Polycarbonate tubs measuring 40 × 22 × 20 cm housed seven rats, and stainless-steel wire-bottom cages measuring 27 × 25 × 22 cm (length × width × height) housed the remaining animals. Previous data of our laboratory showed no differences in cSNC as a function of caging design [23]. In both cases we provided sawdust bedding, placed either in a tray below the wire-bottom cages or directly into the tubs, and replaced it weekly. For their training, we enclosed them in boxes with a diffuse house light, located inside a cubicle with a source of white noise. All procedures were approved by the Institutional Laboratory Animal Care and Use Committee of the Medical Research Institute (IDIM-Universidad de Buenos Aires-CONICET).

2.2. Procedure

Fifty-three animals from the whole set of animals received a 32% sucrose solution (32 g of sugar per 68 g of water) for ten sessions, one each day, and then downshifted to a 4% sucrose solution (4 g of sugar per 96 g of water) for additional five sessions. Thirty animals received the 4% sucrose solution throughout the entire experiment (15 sessions). Each five-minute session commenced after the animal had its first contact with the solution. Five conditioning boxes were used to train the animals, which measured 24.1 cm in length, 29.2 cm in width, and 21 cm in height. Aluminum bars formed the floor of the box (0.4 cm in diameter, 1.1 cm apart from center to center). In the center of one of the lateral walls there was a 5 cm hole, 3.5 cm deep, 1 cm above the floor level, through which a sipper tube could protrude from the outside. When fully inserted, the sipper tube protruded 2 cm into the box. The animals activated photocells when they had contact with the sipper tube and the cumulative amount of time the photocell was activated in a particular session was the main dependent variable in this experiment (goal tracking time, GTT). Data were transferred to a computer running MED-PC software (Med Associates Inc.).

3. Results and partial discussion

3.1. Statistical analysis

A first step in the statistical analysis was to test significant differences among animals across the 4 different experimental groups from which these animals were obtained. We ran this statistical analysis using IBM SPSS (version 23). Among experimental animals, we did not find significant differences across experiments, $F(3, 47) = 0.52$, $p = .66$, partial $\eta^2 = 0.03$; or in the postshift sessions, $F(3, 49) = 1.02$, $p = .39$, partial $\eta^2 = 0.03$. A second step in the analysis was to compare experimental animals ($n = 53$) with control animals ($n = 30$). As can be observed in Fig. 1, we found a significant difference between control

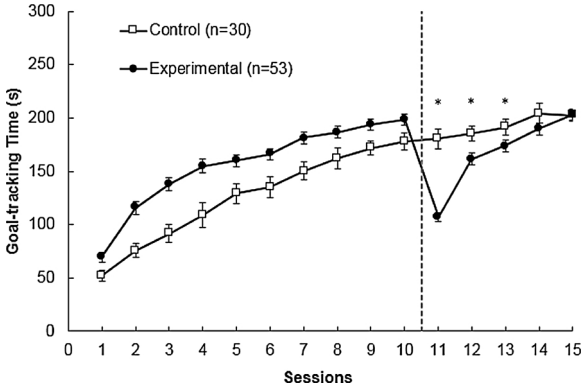

Fig. 1. Mean (± *SEM*) goal-tracking time (GTT) during ten sessions of the preshift and five additional sessions in the postshift. * Indicates statistically significant differences between experimental and control animals during the postshift.

and experimental animals throughout the sessions in the preshift, since a higher level of GTT was observed in the experimental condition, $F(1, 7) = 17.94$, $p < .001$, partial $\eta^2 = 0.18$. More importantly, the analysis found evidence of cSNC as experimental animals stayed significantly less in contact with the sipper tube than the control animals when they were downshifted, $F(1, 81) = 12.56$, $p < .001$, partial $\eta^2 = 0.13$. *Post hoc* analyses indicated no differences between experimental and control animals by session four and five of the postshift phase, $ps > .1$.

Since GTT is highly correlated with consumption [24], it is safe to say that under no additional perturbations, animals exposed to 32% sucrose solution had a higher level of consumption than animals exposed to 4% sucrose solution. This differential effect is due to the magnitude of reinforcement. When the experimental group was downshifted from being exposed to a 32% to a 4% sucrose solution, it consumed less than those animals always exposed to a 4% solution. The experimental animals' expectation of a sweeter solution better explains this effect than the magnitude of reinforcement.

Since we sought to identify different profiles of animals to the same situation and found no significant differences across replication, we decided to run a LCGA. This particular technique is highly relevant for longitudinal data based on relatively small samples. Essentially, assuming that each profile explains a subset of individual variances, LCGA identifies a particular number of profiles that is significantly different from having a lower number of profiles and not significantly different than having a greater number. We ran LCGA with the Mplus software to identify different trajectories in the postshift phase (5 sessions). We did not analyze the preshift since we had no interest in the magnitude of reinforcement but the cSNC. Also, because of the size of the sample ($n = 53$), we employed fixed effects in order to reduce the number of parameters. The dependent variable analyzed was GTT and we did not transform it for the purpose of the analysis, since the non transformed data have a better entropy, a good indicator for separating profiles. The analysis compares a model of k profiles with a model of k-1 profiles and determines some indices indicative of a good fit. For the best fit we considered the Bayesian information criteria (BIC), the value and significance of Lo, Mendell and Rubin, the likelihood ratio test (LMR-LRT) statistic, the bootstrap likelihood ratio test (BLRT) and the entropy. To improve the model fit we considered the lowest values in AIC, BIC and BLRT, significant LRT and high entropy (Table 1 shows these values in bold). To avoid or decrease the chance of having non-convergence or local maximum, we fixed the number of random sets of starting values to 500 and the number of final optimizations to 20.

3.2. Identification of profiles

The models with three profiles and four profiles were still possible but the one with two profiles has stronger support (75.5% of animals in profile 1 and 24.5% of animals in profile 2). We considered the two profiles the best model because for small samples, the LMR-LRT test is a good predictive test. Also, the BLRT indicator is slightly smaller with two profiles than three profiles, and a model with three or four profiles would have produced at least one profile with less than 10% of the subjects. Under small samples, a profile with less than 10% of the subjects is probably not correctly identified [25]. Using several indicators is common in this kind of analysis, one example is offered by the study of Papini et al [17] and the study of Galatzer-Levi et al [26]. See Table 1. Both profiles of animals showed significant positive slopes and intercepts. In profile 1 the intercept was 134.56 ($SE = 7.63$, $p < .001$) and the slope 22.75 ($SE = 1.74$, $p < .001$). In profile 2 the intercept was 95.82 ($SE = 6.65$, $p < .001$) and the slope 16.76 ($SE = 3.63$, $p < .001$).

Table 1
Fit indices for 1- to 4-class latent class growth analysis of goal tracking time (s) change in postshift trials following an incentive downshift ($n = 53$).

Fit indices	AIC	BIC	LMR-LRT	BLRT	Entropy
1 class	2692.20	2705.99	–	–	–
2 class	2626.16	2645.86	**66.46, $p = .02$**	**−1339.10, $p < .0001$**	**.87**
3 class	2612.99	**2638.60**	17.69, $p = .16$	−1303.08, $p < .0001$	.84
4 class	**2611.85**	2643.37	6.59, $p = .21$	−1293.49, $p = .13$	.79

AIC = Akaike information criterion; BIC = Bayesian information criterion; LMR-LRT = Lo-Mendel-Rubin Likelihood Ratio Test; BLRT = Bootstrap Likelihood Ratio Test. P-values indicate the significant difference between a model with K class and K – 1 class models. Numbers in bold indicate the best class model according to the fit index.

We decided to divide the GTT of each postshift session by the average GTT of session 9 and 10 of the preshift phase for each animal. This was done in order to compare the response to incentive downshift of the two groups, regardless the level of response in the preshift phase. An ANOVA of data from the postshift using this rate of change yielded a main significant effect of Session, $F(3.22, 257.79) = 58.21$, $p < .001$, partial $\eta^2 = 0.42$, Profile, $F(2, 80) = 39.77$, $p < .001$, partial $\eta^2 = 0.50$, and the interaction Session x Profile, $F(6.45, 257.79) = 7.46$, $p < .001$, partial $\eta^2 = 0.16$. The Bonferroni-adjusted pairwise tests confirmed the pattern observed in Fig. 2: both profiles of animals showed a negative contrast effect but the recovery was faster in animals of profile 1. Both profiles 1 and 2 showed significantly less rate of change in comparison to the 4-4 group in the postshift phase. In the case of profile 2, these differences were detected in all sessions, $p < .001$, and in the case of profile 1 they were observed in all sessions, $p < .001$, except session 5, $p < .2$. On the other hand, animals of profile 1 showed a higher rate of change in comparison to animals of profile 2 in sessions 2–4, $ps < .03$, though there were not differences in the first session of postshift, $p < .71$.

4. Discussion

The statistical solution of the two profiles is partially consistent with Papini's study. Our two profiles are similar to two of the profiles in that study; however, we did not find a third profile as Papini et al. did [17]. The literature on incentive contrast and cSNC offers no support for the existence of a subpopulation of animals that would lack the expression of this phenomenon. Flaherty found two lines of rats psychogenetically selected on the basis of their response in cSNC. They conducted a selection process through seven generations subjected to cSNC (32→4%),

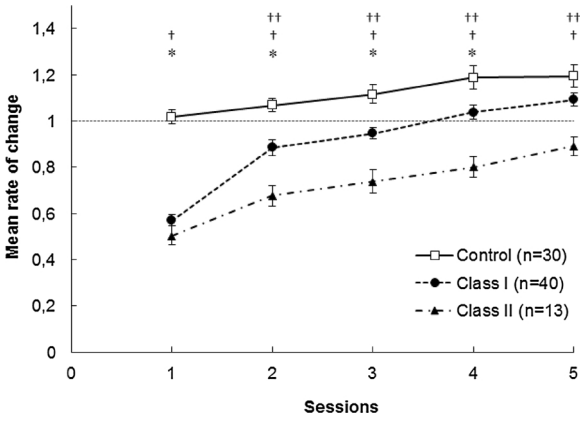

Fig. 2. Mean (± *SEM*) rate of change of the five postshift sessions relative to the last two days of preshift with a 2-profile model, the best solution as indicated by the latent class growth analysis (LCGA). * Indicates statistically significant differences between profile 1 animals and control animals during the postshift; † indicates statistically significant differences between profile 2 animals and control animals during the postshift. †† Indicates statistically significant differences between profile 1 animals and profile 2 animals. GTT: Goal tracking time.

using as a criterion the degree of lick frequency reduction between preshift and postshift for choosing the parents of the next generation. Interestingly, the authors conclude that the selection effect was more pronounced in the direction of high contrast, while in the direction of low contrast the proceedings would have been apparently ineffective. The low contrast animals, even in the F7 generation, did not present a rate of change in their consummatory behavior lower than those of their parental generation [8].

Another source of evidence that fails to support the existence of a third profile comes from studies that analyzed strain differences in cSNC. The cSNC is a robust effect and is present in all the strains previously analyzed [27,28]. Previous studies on strain differences in cSNC show no discrepancies regarding the first response to a reward downshift, even when the comparison was conducted in strains of rats genetically selected on the basis of their extremely divergent anxiety/fear-related responses [29]. For instance, Gomez et al. [30] and Cuenya et al. [31] found no differences when they compared the size of suppression in the first trial of postshift between the inbred strains of Roman High-Avoidance (RHA-I) and Low-Avoidance (RLA-I) rats [32]. These strains show clear behavioral differences in a variety of anxiety/fear tests, with the RLA-I strain being the more anxious [32–35]. The observation of the cSNC phenomena even in the RLA-I rats constitutes an antecedent incongruent with the existence of a subpopulation that naturally does not express the consummatory suppression in situations that involve incentive devaluation. The case against a third profile is also found in the human literature. Recently, Karatzis et al. [36] found two different profiles in people with post-traumatic stress disorder who look for treatment; this study raises the possibility that each profile of typical behavior would also coincide with an abnormal response in some individuals.

One limitation of this study is precisely the small sample we used. This type of analysis usually requires larger samples; however, a similar sample was used by Galatzer-Levi et al to find heterogeneity in the extinction of the fear conditioning response [26], rendering promising results. As they also stated further exploration using larger samples makes additional studies somewhat prohibitive. Our study should be taken with cautions in this respect.

Our report provides evidence against the existence of a third profile. In the three-profile solution just one of many indicators was acceptable, and entropy was lower than when assuming two profiles. In this study one profile indicates a faster recovery to previous levels before the downshift. The second profile had a stronger cSNC and slower recovery that did not allow them to recover their previous levels of response. The two profiles of cSNC that we found are also consistent with other theoretical accounts. McEwen, for example, has proposed that rats develop two principal strategies for coping with stress: one group of animals displays highly energetic coping behaviors, while another group displays more cautious coping behaviors. Reward loss is a stressful situation that requires an appropriate recovery response [37]. All individuals use different strategies to maintain stability through change. As other authors have suggested regarding different profiles of response to stress [38,39], cSNC might cause two different trajectories: one, rapid recovery (resilient), and the other, slow recovery (non resilient).

5. Conclusions

In synthesis, our study suggests, in accordance with other sources of evidence, that incentive downshift provokes two distinctive responses. Both profiles showed an abrupt decrease in the consummatory response to the devaluation of the incentive (negative contrast effect), indicating that individual differences are not expressed in the unconditional response to reward loss (primary frustration). On the contrary, the two profiles showed clear differences regarding recovery expressed in subsequent trials (secondary frustration): while one group of animals expressed a fast recovery, another group expressed a slower recovery.

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