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Using Rescorla-Wagner Modelling to Identify the Relationship Between Autism Spectrum Disorder, Oxytocin, Naltrexone, and Social Motivation

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Theoretical Background

First identified and described by Leo Kanner in 1943, *autism spectrum disorder* (ASD) has since been steadily expanded into the broad spectral condition it is today (American Psychiatric Association, 2013; World Health Organization, 2022). While ASD is considered a complex condition with heterogeneous symptomatology and multiple etiologies (Masi et al., 2017), characterisations of the disorder commonly include four affected core domains: impaired communication, social impairments, and restricted and repetitive behaviours and interests (American Psychiatric Association, 2013; Masi et al., 2017; World Health Organization, 2022). The *social motivation hypothesis* of autism (SMH) assumes that the social deficits those with ASD experience are a developmental downstream consequence of a lack of social motivation (Clements et al., 2018; Stavropoulos & Carver, 2013). Due to experiencing social situations as less intrinsically rewarding, those with ASD exhibit less social seeking and approaching behaviour and thus do not acquire typically developed social functioning during development (Scott-Van Zeeland et al., 2010). As a consequence, the lack of social motivation further disrupts social orienting, social reward, and social maintaining behaviours (Chevallier et al., 2012).

This developmental perspective on social deficits has attracted the attention of multiple other sub-fields of autism research, employing neurocognitive imaging measures (Clements et al., 2018), genetic studies (Loparo & Waldman, 2014), and animal models (Dal Monte et al., 2017; Dichter et al., 2012; Gigliucci et al., 2014; Peñagarikano et al., 2015). In this context, several pharmacological measures have been used to scrutinise the differences in social reward processing between those with ASD and neurotypical controls. The neurotransmitter dopamine has been investigated due to its implication in the human reward system (Schultz, 1998), while the neuropeptide arginine vasopressin has been investigated for its effect on adult bonding behaviour (Gordon et al., 2011). The

neuropeptide *oxytocin* (OXT), primarily synthesised in the hypothalamus and structurally very similar to arginine vasopressin (Gordon et al., 2011; Insel et al., 1999), is currently the most prominent neural substrate in this line of research (Stavropoulos & Carver, 2013).

OXT has previously been found to modulate social behaviours, such as the detection and recognition of emotions (Di Simplicio et al., 2009; Domes et al., 2007; Marsh et al., 2010; Schulze et al., 2011), bonding behaviour (Feldman, 2012), and social memory (Guastella et al., 2008; Rimmele et al., 2009; Savaskan et al., 2008). Furthermore, the administration of exogenous OXT has been shown to increase trusting behaviour (Baumgartner et al., 2008; Kosfeld et al., 2005; Mikolajczak et al., 2010). Most importantly for the present study, OXT has been tied to the social reward pathways in the human brain (Baskerville & Douglas, 2010), and increases the effects of social reinforcement on learning (Hu et al., 2015; Hurlemann et al., 2010; Zhuang et al., 2021).

Research Gap

Although OXT administration shows promising effects in the social domain, no comprehensive treatment regiment for the social deficits of ASD using OXT currently exists (Chevallier et al., 2012; Guastella & Hickie, 2016; Stavropoulos & Carver, 2013). Still, there have been studies aimed at examining the effects of OXT on ASD specifically. Beyond animal models of autism (Gigliucci et al., 2014; Peñagarikano et al., 2015), research on ASD in humans has shown that OXT improved emotion recognition (Aoki et al., 2014; Guastella et al., 2010), processing of social cues (Andari et al., 2010; Hollander et al., 2007), social orientation (Lin et al., 2014), and facilitated social learning (Andari et al., 2010). Additionally, OXT is poised to enhance social reinforcement learning performance in ASD (Kruppa et al., 2019).

However, given the complexity of the neuro-chemical interplay that occurs in the brain, OXT does not unfold its effect in isolation; in its modulatory effects on social behaviours, it is highly interactive with the previously mentioned arginine vasopressin (Gordon et al., 2011) and dopamine systems (Baskerville & Douglas, 2010). Similarly, and

unlike vasopressin levels, OXT levels vary based on *opioid* (OP) levels (Bicknell & Leng, 1982). Specifically, OP inhibits the synthesis of OXT, while OP antagonists promote endogenous OXT release (Bicknell & Leng, 1982; Fan et al., 2020). One such OP antagonist is *naltrexone* (NAL), which is structurally and functionally very similar to the naloxone used in Bicknell and Leng (1982), however it possesses a longer half-life at 3.5 hours and significantly longer receptor occupancy (Gonzalez & Brogden, 1988; Krieter et al., 2019). This bidirectional interaction lays the groundwork for a combinatorial psychopharmacological approach where the pharmacological enhancements to exogenous OXT-mediated social motivation are further improved by exogenous NAL, facilitating the secretion of endogenous OXT (Dal Monte et al., 2017; Fan et al., 2020; Gigliucci et al., 2014).

Research Question

This interactionistic notion leads to the goal of the present study: to investigate the effects of the combined application of OXT and NAL on social motivation. The task devised to capture the combined effect of OXT and NAL is a probabilistic *reinforcement association learning task* (RALT). In this social reinforcement learning paradigm, subjects are to learn the association between target stimuli and subsequent feedback presentation constituting the reward component (Daw, 2011; Sutton & Barto, 2018; Zhang et al., 2020). These subjects are members of the clinical ASD population and a neurotypical control group. Considering that the clinical sample is stratified along the severity of the condition, only high-functioning individuals will be considered for the study (for details, see **Participants**). Importantly for the present design, it is not the learning target stimulus that is social; it is the provided reinforcer (*social reward*). The availability of OXT will be experimentally manipulated via an acute single-dose intranasal administration before any learning occurs. OP availability will be experimentally manipulated in the same manner via a pill of NAL, occurring concurrently to the OXT manipulation. The effect of both medications is temporary, subsiding within hours after administration.

Since the trial-by-trial data generated by the RALT is unsuited to be analysed using ordinary summary statistics or generalised linear modelling, computational reinforcement learning modelling will be used to fit mathematical models to the exhibited learning behaviour (Daw, 2011). The supposed differences in social motivation will then be investigated by comparing these models, allowing for a quantification of a complex cognitive process. The main benefit of this choice-option value-based approach is that computational modelling allows for greater exploitation of the data than ordinary summary statistics, providing a more fine-grained picture of the subjects' association formation (Daw, 2011). Should the combined application of the medications improve social reward processing by acting as a biological facilitator as shown via changes in social learning (i.e. modifying one's behaviour based on social feedback, acquisition of cognitive stimulus-reward associations), inferences on differences in social motivation should become examinable.

Hypotheses

Taking into account the previously detailed theoretical background and the devised task design, it is hypothesised that

- H1a: In neurotypical subjects, the combined application of OXT and NAL will improve learning in the social condition of the RALT.
- H1b: In neurotypical subjects, the effect of a combined application will be greater than the added effects of OXT or NAL alone.
- H2a: In autistic subjects, the combined application of OXT and NAL will improve learning in the social condition of the RALT.
- H2b: In autistic subjects, the effect of a combined application will be greater than the added effects of OXT or NAL alone.
- H3: Neurotypical subjects will exhibit greater learning in the social condition of the RALT than autistic subjects.

Methods

Study Design

In order to investigate the hypotheses postulated above, a pharmacological study following a double-blind, within-subject design was conducted. This means that participants, either members of the ASD group or the healthy control group, were tested four times over the span of eight weeks, with each experimental session under different pharmacological conditions (NAL/OXT; NAL/PLA; PLA/OXT; PLA/PLA). As a consequence, the participants also received two sham-medications in the PLA/PLA sessions to adhere to the double-blind design. The span of two weeks between experimental sessions was chosen to account for the flush-out time of the medication and to minimize learning- or carryover-effects (Krieter et al., 2019; Roy et al., 2015).

The time of day the study was conducted varied based on subject availability, with the earliest three-hour long sessions starting at 9 am and the latest ending at 8 pm. Testing was carried out one-on-one with the subjects, experimenters were matched to participant's gender as per standard procedure. The methods and analysis detailed in this thesis are part of a larger study which focuses on the effect of NAL and OXT on social attention and social motivation, both on humans in general and on ASD. The overarching project was approved by the Ethic committee of the Medical University of Vienna (EK Nr. 1393/2017).

Participants

Potential participants to the study were recruited via various means, including online recruitment on different platforms and recruitment based on a list of previously known test subjects. They received monetary compensation for their contribution to the study, totalling to 30 € per experimental session with a one-time 20 € drug administration bonus. To partake in the study, potential subjects had to fit the following inclusion criteria: aged 18 to 65; possession of a diagnosis from the autism spectrum as high functioning (ASD group only; affirmed by reaching an IQ of at least 70 in an intelligence screening); completion of an online pre-screening; no drug or alcohol addiction; no regular drug use.

Table 1

Demographic Data.

Characteristic	Mean (ASD)	SD (ASD)	Mean (CTRL)	SD (CTRL)	p	t-Statistic
Age	34.95	13.31	28.92	10.36	0.03	2.24
IQ	111.77	18.18	107.40	10.69	0.20	1.30
AQ	23.61	6.31	9.39	4.35	0.00	10.06

Note. N = 79, 39 women.

Failure to adhere to these criteria would result in exclusion from the study. Additionally, being able to read Japanese would also bar potential subjects from participating.

Members of the control group were matched to the members of the ASD group based on age, sex, and intelligence. As previously established, this thesis is part of a larger project; as such, not all of the listed inclusion criteria are immediately relevant to the detailed task and analytic approach. Similarly, sample size calculations were also conducted with the whole study in mind, which resulted in a call for 33 participants per group, or 66 subjects total (assuming f = 0.3; $\beta = 0.2$; $\alpha = 0.05$).

As shown in Table 1, the sample consisted of 56 healthy control subjects (age range 18 to 70) and 40 subjects diagnosed with ASD (age range 18 to 65). Due to several factors (such as participants dropping out of the study after one or more experimental sessions or insufficient data quality) 17 subjects were not included in the data analysis, resulting in an effective sample of 40 controls (mean age = 28.92, SD = 10.36; mean IQ = 107.40, SD = 10.69; mean AQ = 9.39, SD = 4.35; 16 women) and 39 subjects with ASD (mean age = 34.95, SD = 13.31; mean IQ = 111.77, SD = 18.18; mean AQ = 23.61, SD = 6.31; 23 women). Members of the ASD group scored significantly higher in the administered autism-quotient screening questionnaire than the control group ($\Delta M = 14.21$, 95% CI

$[11.37, 17.06]$, $t(46.77) = 10.06$, $p < .001$) (Freitag et al., 2007), confirming group heterogeneity. This sample partook in a combined total of 258 experimental sessions.

Material

Medication

In each of their experimental sessions, subjects received different combinations of medication. A dose of 50mg of NAL was ingested orally in the form of a pill, while its corresponding placebo was an orally ingested pill containing 65mg of mannitol. OXT was administered via a nasal spray using a nebuliser, where one dose equalled 10 international units. Its placebo counterpart was administered in the same way in the form of a nebulised saline solution. Notably, participants also received both placebos in the sham-condition to uphold the double-blind design.

Stimuli

The main task was presented to the participants on a laptop screen (1920 by 1080p; 13 inches diagonal), where they gave their responses using an external computer mouse or the laptop's integrated trackpad by moving a slider bar on screen. No further inputs were necessary. Two pairs of Japanese kanji served as the associative learning targets in the task. Parts of the video feedback participants received after completing a trial was sourced from the Amsterdam Dynamic Facial Expressions Set (van der Schalk et al., 2011); four models were chosen (two female, two male), each with three videos displaying dynamic expressions of emotion (neutral, joy, anger). The remaining video feedback, colourful, shifting mandalas, were specifically designed for the present study. The utilisation of these materials is detailed below.

Procedure

Before any testing was done, participants gave their informed consent regarding the study, and were notified of the potential adverse effects of OXT and NAL. In the first of their testing sessions, all subjects completed short screening tests for intelligence (IQ) and

autism-spectrum-quotient AQ (Freitag et al., 2007). All sessions featured additional screenings for current mood and menstrual cycle, where applicable. Since this thesis is part of a larger project, experimental sessions also included testing that is not immediately relevant to the present research questions. These other tasks include an eyetracked semi-structured interview, aimed to investigate social attention and social motivation via fixations on specific face regions, and a music curiosity task, which attempts to utilise the experimental paradigm to shed light on interest in new and unfamiliar musical stimuli. Task order was balanced across participants. Experimental sessions included ample time for the medication to take effect.

In order to assess the learning performance under different psychopharmacological conditions, a RALT specifically designed for this study was employed (a slightly different, but functionally equivalent version of the task was previously validated on a neurotypical sample). In the task, participants were instructed to indicate on a marked slider which one of two abstract-symbol choice options (Japanese kanji) they believed to represent a specified phrase; depending on the experimental condition (social; non-social), the symbols were associated with different phrases. The response slider featured a continuous 5-point scale, with potential responses ranging from *definitely left* to *definitely right*, with a central neutral option.

In the social condition, the "correct" choice option would signify praise to be given to a person depicted on the screen, while the incorrect option would be taken as an insult by the presented person. In the non-social condition, the choice options corresponded to a "Start" and "Stop" command given to a depicted mandala. If the participant gave a correct answer in a trial, they would receive positive feedback in the form of the person on screen smiling at them in the social condition (social reward), and the mandala spinning and changing colours in the non-social condition (non-social reward). Conversely, the person would express anger, and the mandala would lose colour and stop moving in the case of an incorrect choice. The task display is depicted in Figure 1. All instructions were

given in German.

In either case, the feedback delivery followed a probabilistic association unknown to the participants. In 75% of cases, a correct choice would also be followed by positive feedback (congruent feedback); in the remaining 25% of cases, a correct choice would be followed by negative feedback (incongruent feedback). This design decision was necessary to accommodate for the amount of choice options per trial in order to retain participant interest and prevent subjects from "solving" the task, thus limiting the effectiveness of the trial-by-trial data. Additionally, the available choice options occasionally switched positions to prevent participants from acquiring simple motor associations instead of the desired cognitive reinforcement learning. Consequently, participants had to learn the associations between choice options and feedback through trial and error, where response behaviour is expected to begin at chance level, and subsequently increase over the following trials.

The task comprised two blocks of each experimental condition, each consisting of 24 trials for a total of 96 trials. Participants were given the option to complete training trials to familiarize themselves with the task setup. Blocks were presented in alternating order, where the first experimental condition was pseudo-randomly selected each session.

Data Analysis

Reinforcement Learning Modelling

To investigate the behavioural choice data on a trial-by-trial basis, a Rescorla-Wagner reinforcement learning modelling approach was chosen (Rescorla & Wagner, 1972). This modelling approach assumes error-based learning and is particularly suited for the present data, since it can reliably model choice behaviour with comparatively few free parameters (Daw, 2011; Kording et al., 2018). Additionally, it is not necessary for this analysis to explain the behavioural data, the model is merely required to give a descriptive summary of the dynamic learning process (Kording et al., 2018; Wilson & Collins, 2019).

To calculate the internal value of a choice option V that an agent holds for a trial t,

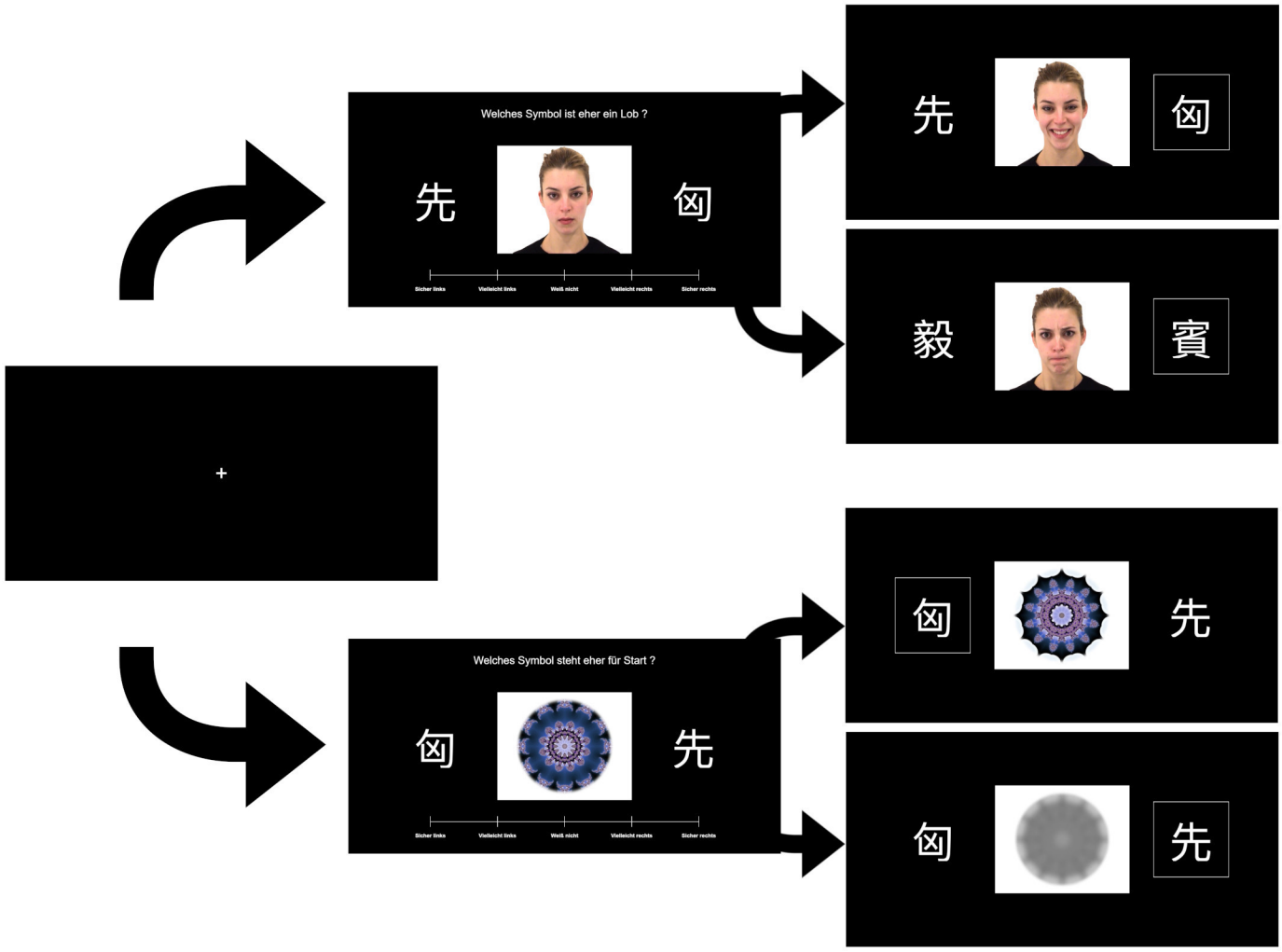

Figure 1

The Structure of the RALT. After a short fixation period, subjects are presented a trial based on the current condition (social/non-social). For each trial, they receive positive feedback (reward) or negative feedback, based on their response and the reward schedule.

Rescorla-Wagner modelling relies on a learning rate α and the prediction error PE, which is derived from the difference between the last actual outcome and its expected value (commonly referred to as *expectation* and *expectation violation*). These two components then modify, or update, the value of an option based on its last value in the previous trial V_{t-1}. Since the task at hand offers two choice options, both options are assumed to be equally attractive in the first trial of each block. When expressed mathematically, this means that the initial internal value of each option is assumed to be 0.5, which then wavers across the following trials. Another consequence of presenting subjects with two choice options is that only one equation can express the internal value of both options, since the value of the secondary option equals 1 minus the value of the primary option. When a reward is received, the value of the corresponding choice option increases.

$$V_t = V_{t-1} + \alpha \times PE$$

In this particular modelling approach, the learning rate α is assumed to be constant across trials. Consequently, a model calculated for a particular subject who received a certain medication and performed one of the conditions of the task will feature exactly one learning rate. This parameter is bounded between 0 and 1, and serves as a weight for the prediction error (Zhang et al., 2020). As such, a high learning rate does not necessitate faster or "better", learning; it merely indicates the extent to which the prediction error updates the value of that choice option (Wilson & Collins, 2019; Zhang et al., 2020).

Model-Independent Analysis

The presently used RALT aims to quantify learning behaviour via an observed increase in the amount of correctly solved trials. To confirm that learning occurred across trials and to ensure task fidelity, a secondary, model-independent analysis was conducted. Trials belonging to one experimental condition were aggregated separately for each experimental session, and the percentage of correct responses for each aggregated set of trials was calculated. Values were then averaged across groups, medications, and

conditions. A Python-script was specifically written to summarise the data. This approach is more akin to summary statistics, but technically no statistical analysis was done. Neither does it make use of the data on a trial-by-trial basis, like the Rescorla-Wagner model. Seen as the model-independent data analysis merely serves as a control measure to ensure task fidelity, it is not meant to produce interpretable results.

Repeated Measures ANOVA

Data preparation and preprocessing was handled in R Studio (version 4.3.0, R Core Team, 2023), while the modelling was done in Python. This includes the estimation of all parameters necessary to construct a Rescorla-Wagner model. As previously established, these mathematical models are merely observational; their goal is not to produce clinically relevant insights or to train an artificial agent to learn the exhibited choice behaviours, but to estimate parameters to identify and quantify meaningful differences between groups, medications, and conditions. As such, the analysis does not end with the model estimation. To identify meaningful differences and answer the research question, a repeated measures ANOVA was performed on the dependent variable of the modelled *learning rates*. The administered *Medication* and experimental task *Conditions* served as factors, while the *Group* denoted the between-subject factor. Calculations were done in R (R Core Team, 2023) using the *afex* package (version 1.3-1, Singman et al., 2024). The results of this approach are detailed below.

Results

Reinforcement Learning Modelling

In total, 608 sets of model parameters were calculated for the participating sample. One such model is based on the information of the subject and their respective group, the medication they received, and the experimental condition of the task they performed. This $2 \times 4 \times 2$ design results in eight models per subject, 288 models for the ASD group, and 320 models for the control group. Histograms depicting the distribution of the learning rate for different factor combinations of *Group* and *Medication* can be found in the

Table 2

Learning Rates by Medication and Condition for ASD Group.

Medication	Mean Social	SD Social	Mean Non-social	SD Non-social
NAL.OXT	0.25	0.33	0.20	0.20
NAL.PLA	0.23	0.27	0.20	0.23
PLA.OXT	0.29	0.32	0.25	0.35
PLA.PLA	0.21	0.29	0.26	0.32

Appendix, the relevance of which will be discussed later.

Models were fit based on a maximum-likelihood approach using a negative log-likelihood function (Wilson & Collins, 2019). As an additional measure for model comparison and selection, the *Bayes Information Criterion* was consulted to ensure appropriate model fitting (Daw, 2011; Wilson & Collins, 2019). Missing parameter values were imputed based on the values of their respective subgroups (Medication; Condition) via a classification and regression tree algorithm, which respected all parameter characteristics. Overall, 152 sets of parameters had to be imputed; this was almost entirely due to participants dropping out of the study prematurely. Missing data was handled under the assumption that data was missing at random, i.e. not systematic. While this can be seen as a potential limitation to the analytical approach, the assumption is based on the fact that subjects were not aware of which medications they would be receiving during experimental sessions due to the double-blind design. Details on the generated parameters can be found in Tables 2 and 3, as well as Figures 2 and 3.

Model-Independent Analysis

The depiction of the results of this superficial analysis indicates a clear increase in the percentage of correct responses over trials, well above chance-level. Put differently, the model-free analysis shows patterns of learning behaviour, indicating that the RALT

Table 3

Learning Rates by Medication and Condition for CTRL Group.

Medication	Mean Social	SD Social	Mean Non-social	SD Non-social
NAL.OXT	0.23	0.31	0.23	0.30
NAL.PLA	0.25	0.32	0.22	0.30
PLA.OXT	0.22	0.26	0.24	0.31
PLA.PLA	0.25	0.26	0.32	0.34

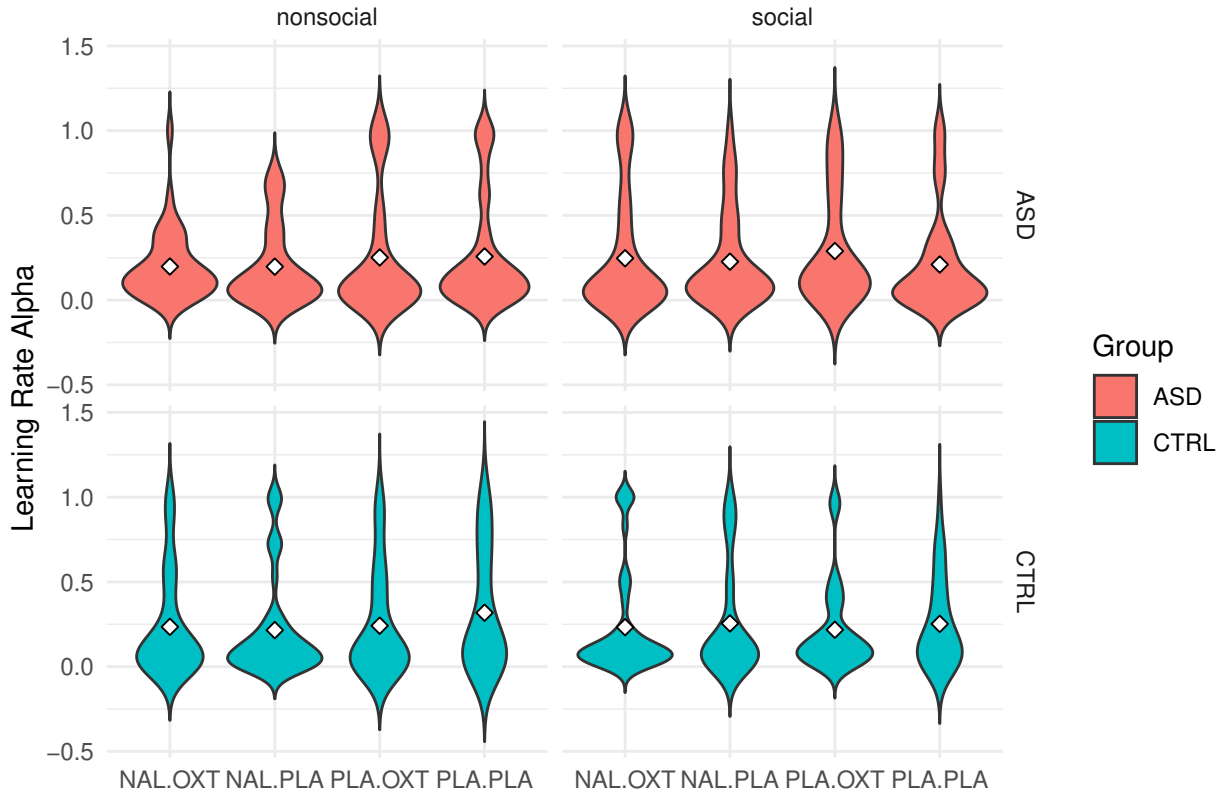

Figure 2

Violin Plot of the Learning Rate Distribution.

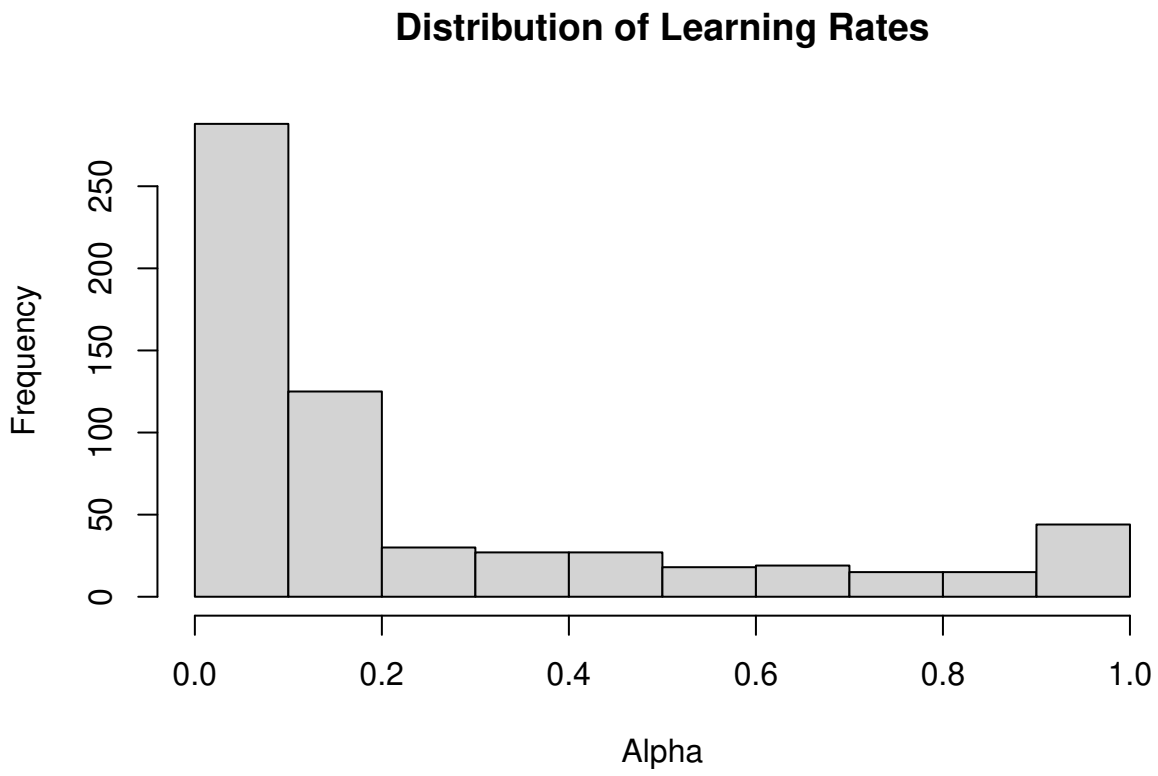

Figure 3

Histogram of the Learning Rate Distribution, n = 608

engages the targeted cognitive process and is thus valid. One should note that this approach was not pursued further to not stray too far from the original intent of the design. Additionally, the mere presence of learning behaviour is not sufficient to show significant differences between groups, medications, or conditions; neither is it supposed to. A more detailed visualisation than the one in Figure 4 can be found in the **Appendix**.

Repeated Measures ANOVA

The repeated measures ANOVA conducted on the data generated in the modelling approach yielded no significant results. There were no significant differences between groups ($F(1, 74) = 0.10$, $p = .753$, $\hat{\eta}^2_G = .000$, 90% CI [.000, .024]), combinations of medications ($F(2.77, 204.90) = 0.58$, $p = .614$, $\hat{\eta}^2_G = .003$, 90% CI [.000, .006]), or

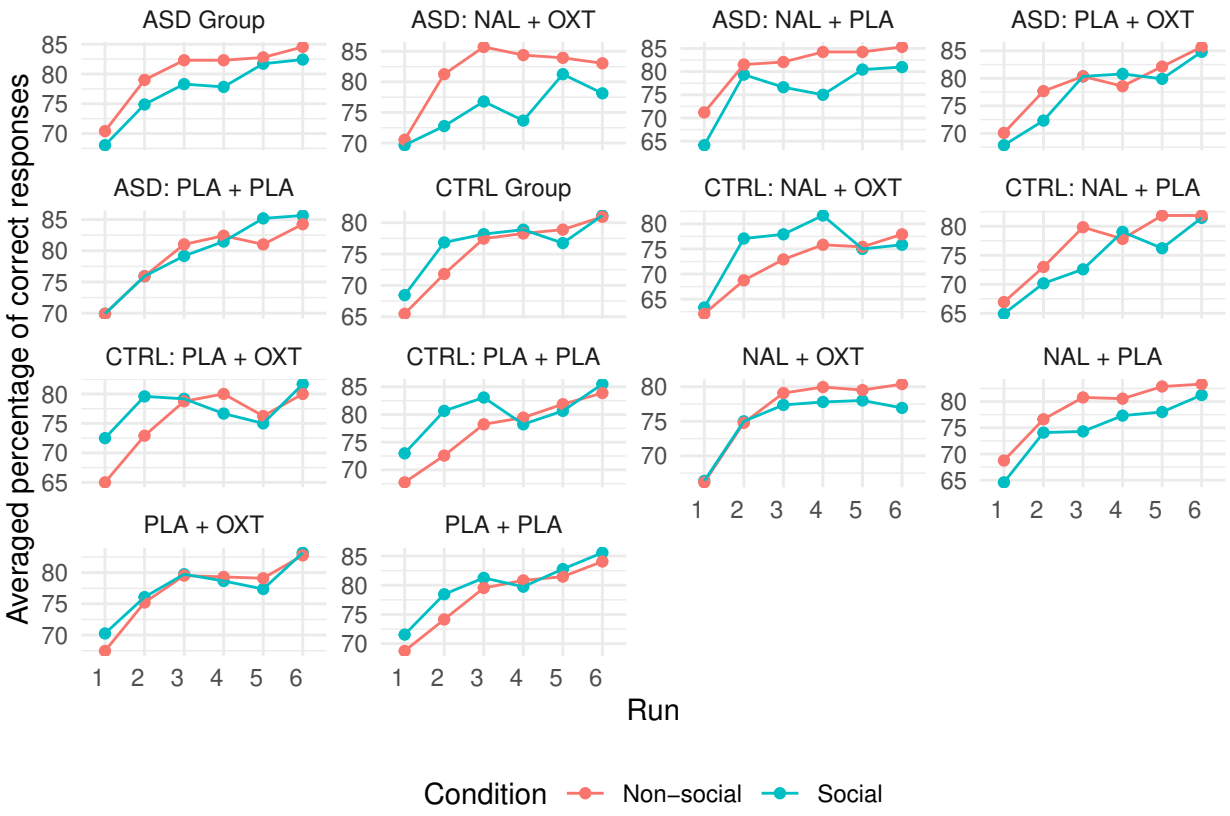

Figure 4

Results of the Model-Independent Analysis for Different Groups and Group × Medication interactions. Trials were aggregated into runs and then averaged across subjects. An increase in correct responses over time indicates learning behaviour.

experimental conditions ($F(1, 74) = 0.01$, $p = .915$, $\hat{\eta}^2_G = .000$, 90% CI [.000, .000]). Similarly, the *Group* × *Medication* ($F(2.77, 204.90) = 0.74$, $p = .518$, $\hat{\eta}^2_G = .003$, 90% CI [.000, .010]) and the *Group* × *Condition* ($F(1, 74) = 0.65$, $p = .424$, $\hat{\eta}^2_G = .001$, 90% CI [.000, .034]) interactions were not significant. The same is true for the *Medication* × *Condition* interaction ($F(2.40, 177.90) = 0.79$, $p = .475$, $\hat{\eta}^2_G = .004$, 90% CI [.000, .008]), and the three-way *Group* × *Medication* × *Condition* interaction ($F(2.40, 177.90) = 0.13$, $p = .914$, $\hat{\eta}^2_G = .001$, 90% CI [.000, .000]). Unsurprisingly, none of the subsequently calculated post-hoc tests were significant as well. These results completely contrast the assumptions made in the hypotheses, the consequences of which

will be discussed below.

Discussion

The present study aimed to shed light on the complex relationship between NAL, OXT, social motivation, and ASD. To do so, a RALT was conducted under separate pharmacological conditions on two groups to assess differences in learning performance. Rescorla-Wagner reinforcement learning models were calculated based on the performance, the learning rate parameter alpha was then used as the dependent variable to conduct a repeated measures ANOVA.

The present approach's strength lies in its inherently multi-disciplined nature; hypotheses derived from a neurobiological viewpoint are tested on a clinical sample using aspects of clinical psychology, cognitive neuroscience, psychopharmacology, and computational behavioural modelling. This multifaceted strategy allows for the investigation of the association between social motivation and ASD using social reinforcement learning. A major benefit of the used RALT is that the feedback delivery in *both* experimental conditions occurred in the same domain via short videos, making for a more valid comparison between experimental conditions.

The results of the previously detailed analytical approach provided no significant results in any metric or examined contrast, implying that there is no meaningful relationship between NAL, OXT, social motivation, and ASD. A potential interaction between NAL and OXT is not discernible from these results. Likewise, the two groups do not exhibit differing learning behaviour, regardless of administered medication or the type of feedback delivery of the experimental condition. This finding serves as the basis of the assumption that subjects with ASD and neurotypical controls are affected by social motivation in the same way. Seen as the present design is a laboratory study, the external validity, or generalisability of these findings to the ASD populations, is limited at best. The fact that the study represents basic research also bars any clinically relevant interpretations. As such, there is little practical relevance for the presented results.

Alternative Explanations for the Present Findings

While the reported results starkly contrast the postulated hypotheses and aforementioned previous research findings in the context of the SMH (Dal Monte et al., 2017; Fan et al., 2020; Hurlemann et al., 2010; Kruppa et al., 2019), there are still multiple alternative explanations for this outcome that are left open to discussion. Crucially, these explanations do not mean to imply that there are undiscovered causal pathways or alternative mechanisms at work. They specifically aim to provide a deeper insight into the reinforcement learning modelling at hand, and the interpretation thereof.

The conducted statistical analysis of the model parameters provided no significant results. When inspecting the histogram depicting the learning rate distribution in Figure 3, a skewness with data points clustering towards 0 becomes apparent (histograms for different factor combinations are depicted in the **Appendix**). A learning rate of 0 implies that during value updating, very little attention is paid to the prediction error, or that participants do not consider the result of the previous trial. This does not mean that no learning occurred in these cases; moreover, neither does it immediately prompt outlier exclusion, since a learning rate of or around 0 is still an interpretable parameter that potentially provides valuable insights. So, while learning did discernibly occur as shown in the model-independent analysis, and the chosen model is capable of depicting said learning (as shown in the **Theoretical Background**), it was unable to generate stable and heterogeneous parameters.

A potential explanation for this outcome is that the model lacked the necessary amount of data to produce satisfactory parameters. Specifically, the amount of trial data per model is of interest here, not the number of total models estimated. Generally speaking, computational models are only ever as good as the data they are based on (Wilson & Collins, 2019). So even if a computational model is perfectly appropriate to the given data, and the analysis works flawlessly, the whole approach still stands and falls with the quality of the trial data. All things considered, the current situation points to the trial

data component as the weakest link of this chain. Fortunately, there are several ways to tackle this problem and solidify parameter estimation.

Adressing the Alternative Explanations

The easiest way to generate more evenly distributed parameters is to increase the amount of data fed into the model. This, however, is not as easy as simply increasing the number of trials to be used as input, as will be shown below. Similarly, it is unlikely that the generated results are due to a lack of statistical power; the sample size even exceeded the one called for in the design phase, and can be considered as adequate. Furthermore, adapting a modified version of the RALT might provide more serviceable model data.

Adapting the Model

One could increase model stability by aggregating more trials into its calculation. However, depending on the axis of this aggregation, several problems are likely to arise. When aggregating trials across subjects, the internal validity of the design becomes a major concern; additionally, the study does not aim to reconstruct the choice behaviour of singular subjects. The goal is to show discernible differences between medications, conditions, and groups. As such, this approach would not yield constructive results. Should one instead try to aggregate data across experimental sessions, model validity will be threatened. Using all 96 trials of the four blocks in the RALT as input for a single model will confront the Rescorla-Wagner-approach with an issue it cannot account for: Since each block contains a different set of associations to be acquired, the value of both choice options is expected to normalise to 0.5 for each first trial per block (and then increase or decrease based on condition circumstances). As the model cannot account for the presence of new associations in the data, this approach will do more harm than good for parameter calculation.

Adapting the Task

If instead one aims to collect data using a slightly modified version of the RALT, they should not mistakenly assume that model validity can be achieved by increasing the

number of trials in each block. While increasing the number of trials per block from the current 24 will yield more data for parameter estimation, the quality of the additionally gathered data will be questionable at best. The reason for this is that more trials do not necessarily mean that subjects will have more time to exhibit learning behaviour. Instead, one risks that participants grow bored of the task in the face of only two choice alternatives, or even solve the task (always choosing the correct option, even when presented with incongruent feedback). These potential ceiling effects in response behaviour are not indicative of learning and negatively influence the parameter estimation.

A more fruitful modification to the design of the RALT would be to increase the amount of choice options presented to the subject. Since there are now more associations to be learned between target stimuli and feedback, the number of trials per block can easily be increased, as long as close attention is paid to the ratio of trials and options. While this would make the Rescorla-Wagner-model more complex, this should not pose a problem for the analysis since the model is able to consider the internal value of multiple choice options with few free parameters and a single learning rate (Rescorla & Wagner, 1972; Sutton & Barto, 2018; Zhang et al., 2020).

Limitations

In its current form, the administered RALT has two potentially concerning issues. Firstly, participants might not perceive the positive feedback of a colourful mandala in the non-social condition as rewarding, threatening the aspect of motivation in the design. This potential imbalance of rewards is mediated by the assumption that subjects perceive successfully completing a trial as rewarding, but should be addressed in a future version of the task. Secondly, even though subjects gave their responses on an incrementally marked slider, their answers were only coded as *correct* and *incorrect*. This signifies a loss of information, and does not represent the original intent of the participants during data acquisition; even unsure answers in the middle of the slider were scored as the extremes of either *correct* or *incorrect*. Future designs should either modify the slider response or how

continuous responses flow into the computational modelling.

As for the reinforcement learning modelling, each model was fitted with a specific combination of medication and condition in mind, even though each experimental condition consisted of two blocks where different associations were learned. While this is not optimal, as touched upon above, this step proved necessary to provide the modelling algorithm with enough data points to function properly. Keeping the blocks separate, i.e. calculating twice the number of models, would have harmed parameter estimation further. A future modelling approach would have to pay close attention to the allocation of trials to different learning models.

Lastly, one might question the validity of the repeated measures ANOVA conducted on the learning rates, since the parameters are so decidedly skewed. In addition to the violation of the distribution assumption, the parameters serving as the dependent variable are also bounded (between 0 and 1, see **Data Analysis**). However, in this particular case and as argued above, this should not considerably amount to the insignificant results. As detailed, the ANOVA could not produce significant results based on homogeneous data, which in turn is likely due to insufficient trial data. Still, future analyses should consider additional measures to quantify differences between groups, medications, and experimental conditions, such as computational modelling comparison measures (Wilson & Collins, 2019).

Conclusion and Future Research

While the present study was not able to establish a relevant relationship between groups, pharmacological, and experimental condition, there is reason to believe that a slightly modified version of the approach could highlight these supposed differences. Apart from updating the study design to remedy its current limitations, there are also other exciting prospects for this field of research. There is still a great lack of insight into the effects of intranasally administered OXT on social cognition, as well as the proper dosage of the neuromodulator (Guastella et al., 2013). Similarly, there is still much research to be

done on social reinforcement learning in ASD, both in high functioning individuals and those with more severe cases of the disorder (Schuetze et al., 2017). Even the data from the present study still has room for reinterpretation. For example, an exploratory analysis of a pooled Rescorla-Wagner-modelling approach could highlight superficial differences between factors of the design. One such model would comprise of the trial data of one group, a pharmacological condition, and an experimental condition (e.g. ASD; NAL, OXT; social condition). In this case, summary statistics would not suffice for the analysis; instead, model comparison measures would be necessary.

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Appendix A

Abstracts

English Abstract

Autism spectrum disorder is a clinical condition associated with social impairments. The *social motivation hypothesis* of autism assumes these deficits to develop as a consequence of a lack of social motivation. The neuropeptide *oxytocin* has been shown to modulate social behaviour, while the opioid antagonist *naltrexone* has been shown to interact with the oxytocinergic system. The present study investigates the combined effect of oxytocin and naltrexone on social motivation in both autistic and healthy subjects. A socially reinforced learning task is used to monitor changes in social motivation under the effect of the drugs. Computational reinforcement learning modelling is used to analyse the data on a trial-by-trial basis. The analysis of the generated models shows no significant main effects, implying that oxytocin and naltrexone have no effect on social motivation. Several reasons for these results are discussed, pointing towards the trial data as the weakest point of the present design.

German Abstract

Autismus-Spektrum-Störung ist eine klinische Bedingung, die mit sozialen Beeinträchtigungen verbunden ist. Die *Soziale Motivationstheorie* des Autismus geht davon aus, dass sich diese Defizite als Folge eines Mangels an sozialer Motivation entwickeln. Das Neuropeptid *Oxytocin* hat sich als Modulator sozialen Verhaltens erwiesen, während gezeigt wurde, dass der Opioidantagonist *Naltrexon* mit dem oxytocinergen System interagiert. Die vorliegende Studie untersucht die kombinierte Wirkung von Oxytocin und Naltrexon auf die soziale Motivation, sowohl bei autistischen als auch bei gesunden Probanden. Eine sozial-verstärkte Lernaufgabe wird verwendet, um Veränderungen der sozialen Motivation unter dem Einfluss der Medikamente zu überwachen. Ein computergestütztes Verstärkungslernmodell wird verwendet, um die Daten auf trial-by-trial-Basis zu analysieren. Die Analyse der generierten Modelle zeigt keine signifikanten Haupteffekte, was impliziert, dass Oxytocin und Naltrexon keine Wirkung auf die soziale Motivation haben. Mehrere Gründe für diese Ergebnisse werden diskutiert, wobei auf die Versuchsdaten als schwächstes Glied des vorliegenden Designs hingewiesen wird.

Appendix B

Supplementary Materials

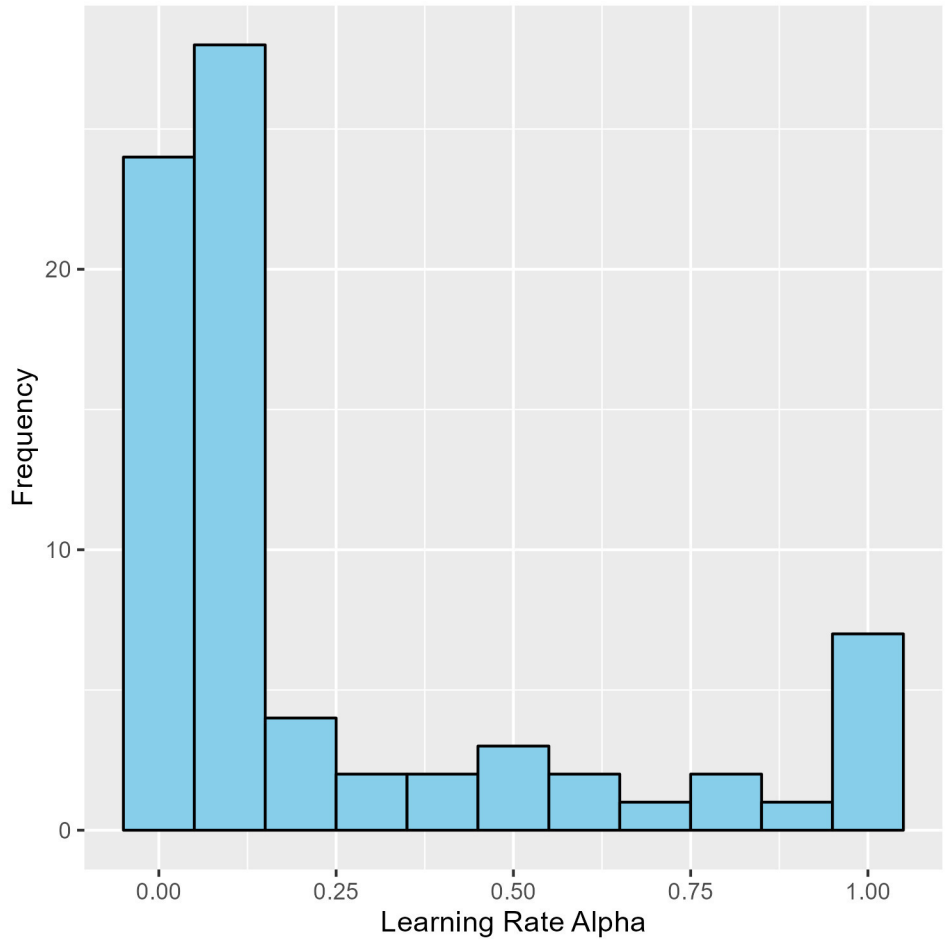

Figure B1

Histogram depicting the Learning Rate Distribution for the NAL.OXT × Social interaction.

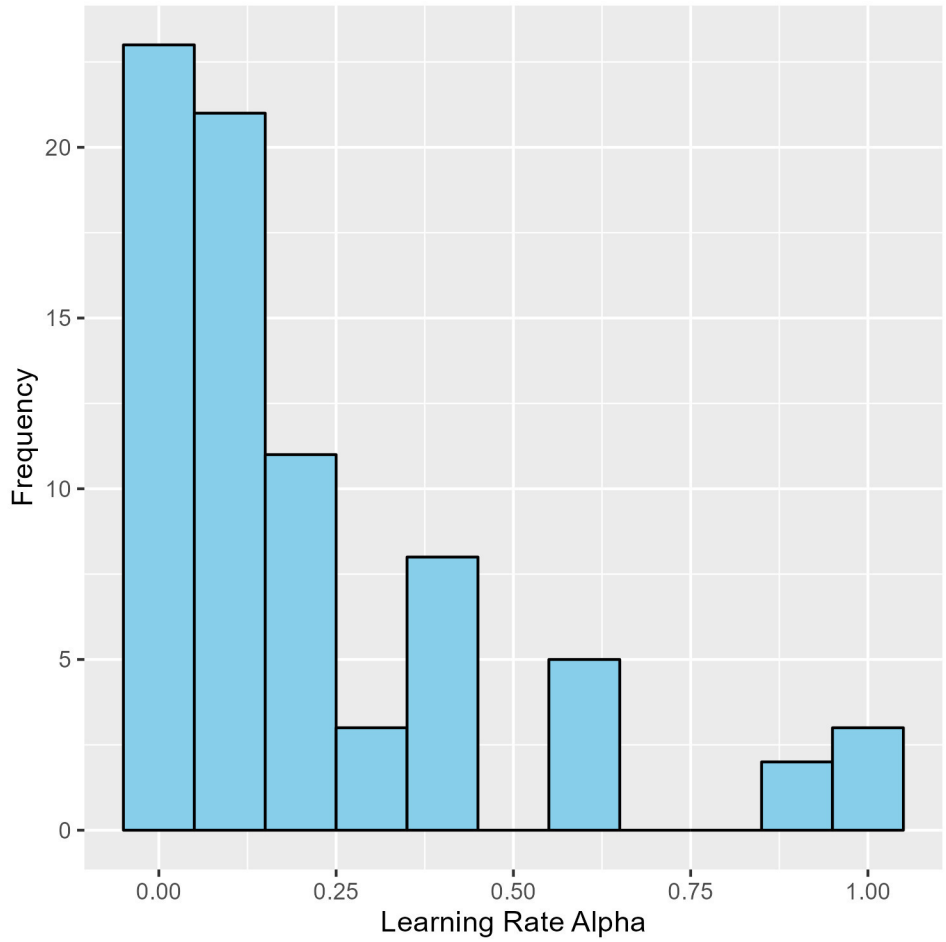

Figure B2

Histogram depicting the Learning Rate Distribution for the NAL.OXT × Non-social interaction.

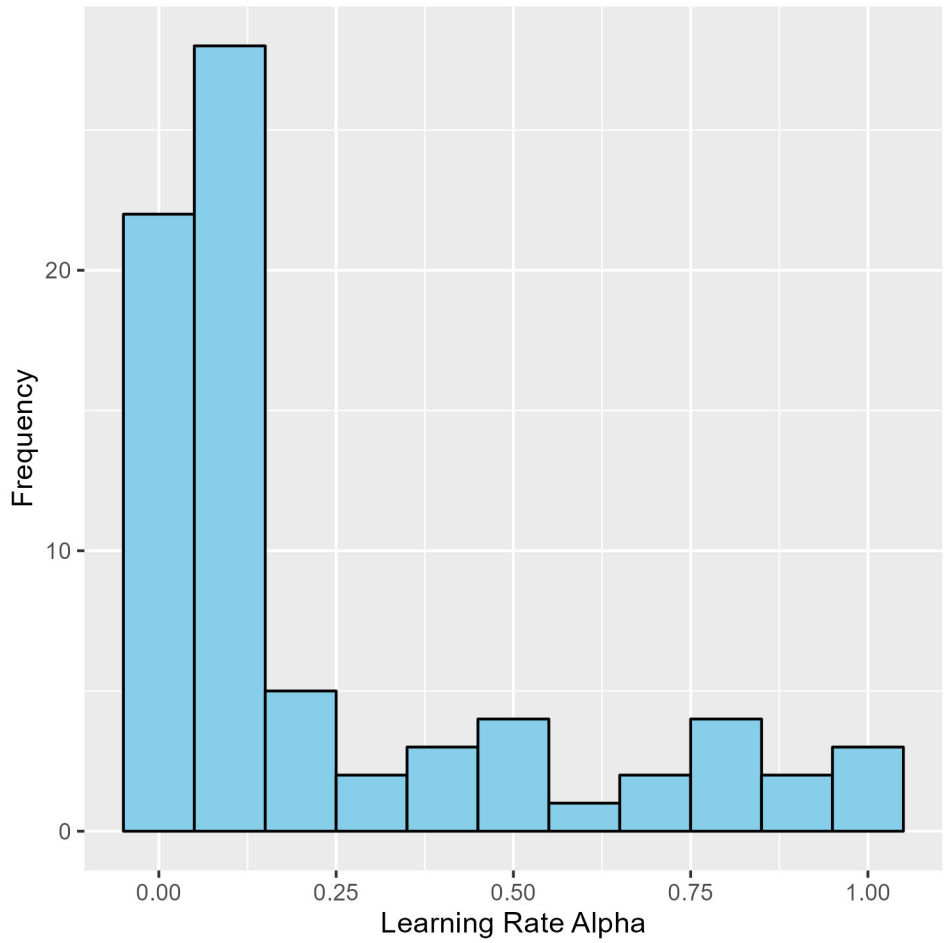

Figure B3

Histogram depicting the Learning Rate Distribution for the NAL.PLA × Social interaction.

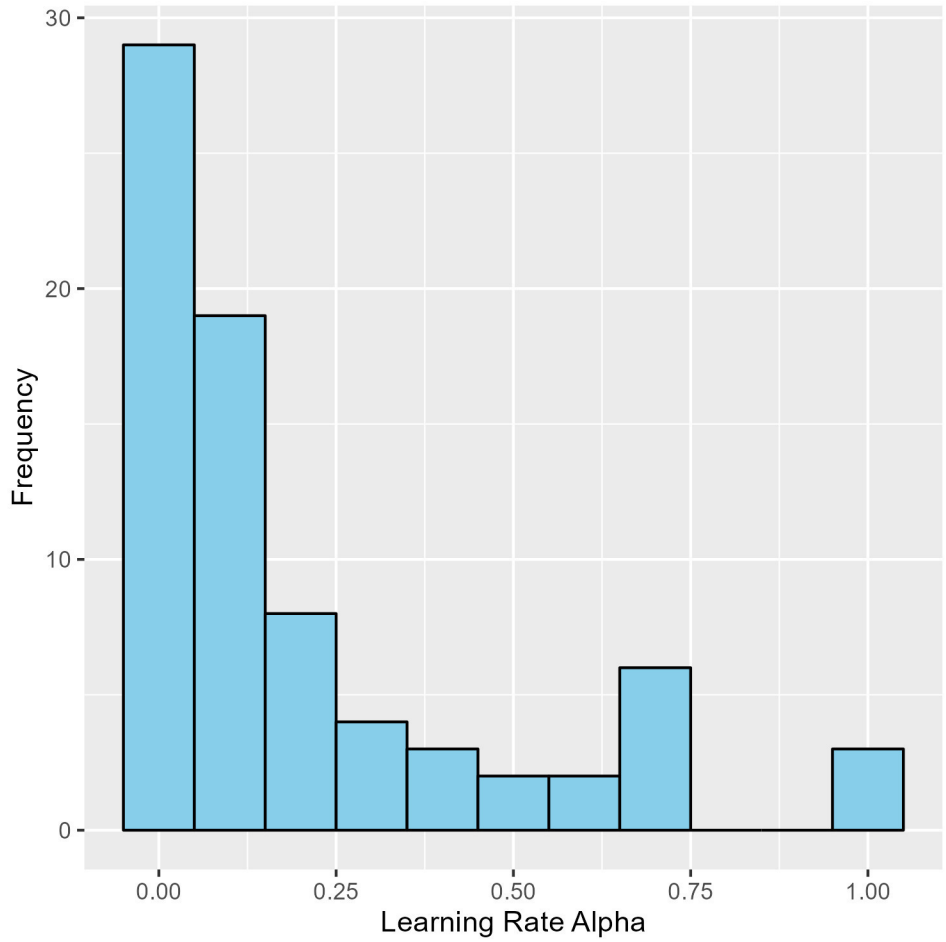

Figure B4

Histogram depicting the Learning Rate Distribution for the NAL.PLA × Non-social interaction.

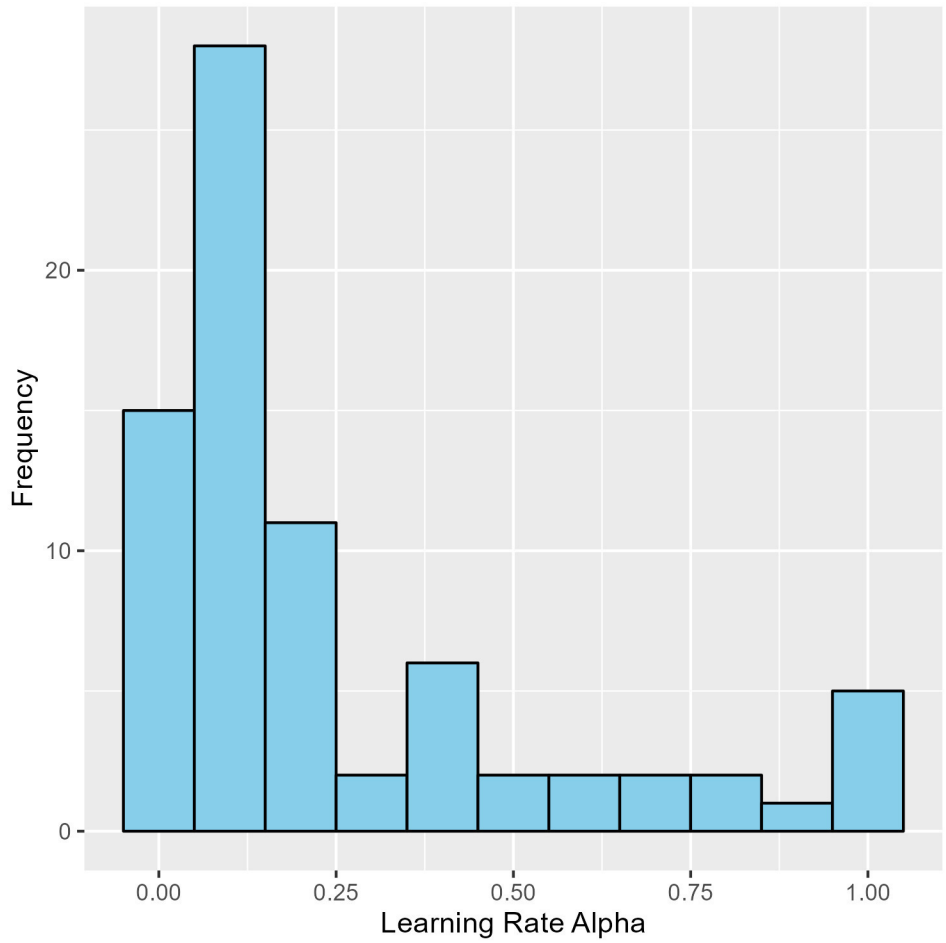

Figure B5

Histogram depicting the Learning Rate Distribution for the PLA.OXT × Social interaction.

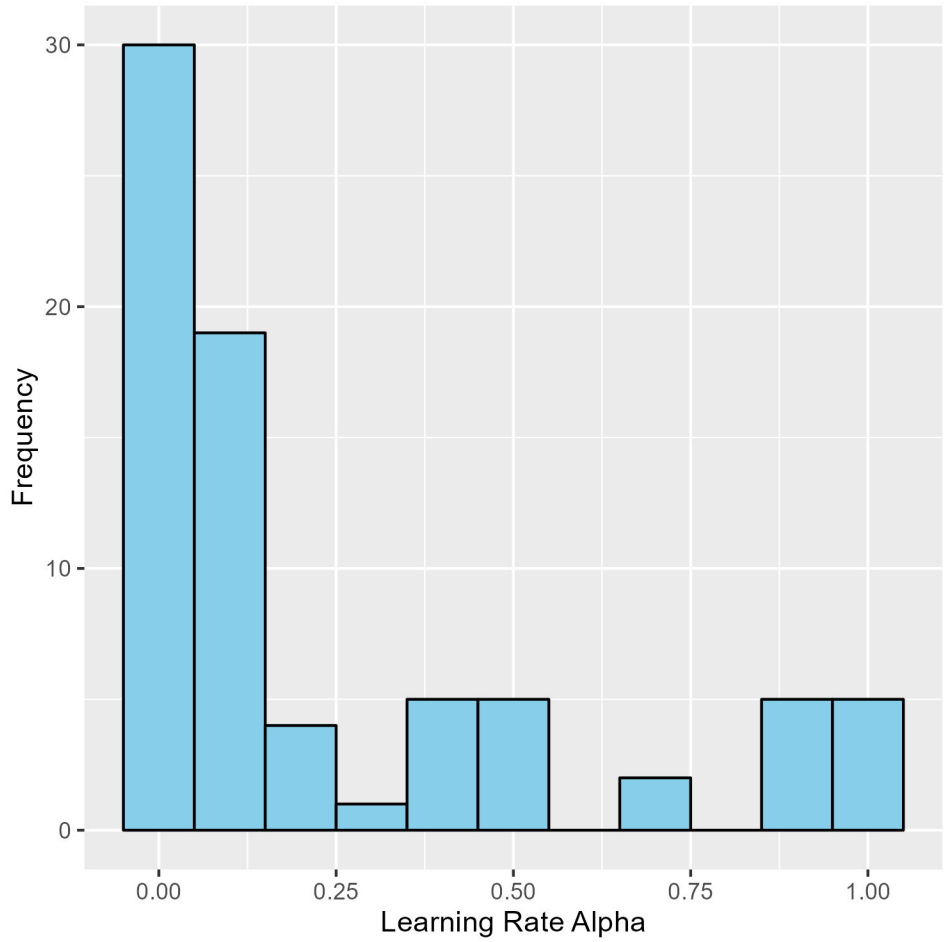

Figure B6

Histogram depicting the Learning Rate Distribution for the PLA.OXT × Non-social interaction.

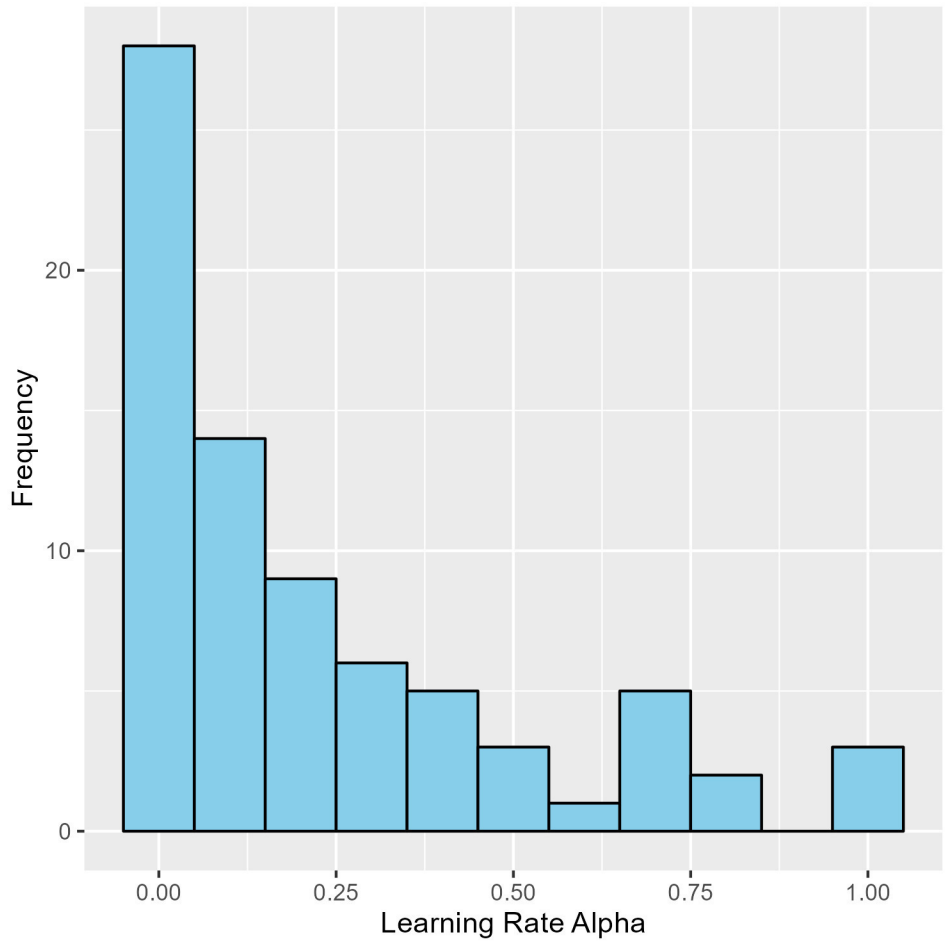

Figure B7

Histogram depicting the Learning Rate Distribution for the PLA.PLA × Social interaction.

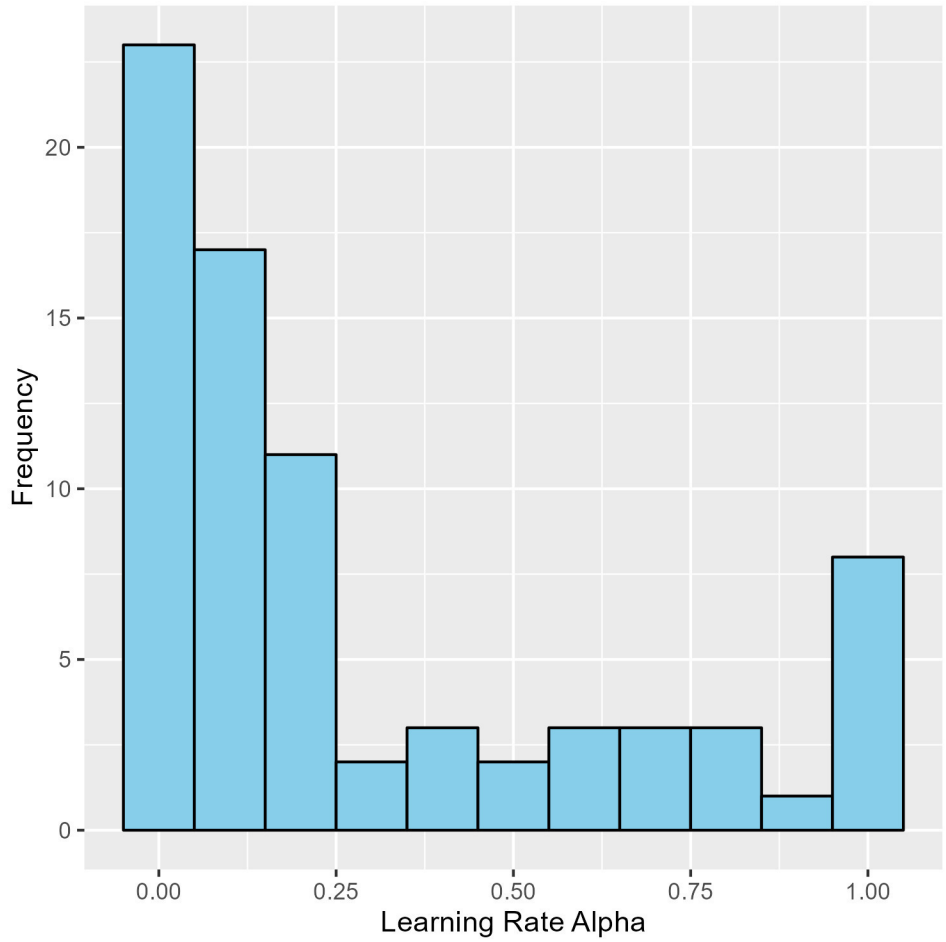

Figure B8

Histogram depicting the Learning Rate Distribution for the PLA.PLA × Non-social interaction.

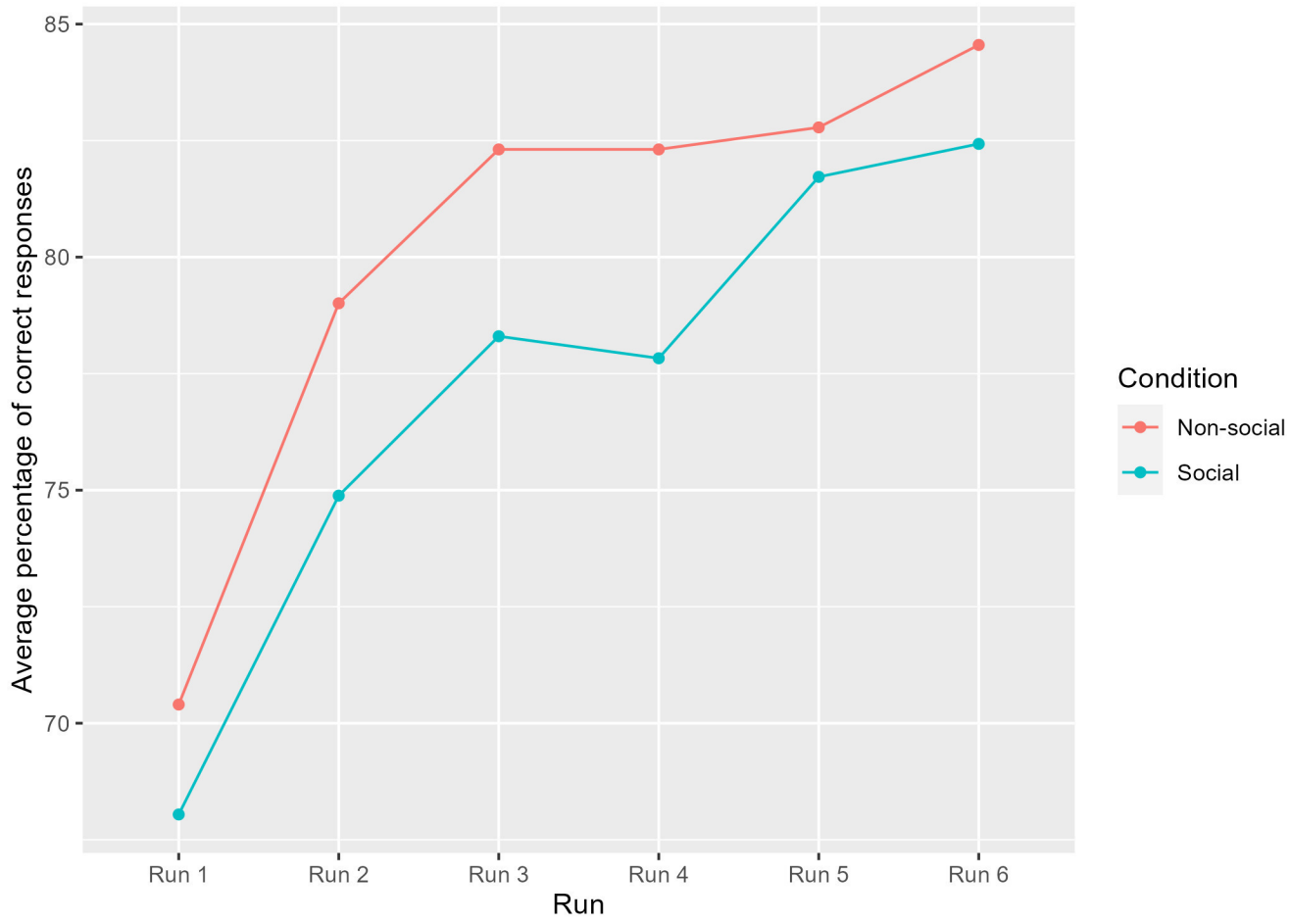

Figure B9

Results of the Model-free Analysis for the ASD Group.

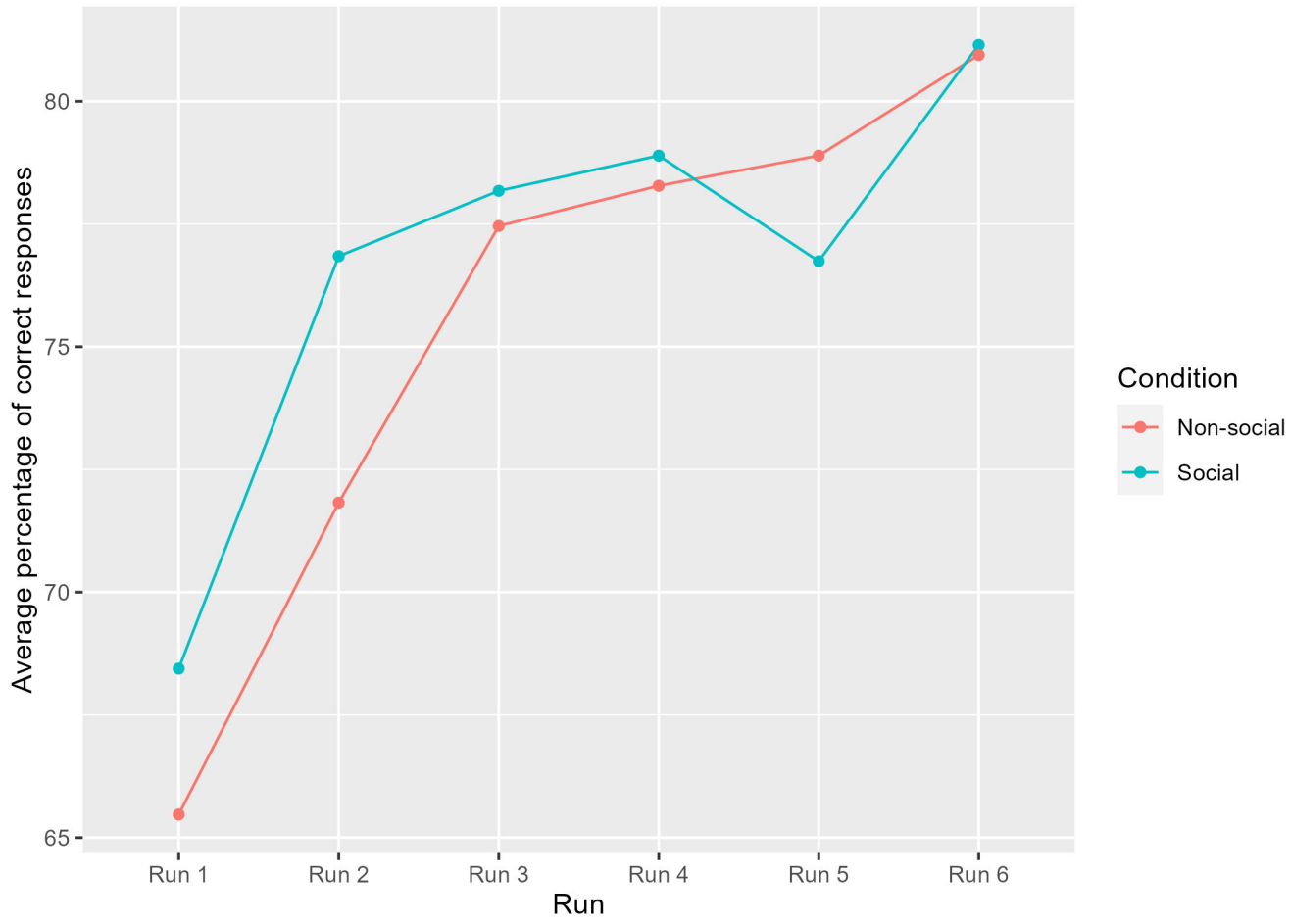

Figure B10

Results of the Model-free Analysis for the Control Group.

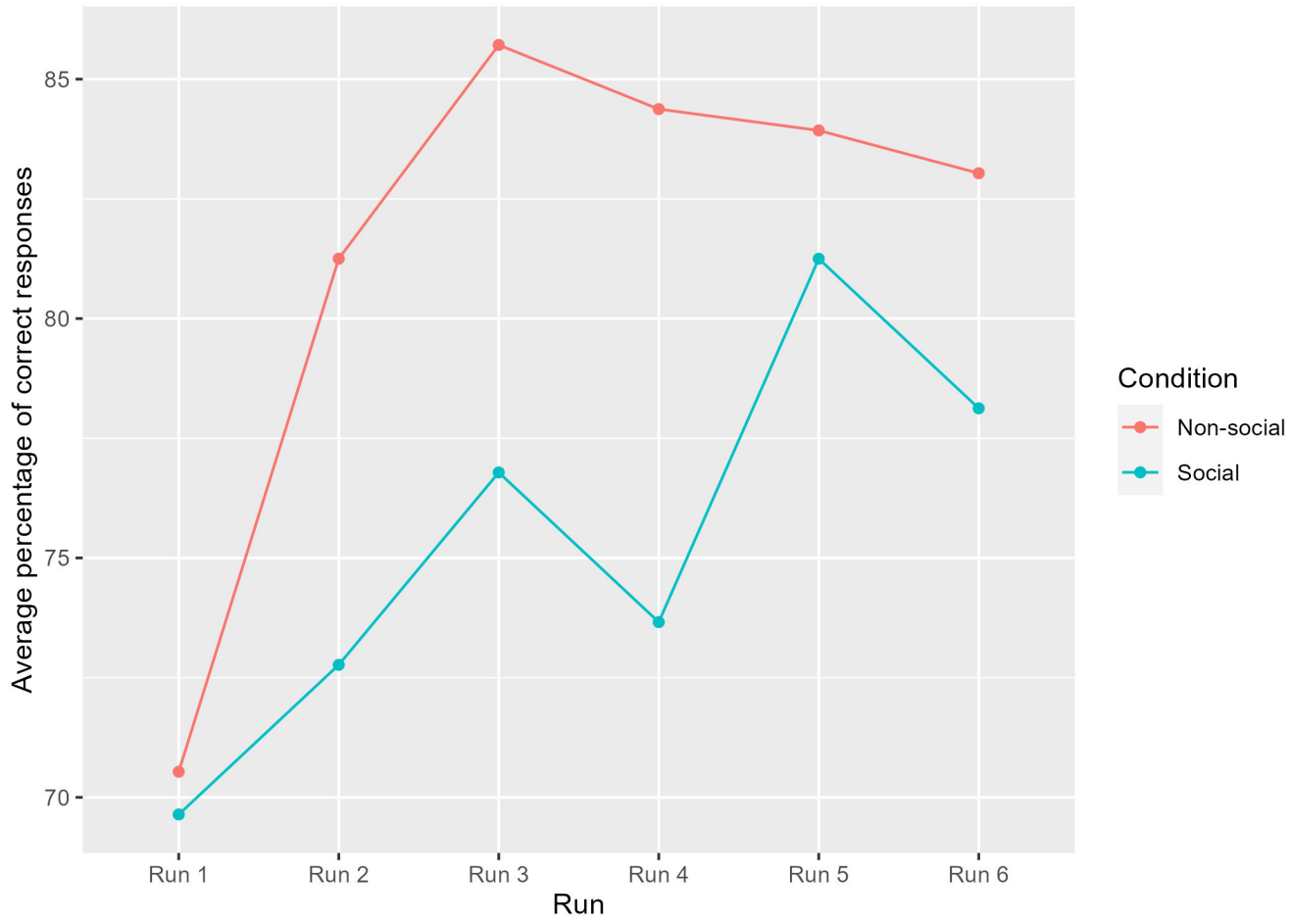

Figure B11

Results of the Model-free Analysis for the ASD × NAL.OXT Interaction.

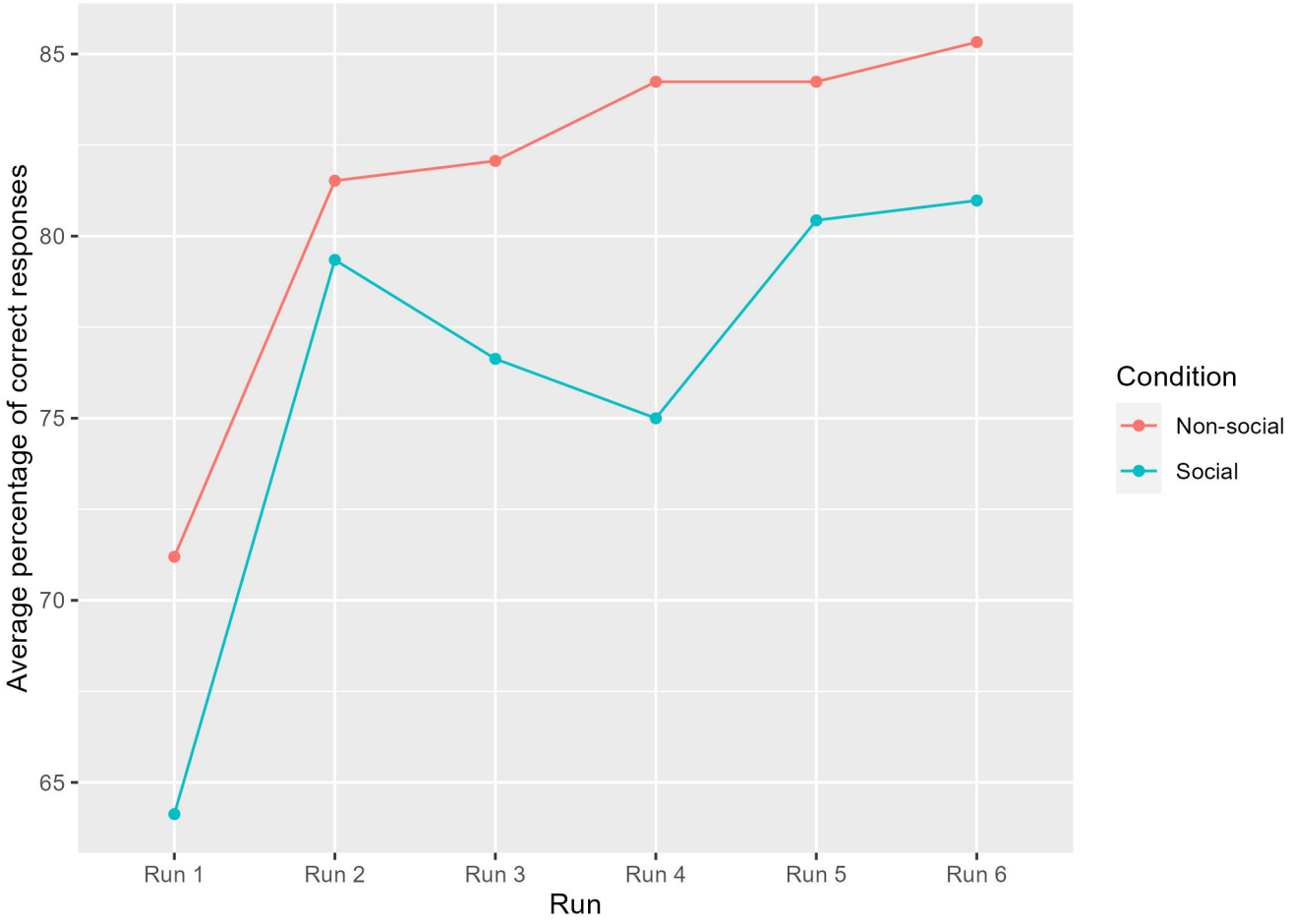

Figure B12

Results of the Model-free Analysis for the ASD × NAL.PLA Interaction.

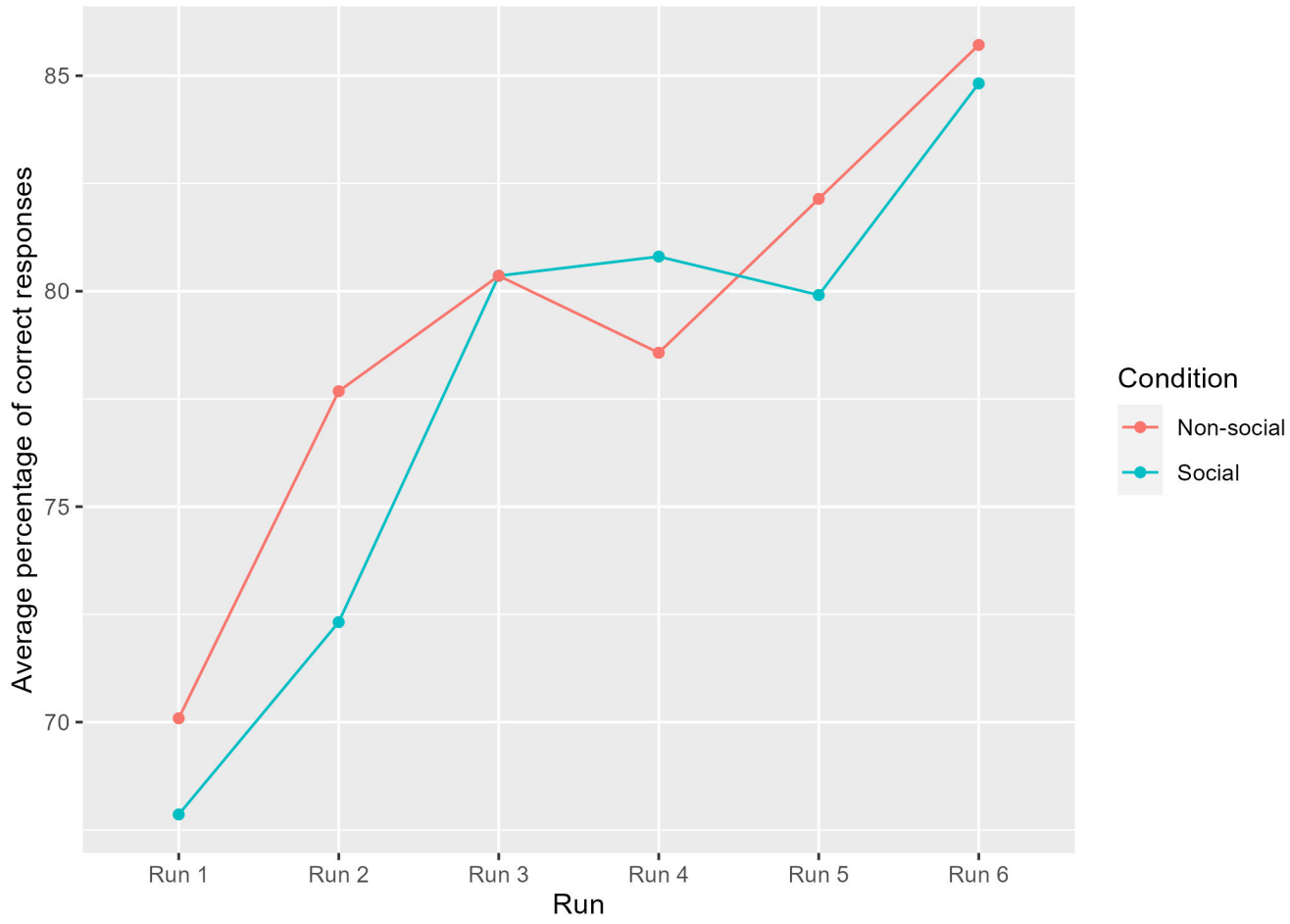

Figure B13

Results of the Model-free Analysis for the ASD × PLA.OXT Interaction.

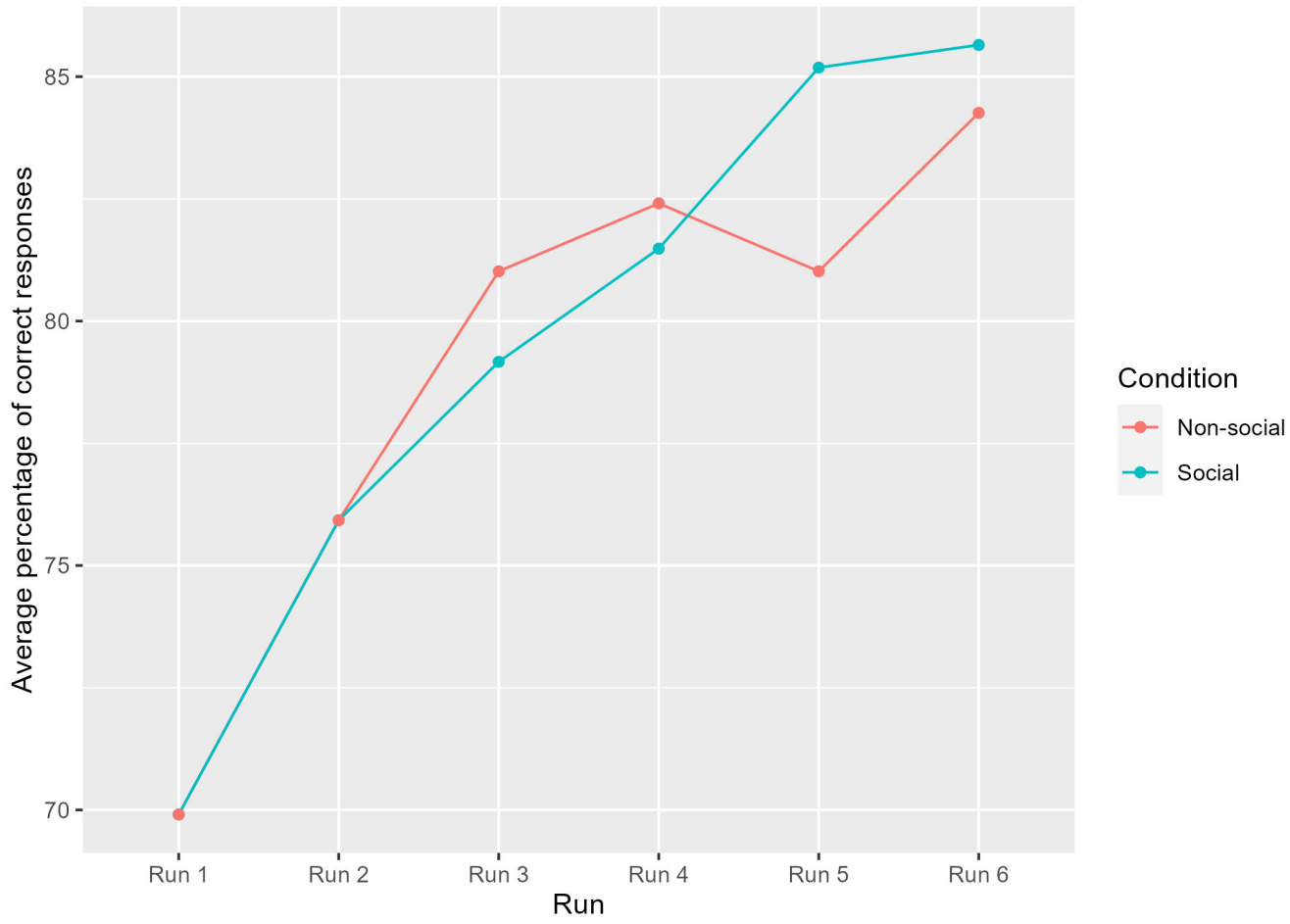

Figure B14

Results of the Model-free Analysis for the ASD × PLA.PLA Interaction.

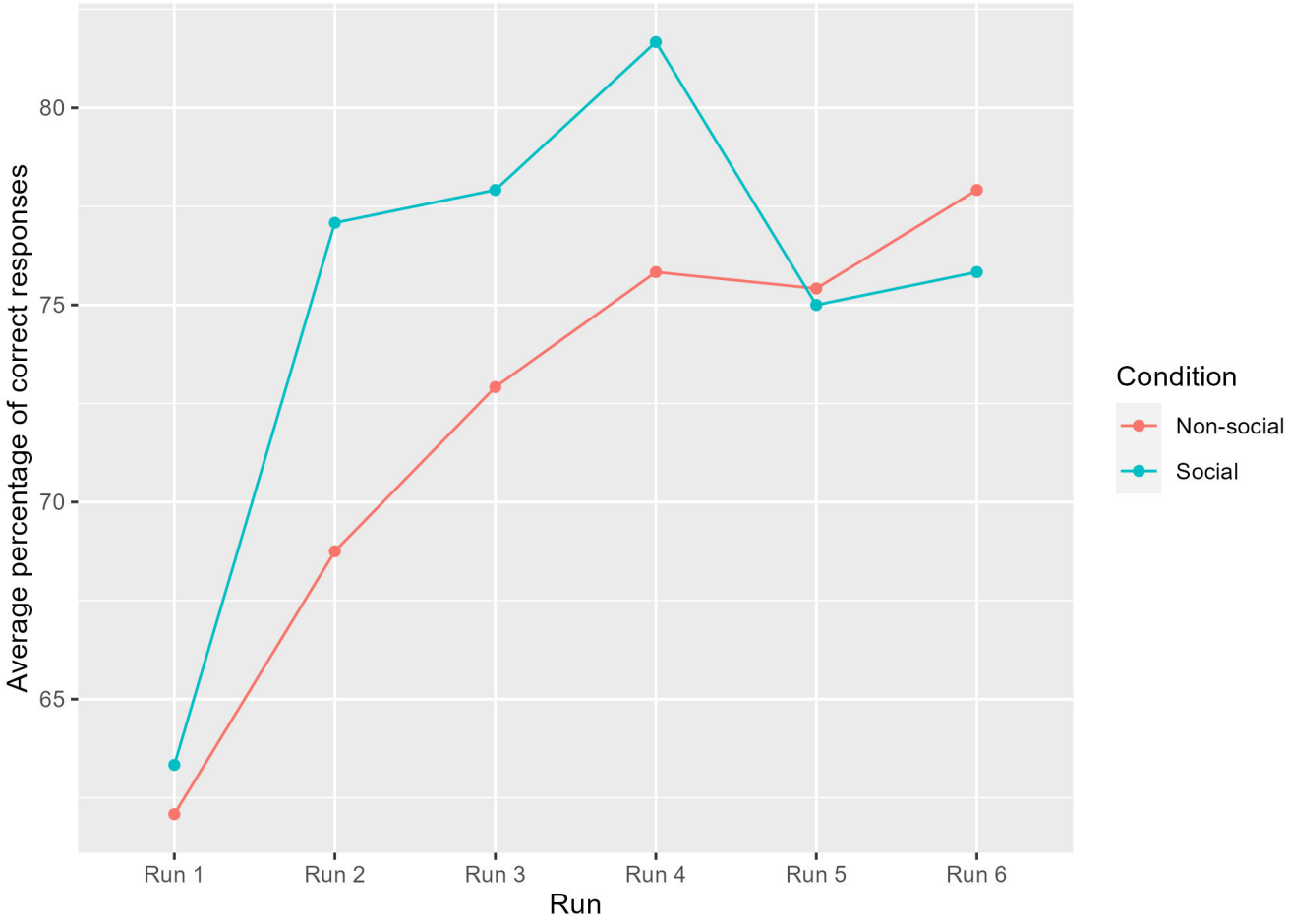

Figure B15

Results of the Model-free Analysis for the Control × NAL.OXT Interaction.

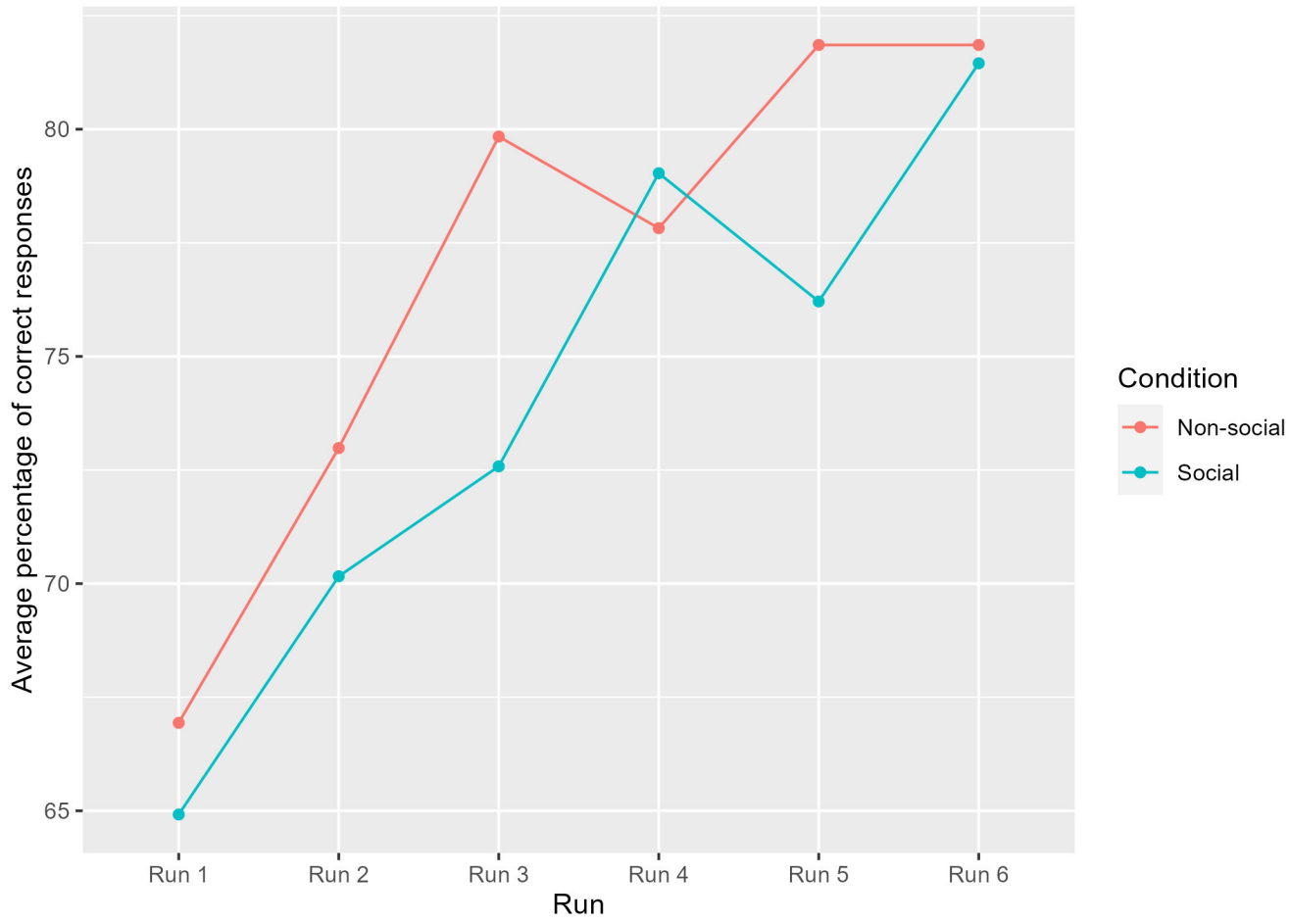

Figure B16

Results of the Model-free Analysis for the Control × NAL.PLA Interaction.

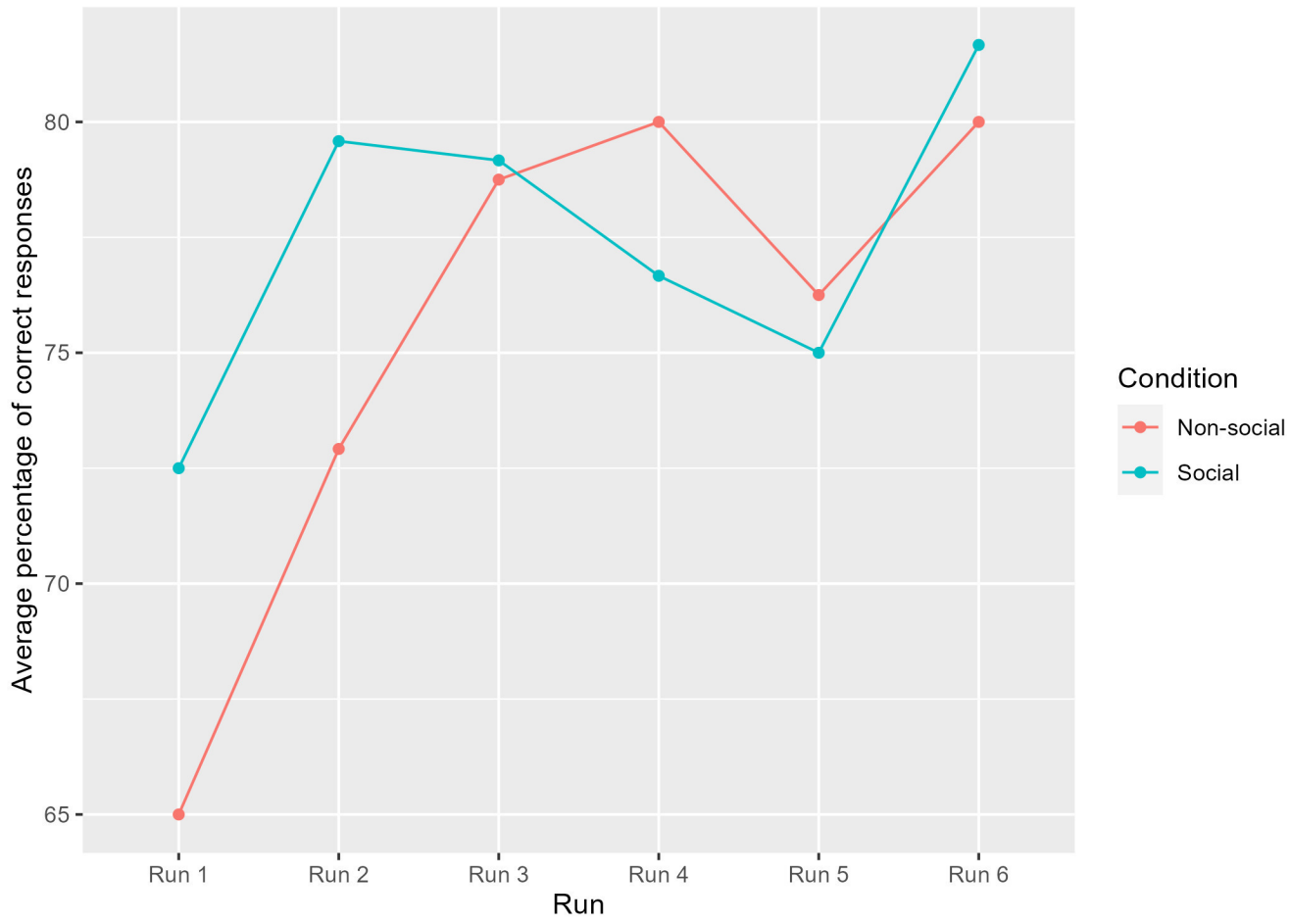

Figure B17

Results of the Model-free Analysis for the Control × PLA.OXT Interaction.

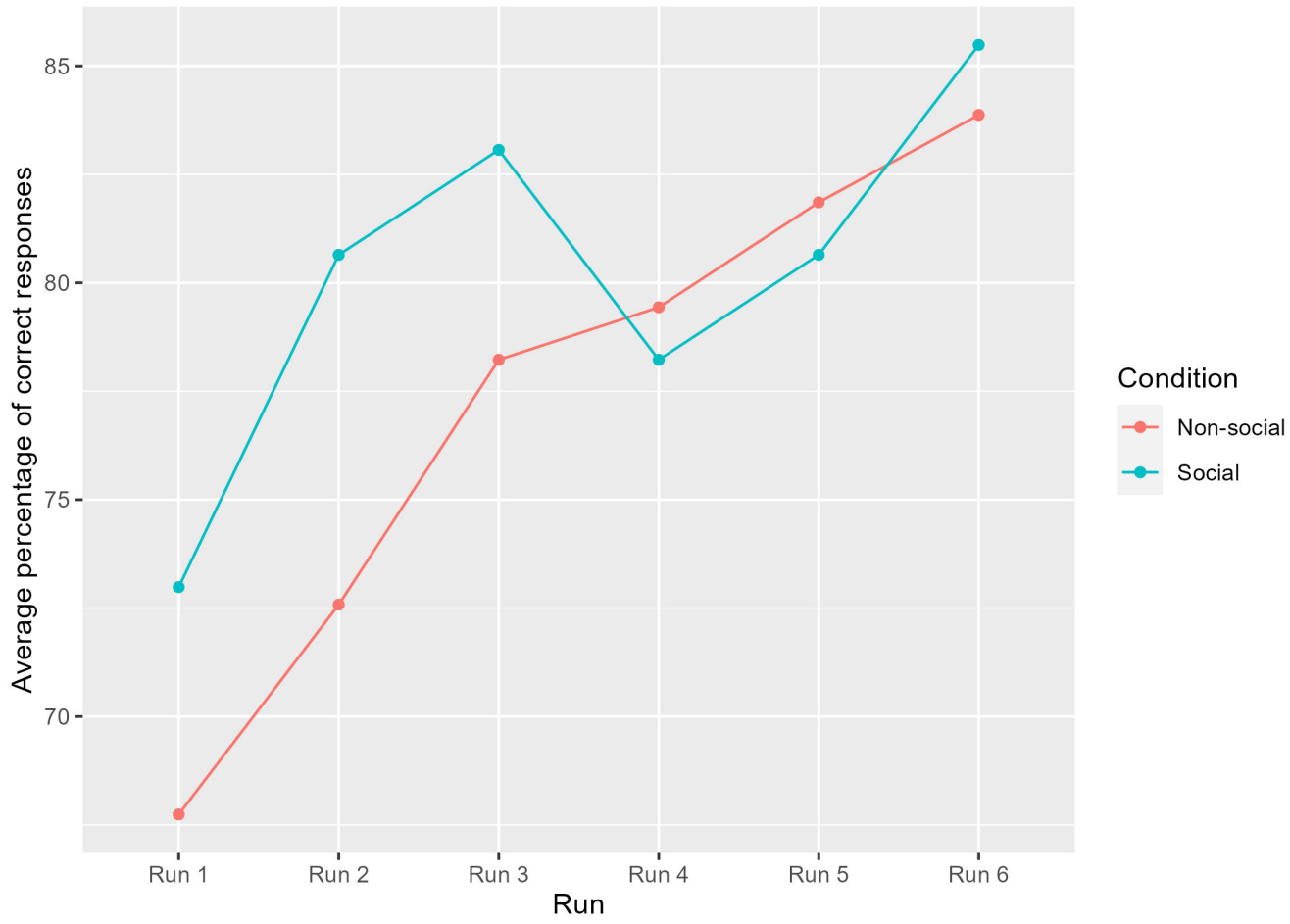

Figure B18

Results of the Model-free Analysis for the Control × PLA.PLA Interaction.

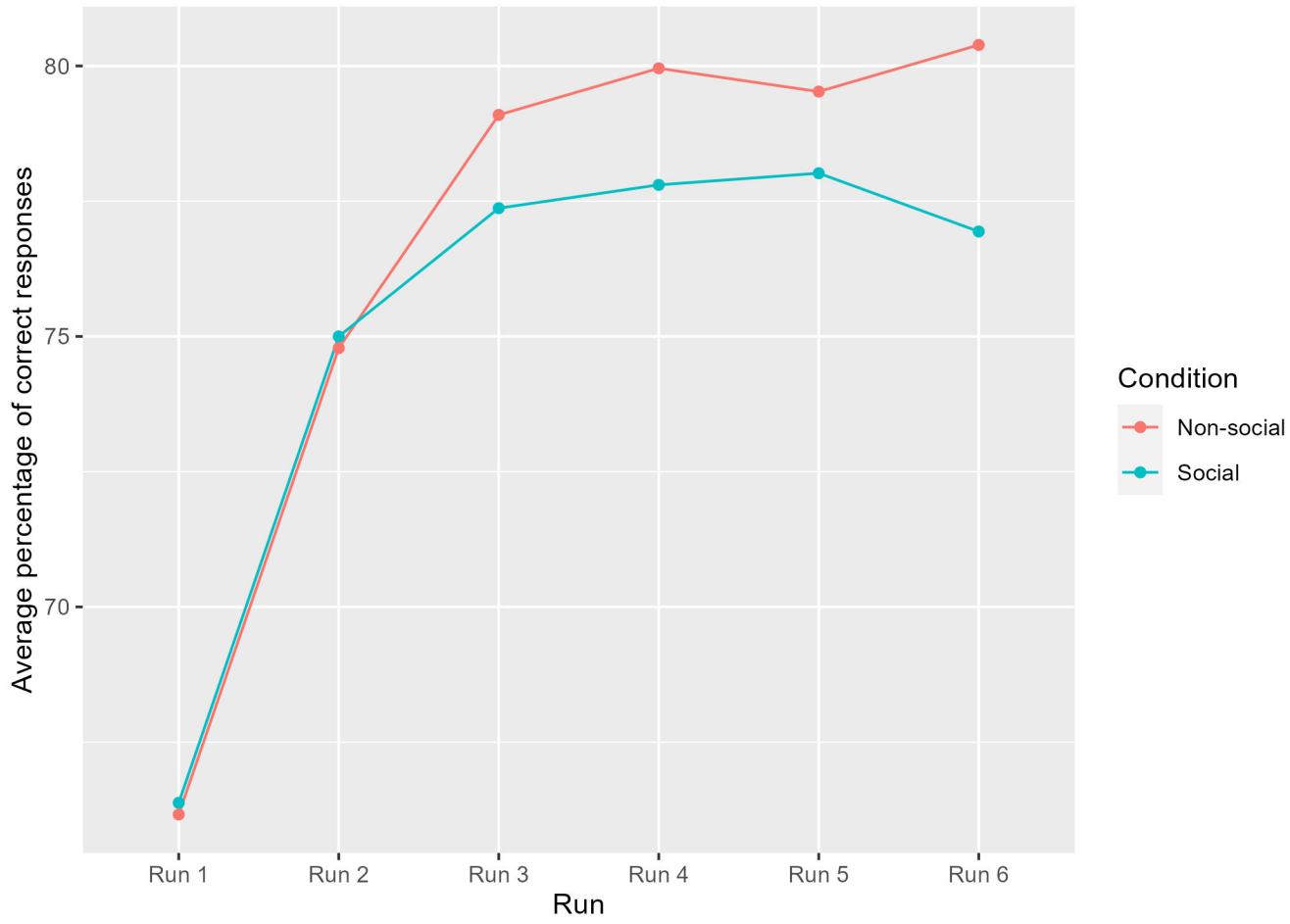

Figure B19

Results of the Model-free Analysis for the NAL.OXT Medication.

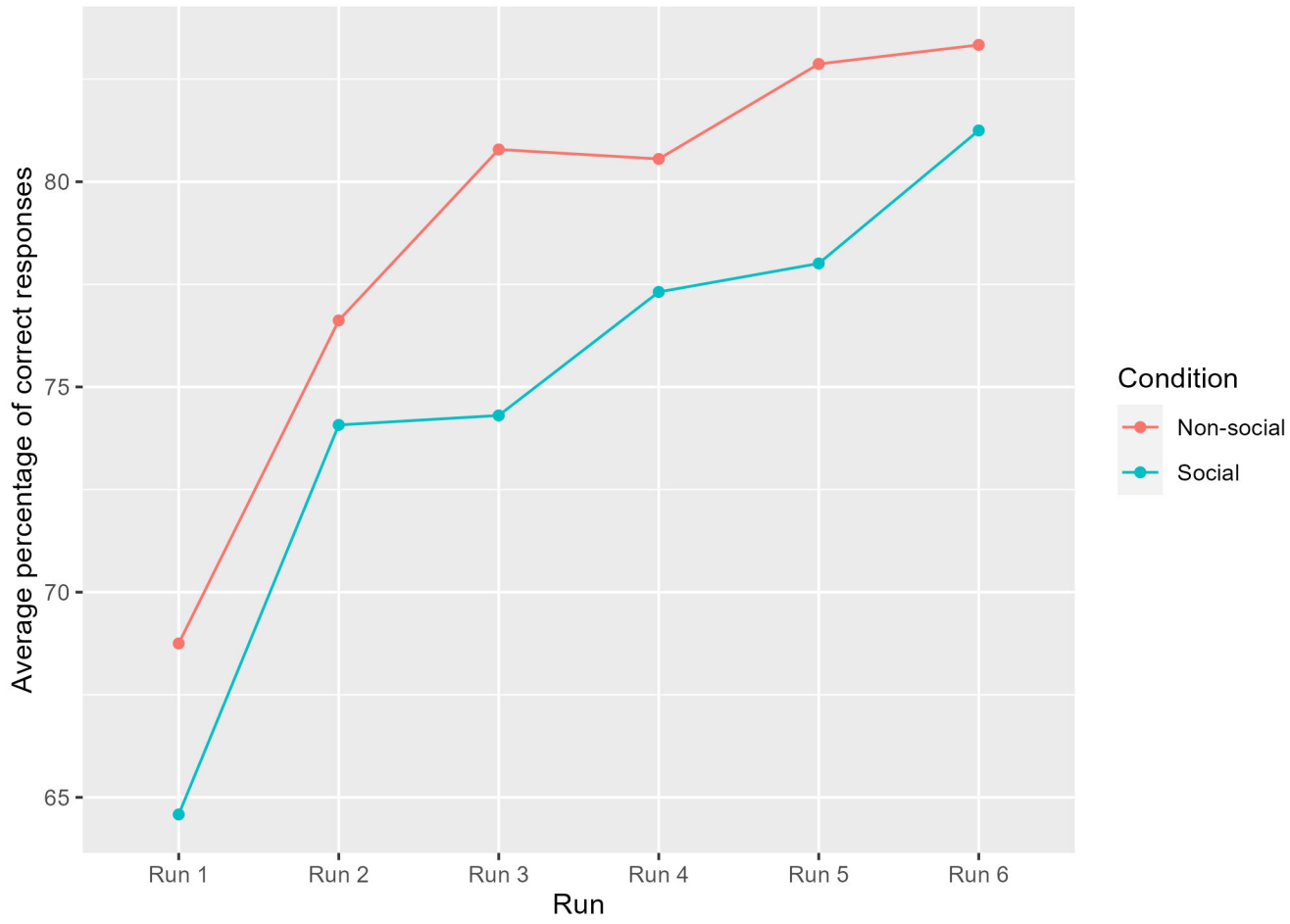

Figure B20

Results of the Model-free Analysis for the NAL.PLA Medication.

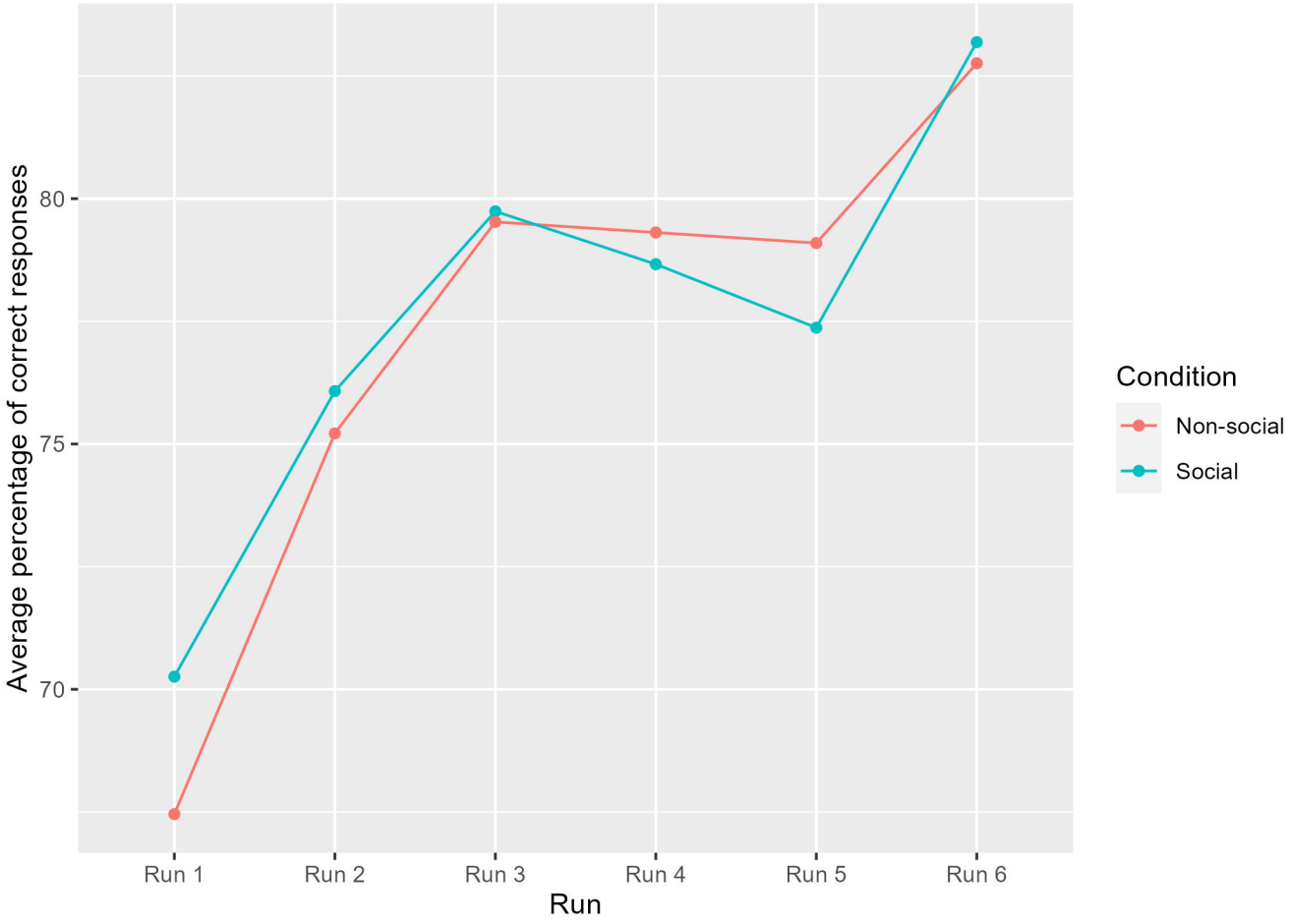

Figure B21

Results of the Model-free Analysis for the PLA.OXT Medication.

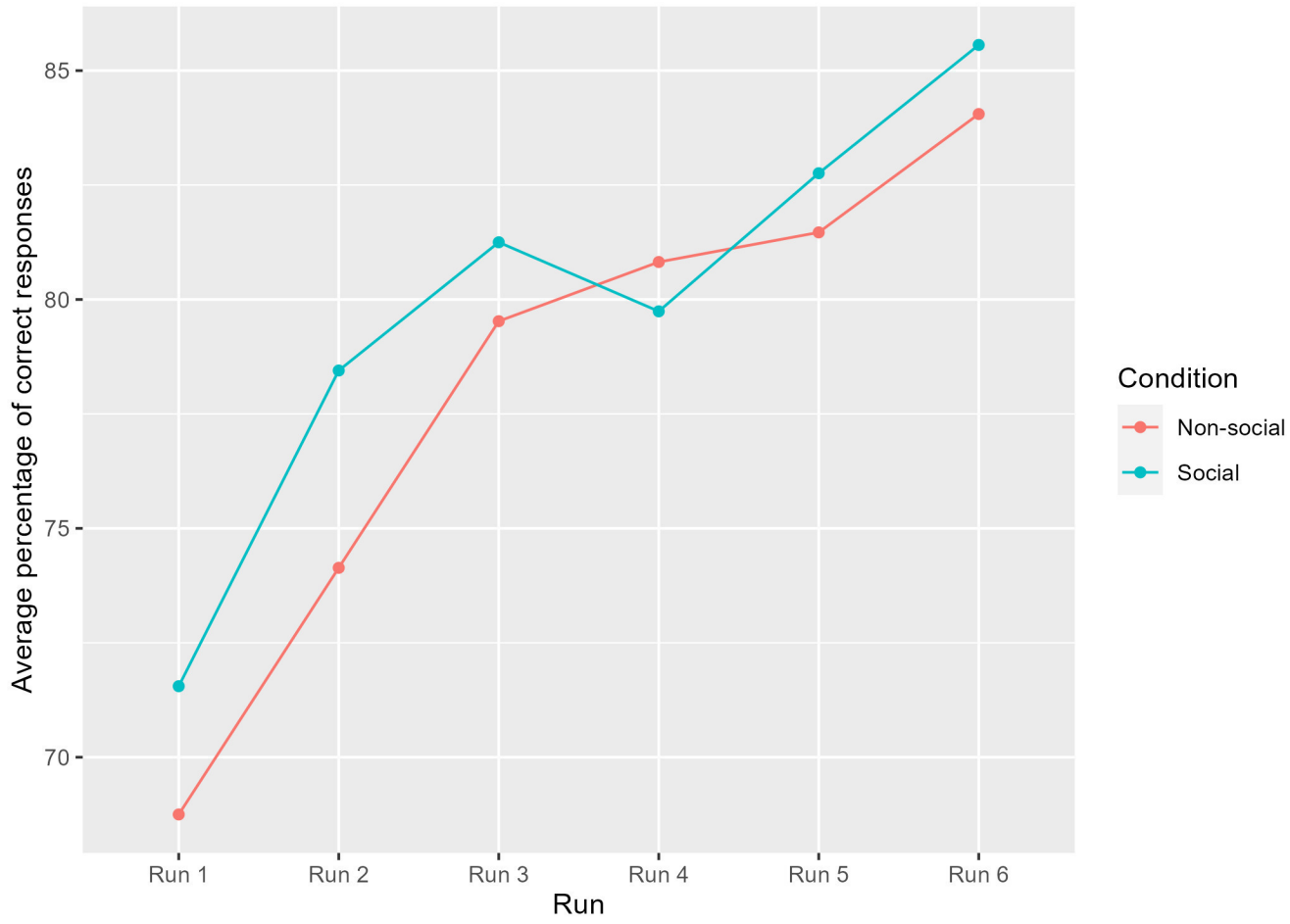

Figure B22

Results of the Model-free Analysis for the PLA.PLA Medication.

Table B1

Full Results of the Repeated Measures ANOVA Conducted on the Learning Rate Parameters.

Effect	$\hat{\eta}^2_G$	90% CI	F	df^{GG}	$df^{\mathrm{GG}}_{\mathrm{res}}$	p
Group	.000	[.000, .024]	0.10	1	74	.753
Medication	.003	[.000, .006]	0.58	2.77	204.90	.614
Condition	.000	[.000, .000]	0.01	1	74	.915
Group × Medication	.003	[.000, .010]	0.74	2.77	204.90	.518
Group × Condition	.001	[.000, .034]	0.65	1	74	.424
Medication × Condition	.004	[.000, .008]	0.79	2.40	177.90	.475
Group × Medication × Condition	.001	[.000, .000]	0.13	2.40	177.90	.914