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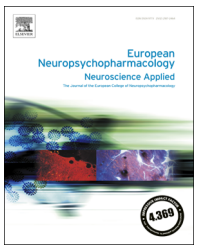

Differential effect of clomipramine on habituation and prepulse inhibition in dominant versus subordinate rats

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Abstract
Many patients with depression have comorbidities associated with an impairment of sensorimotor gating, such as e.g. schizophrenia, Parkinson Disease, or Alzheimer disease. Antidepressants like clomipramine that modulate serotonergic or norepinephrinergic neurotransmission have been shown to impact sensorimotor gating, it is therefore important to study potential effects of clomipramine in order to rule out an exacerbation of sensorimotor gating impairment. Prior studies in animals and humans have been inconclusive. Since serotonin and norepinephrine levels are closely related to anxiety and stress levels and therefore to the social status of an animal, we tested the hypothesis that acute and chronic effects of clomipramine on sensorimotor gating are different in dominant versus subordinate rats, which might be responsible for conflicting results in past animal studies. We used habituation and prepulse inhibition (PPI) of the acoustic startle response as operational measures of sensorimotor gating. After establishing the dominant animal in pair-housed male rats, we injected clomipramine for two weeks and measured acute effects on baseline startle, habituation and PPI after the first injection and chronic effects at the end of the two weeks. Chronic treatment with clomipramine significantly increased habituation in subordinate rats, but had no effect on habituation in dominant animals. Furthermore, PPI was slightly enhanced in subordinate rats upon chronic treatment while no changes occurred in dominant animals. We conclude that the social status of an animal, and therefore the basic anxiety/stress level determines whether or not clomipramine has a beneficial effect on sensorimotor gating and discuss possible underlying mechanisms.

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1. Introduction

Clomipramine is widely prescribed to treat depression and anxiety disorders (Dell'Osso et al., 2006). It is a competitive antagonist that binds to monoamine transporters, so that binding of the endogenous monoamine neurotransmitter is inhibited (Apparsundaram et al., 2008). The resulting increase of monoamines at synaptic sites may cause an initial increase in anxiety levels (Browning et al., 2007; Grillon et al., 2007). As chronic treatment persists, adaptive changes seem to occur and therapeutic anxiolytic effects can be seen (Bosker et al., 2010). While many monoaminergic re-uptake inhibitors have a limited selectivity and affect serotonergic, norepinephrinergic and dopaminergic systems, clomipramine has a high potency as a serotonin and norepinephrine re-uptake inhibitor, but very limited effects on the dopaminergic system. This is important, as dopaminergic modulators are commonly known to impair sensorimotor gating. Sensorimotor gating disruptions are observed e.g. in schizophrenia, autism spectrum disorders, and many neurodegenerative diseases, and they have been shown to correlate with psychotic symptoms and/or cognitive impairments. It is therefore specifically critical that sensory gating deficiencies are not exacerbated when clomipramine or other monoamine re-uptake inhibitors are applied (Swerdlow et al., 2006b). Reports on the effects of acute or chronic monoamine re-uptake inhibitors on sensorimotor gating in animals and humans have been conflicting in the past (for details please see Section 4), probably due to differences in the specificity of re-uptake inhibitors, and their affinity for different monoaminergic systems. Another confounder might be the differences in basic anxiety or stress level among patients and human volunteers or between individual animals used in the studies. We here address the latter by exploring the effect of clomipramine in dominant versus subordinate rats, thereby taking differences in baseline anxiety and stress levels into account.

Social ranking in male rats and various other animals correlates with anxiety and stress levels: rats demonstrating lower anxiety related behaviour are considered to be more active and aggressive in social behaviour (Henniger et al., 2000) and they become dominant, as this behaviour is an important part of survival and resource allocation in social hierarchies (Davis et al., 2009). Interestingly, aggressive behaviour and serotonin activity are closely related (Jansen et al., 2011; Passamonti et al., 2012), as are social status and serotonergic activity (for review see Chiao, 2010; Whitaker et al., 2010; Morrison and Cooper, 2011; Morrison *et al.*, 2011; Issa et al., 2012). Increased stress levels also induce norepinephrine release (Hajos-Korcsok et al., 2003). We therefore hypothesise that the effect of monoamine re-uptake inhibitors might be influenced by the social status of an individual rat.

In order to address this hypothesis, we tested the acute and chronic effects of clomipramine on the acoustic startle response, habituation, and PPI in dominant versus subordinate rats. Modulations of the acoustic startle response is the most common method for studying sensorimotor gating in humans and animals, whereas the baseline startle response amplitude is an indicator of fear and anxiety levels.

2. Experimental procedures

2.1. Animals

A total of 54 Male Wistar Rats (Charles Rivers, Canada) of approximately six weeks, weighing 250–320 g at the start of the experiments were used in these studies. They were housed in cages of two animals under continuous 12 h light–dark cycles, with water *ad libitum*. The entire experiment was run three times. For the second and third run, sexually experienced rats were used and they were food restricted (20 g of standard rat chow per cage) for one week prior to the startle experiments in order to increase aggressive behaviour. All rats were weighed every two days to calculate appropriate dosages of drugs. The experiments were done in accordance with the ethical guidelines for the care and use of laboratory animals for experiments by the Canadian Council for Animal Research, and were approved by the local animal care committee (University of Western Ontario).

2.2. Study design

The entire study was run three times each with 8 pairs of rats (dominant and subordinate). An additional group of 6 rats that were injected with saline through the entire study was run concurrently with the second batch as a control group. For data analysis, we used a within subject design, comparing initial startle data with data after acute clomipramine treatment, chronic treatment, and after 2 weeks of recovery for each animal. All three experiments with drug injections showed the same results, data for each group was therefore merged and averaged across all three runs.

2.3. Determination of social status

Animals were housed in pairs and social behaviour was monitored twice daily by two independent observer, once per light and per dark cycle, for one week. Aggressive behaviour (fighting, threatening) as well as resting positions in the cages were noted and used to determine the dominant and subordinate animals (Henniger et al., 2000). Fighting was monitored amongst pairs, as the winner established his dominance through always gaining a superior position on the subordinate rat. The latter often lied on its back or submitted its head while the dominant one was stepping on top of it. Resting/sleeping locations were also observed, as dominant rats tended to rest inside a tube placed in the cage, and would fight the subordinate rat in order to establish its position. Alternatively, the dominant rat would lie on top of the subordinate. After each observation, rats within one cage were ranked dominant or subordinate or as being inconclusive. After one week of observations, dominance rankings were tallied. Animals were considered being dominant when at least 75% of observations were consistent with dominant behaviours. Data of animals in a total of three cages was omitted because no clear distinction could be determined between the dominant and subordinate rat. In the last run of 16 rats, observation of social status was repeated immediately after chronic treatment in order to see whether animals changed social ranks through the treatment.

2.4. Injections

All rats were injected subcutaneously with saline (0.9% sodium chloride) once every 12 h, for three days. Acoustic startle responses were then measured for the control treatment. Testing was repeated the next day after one subcutaneous injection of

clomipramine (Sigma, Canada) to measure the acute effect of clomipramine on startle response. A commonly used dose of 10 mg/kg body weight per injection was chosen. Other studies have shown effects with doses as low as 1 mg/kg (e.g. Stuart et al., 2013), or as high as 15 mg/kg per injection (e.g. Piras et al., 2014). A small control group ($n=6$) received saline injections throughout the experiment instead. Saline rats were not mixed with drug treated animals in a cage in order to avoid that injections alter the social status. Subcutaneous injections of clomipramine (or saline) were continued every 12 h, for a total of 14 days and then the startle response corresponding to chronic treatment was measured. Upon completion of chronic treatment, rats were allowed to rest for 14 days with no injections. They were then injected with saline once, and startle response was recorded as a measure of recovery from clomipramine. All measures of startle response occurred 15-30 min after injection.

2.5. Acoustic startle response measurements

Four identical sound-attenuated chambers ($100 \times 80 \times 60\ cm^3$) were used to measure acoustic startle responses (Med Associates, St Albans, VT) using the Startle Reflex Software 5.95 (Med Associates, St. Albans, VT). The differences between peak-to-peak voltage outputs of the transducers were used to measure startle amplitudes. Animals were first subjected to a ten minute acclimation period with a 65 dB white noise background, but without further stimulation. They were then exposed to 30 startle pulse alone trials (20 ms, 110 dB white noise, every 20 s) for habituation (Block I). Immediately following Block I, they were subjected to 50 pseudo-randomized trials consisting of five different stimulation types (Block II): startle pulse alone trials, and four different prepulse-pulse trials with either 30 ms or 100 ms inter-stimulus intervals (ISI) between prepulse and startle pulse and either 75 dB or 85 dB prepulse intensity (4 ms, white noise). Trials were 20 s apart (for experimental detail see Schmid et al., 2010; Valsamis and Schmid, 2011). All animals were exposed to startle testing for five times: after determination of social status, they were injected with saline for 3 days. On the second day of injection they underwent a pre-test in to get the animals used to the startle testing procedure. This data was discarded. On the third day of saline injection, the second test was performed for control measurements. On the subsequent day, they were again tested after their first injection of clomipramine (acute). The fourth startle testing session was two weeks later, after their last clomipramine injection (chronic). The last testing was done another two weeks later, after the animals had recovered from the clomipramine (recovery). Since all other startle testing sessions were preceded by an injection, we injected saline before this last testing session.

2.6. Data and statistical analysis

Baseline startle was calculated by averaging the 10 startle alone trials in Block II. Since habituation occurs most prominently within the first 5-10 startle responses in rats, habituation score was determined by dividing the mean of the last five startle responses by the mean of the first two startle responses in block I; it was expressed as a fraction of the initial startle response (1.0) at the end of block I. PPI was calculated by obtaining an average of the 10 trials corresponding to a particular prepulse and ISI and dividing that value by the baseline startle response (see above), according to the formula: *1-(startle response with prepulse/baseline startle response)*. All PPI trials were verified for a zero response to the prepulse before further analysis.

Repeated measure, one or two-way ANOVAs were used to compare the effects of social status overall, as well as the effects of treatments and interaction of treatments with social status. Where Mauchly's test of sphericity was violated, either Huynh-Feldt corrections (when $\varepsilon > 0.75$) or Greenhouse Geisser corrections (when $\varepsilon < 0.75$) were used. Where significant effects were found, *t*-tests were run between the respective groups with the respective Bonferroni correction for multiple comparisons. Statistics were run in SPSS. In all experiments, *n* refers to the number of animals. A *p* value of <0.05 was used as the criterion for statistical significance.

3. Results

3.1. Baseline startle

Baseline startle was measured after control injections of saline (test 1, control), after one acute injection of clomipramine (test 2, acute), after 14 days of chronic exposure to clomipramine (test 3, chronic), and two weeks after cessation of injections (test 4, recovery). A repeated measures, two-way mixed design ANOVA revealed no significant difference of baseline startle amplitudes between dominant and subordinate rats ($F_{(1,45)}=0.13$, $p<0.72$), but a significant effect of test number ($F_{(3,135)}=26.99$, $p<0.0001$), and no interaction between test number and social status ($F_{(3,135)}=0.89$, $p=0.97$). In fact, subordinate rats showed a consistent trend to exhibit higher startle responses than dominant rats under control conditions, but it failed to reach statistical significance ($t=1.75$, $p=0.092$, $n=24$ per group). In general, there was a continuous increase in baseline startle across testing sessions in all rats (Figure 1 *left*). In order to test whether this increase was due to the drug treatment or to weight gain during repeated testing over time, we ran a separate control group that received saline throughout the entire time (Figure 1 *right*). A one-way repeated measure ANOVA revealed a significant increase in baseline startle response amplitude over testing sessions in these saline injected animals as well ($F_{(3,12)}=5.832$, $p=0.011$), and a two-way repeated measures ANOVA (mixed design) comparing saline and clomipramine injected animals over the testing sessions confirmed a significant change in baseline startle amplitude over testing sessions ($F_{(3,171)}=21.7$, $p<0.0001$), but no effect of drug ($p=0.15$) or interaction of drug with testing sessions ($p=0.083$). In summary, while baseline startle amplitude increased throughout the experiment in both the clomipramine and saline treated animals, we did not detect a significant influence of social status or drug treatment on baseline startle.

3.2. Short-term habituation

Next, we tested short-term habituation in dominant versus subordinate rats and how acute and chronic clomipramine affected short-term habituation in rats with different social status (Figure 2). A repeated measure, two-way ANOVA demonstrated that there was no effect of treatment ($F_{(3,135)}=1.516$, $p=0.22$) or social status ($F_{(1,41)}=0.004$, $p=0.95$), but a significant interaction between social status and drug treatment ($F_{(2.47,123)}=3.73$, $p=0.02$). A posthoc test revealed that subordinate animals had a significantly higher habituation score (i.e. habituated significantly less) under control conditions than their dominant cage mates ($p=0.013$). Dominant rats did not display a significant change in habituation scores due to acute or chronic clomipramine injections, although there was a trend towards less habituation after chronic treatment when compared to control ($p=0.078$). In contrast, subordinate rats showed a significant increase in habituation (decrease of scores) between control (test 1) and chronic treatment (test 3, $p=0.016$). There was also a significant difference in habituation between the dominant and subordinate rats after

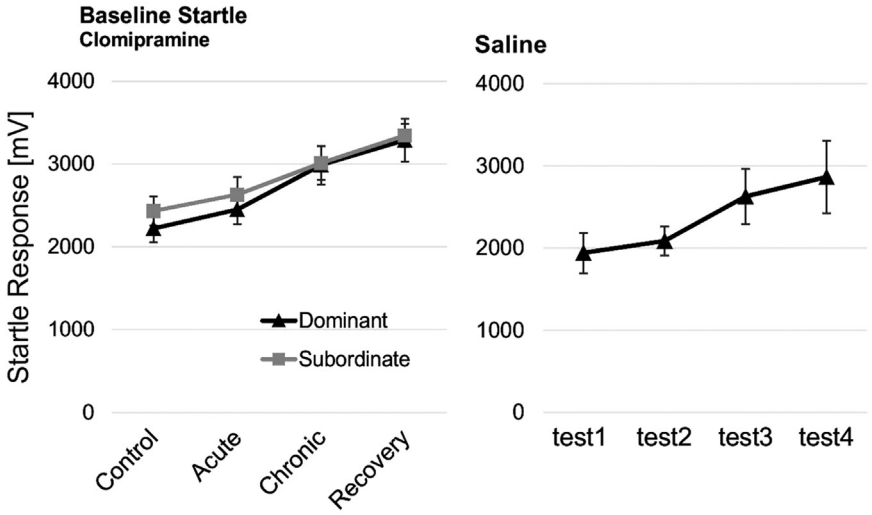

Figure 1 Baseline startle responses. *Left:* baseline startle responses for dominant and subordinate animals (n=24 per group). Baseline startle responses increased throughout the experiment. Although subordinate animals tended to display higher startle responses initially, there was no statistical difference between dominant and subordinate animals. *Right:* a control group (n=6) underwent exactly the same procedures but animals were injected with saline instead of clomipramine throughout the experiment. Baseline startle also increased in this group of animals. There was no statistical difference in weight gain between clomipramine and saline injected animals. Error bars show SEM.

chronic clomipramine treatment (p=0.043). In summary, habituation increased in subordinate animals, whereas the stayed the same or deteriorated in dominant animals. Interestingly, this was accompanied with a shift in social status upon chronic treatment: in 7 out of 8 cages observed for social ranking after chronic treatment in the third run of the experiment the animals either flipped their rank order or no clear rank could be determined anymore. No change in habituation upon repeated testing was observed in the control animals that were injected with saline throughout the experiment ($F_{(3,12)}$=0.318, p=0.81). In summary, chronic treatment with clomipramine significantly increased habituation (i.e. decreased habituation scores) in subordinate rats but had no effect (with a trend to the opposite effect) on habituation in dominant rats, demonstrating that social status plays a role in clomipramine modulation of short-term habituation.

3.3. Prepulse inhibition

The amount of PPI depends on the prepulse intensity and the interval between the prepulse and the startle stimulus (ISI). Lower prepulse intensities lead to lower PPI that is often more vulnerable to pharmacological interventions. We therefore used prepulses of 75 dB (4 ms), and 85 db (4 ms); the latter prepulse induces very strong and robust PPI. PPI disruptions have shown to be also dependent on the ISI, with different neurotransmitters affecting PPI at distinct ISIs (Bosch and Schmid, 2006; Vollenweider et al., 2007; Bosch and Schmid, 2008; Yeomans et al., 2010). We therefore tested PPI with two different ISIs of 30 ms and 100 ms. PPI with different ISIs was analysed separately.

With the lower 75 db prepulse and an ISI of 30 a repeated measure two way ANOVA revealed a significant effect of treatment ($F_{(2.55,99.48)}$=3.98, p<0.014), but not of social status ($F_{(1,39)}$=0.76, p<0.78) or interaction of social status and treatment ($F_{(2.55,99.48)}$=1.60, p<0.20). Pairwise comparison showed that PPI was significantly enhanced after chronic injections in subordinate animals only when compared to initial PPI under saline conditions (Figure 3, *top*). There was no change in PPI in the saline injected animals ($F_{(3,12)}$=0.223, p=0.812). With the 75 dB prepulse and an ISI of 100 ms, no significant effects were found of treatment ($F_{(3,117)}$=2.159, p=0.097), social status ($F_{(1,39)}$=0.399, p=0.531), or interaction of treatment an social status ($F_{(3,117)}$=0.70, p=0.554), see figure 3*bottom*. There also was no change in PPI with a 75 dB prepulse at ISIs of 100 ms in the saline injected group ($F_{(3,12)}$=1.180, p=0.358), indicating that the observed increase in PPI at 75 dB/30 ms ISI was in fact due to the drug treatment and not an improvement due to repeated testing.

At the stronger prepulse of 85 dB and an ISI of 30 ms, ANOVA revealed a significant effect of treatment ($F_{(1.717,66.56)}$=11.40, p<0.0001), but no effect of social status ($F_{(1,39)}$=0.021, p=0.866) or interaction between social status and treatment ($F_{(1.71,66.56)}$= 1.44, p=0.245). Posthoc tests revealed a significant increase in PPI after chronic treatment in subordinate animals. There was no change in PPI in the saline injected group ($F_{(3,12)}$=0.173, p=0.913, Figure 4, *top*). With the 100 ms ISI, there was also a significant effect of treatment ($F_{(3,117)}$=3.57, p=0.016), but no effect of social status ($F_{(1,39)}$=0.048, p=0.828), or interaction between social status and treatment ($F_{(3,117)}$=0.42, p=0.738) on the amount of PPI. Again, posthoc tests revealed a significant increase in PPI only after chronic treatment in subordinate animals. There was no change in PPI in the saline injected group ($F_{(3,12)}$=1.218, p=0.346), indicating that the observed increase in PPI was in fact due to the drug treatment and not an improvement due to repeated testing (Figure 4 *bottom*). In summary, PPI testing revealed a significant increase in PPI mostly after chronic treatments in subordinate animals only.

In summary, clomipramine treatment did not seem to cause any changes in baseline startle response amplitudes, but chronic treatment significantly improved habituation

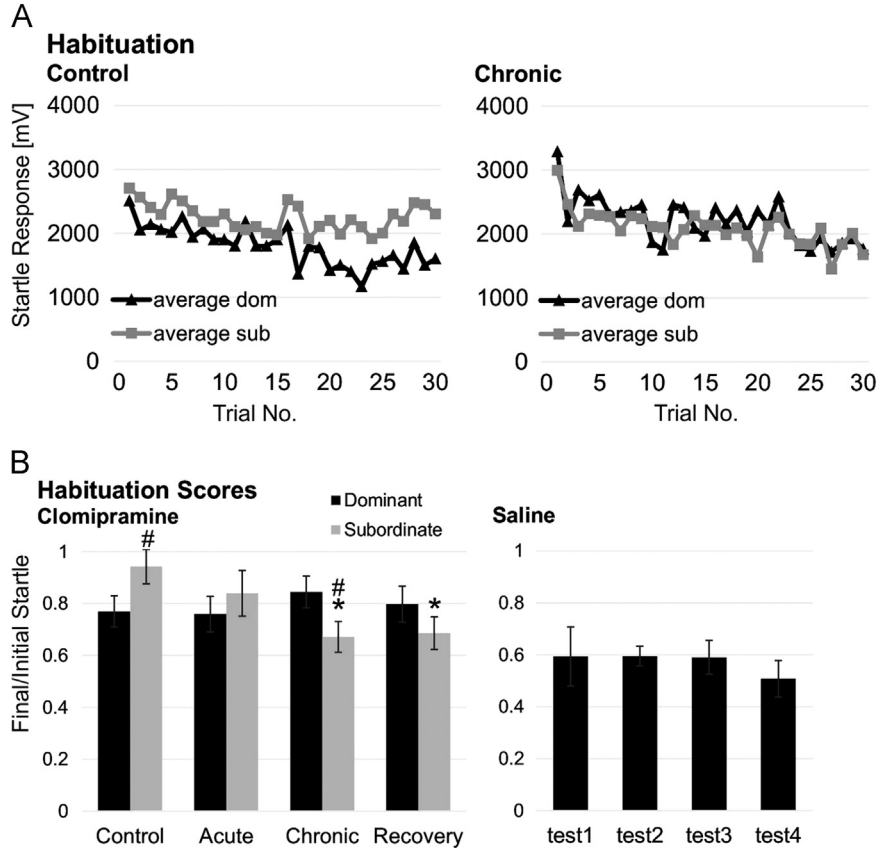

Figure 2 Short-term habituation. (A) *Left:* average startle responses of 30 consecutive trials reveal short-term habituation in dominant, but almost no habituation in subordinate rats under control conditions. *Right:* after chronic clomipramine treatment, both groups show short term habituation to a similar extent. (B) *Left:* habituation scores were calculated for each animal averaging the last five trials and divide them through the average of the first two startle responses, since most habituation occurs within the first 5–10 startle responses in rats. Mean habituation scores are plotted as for dominant and subordinate rats after different drug treatments. Dominant rats habituated to around 75–80% of their initial startle response under control conditions and after treatments without any significant changes. Subordinate animals habituated significantly less than dominant animals under control conditions (#). Habituation scores significantly improved after chronic clomipramine treatment in subordinate rats when compared to control measurements (*). After chronic clomipramine treatment the former subordinate rats showed significantly more short-term habituation than the former dominant rats (#). $N=22$ per group. *Right:* for direct comparison, habituation scores are plotted for all animals treated with saline, showing that repeated testing or aging did not significantly alter short-term habituation ($n=6$). Error bars show SEM.

specifically in subordinate animals, while habituation in dominant animals was mainly unaffected. Chronic clomipramine treatment also mildly enhanced PPI in subordinate animals, whereas it had no effect in dominant animals.

4. Discussion

Clomipramine is a widely used tricyclic antidepressant with a very potent action on serotonin and norepinephrine reuptake and very limited effect on the dopaminergic system. We here studied its effect on sensorimotor gating and to what extent it depends on social status, without trying distinguish between effects on the serotonergic versus epinephrinergic systems. Both systems have previously shown to modulate startle responsiveness, habituation, and PPI, but results have been contradictory in the past, especially in terms of serotonergic modulation (see detailed discussion below). However, differences of basic anxiety levels in humans or social status of laboratory animals have not been monitored during experiments in the past. The situation is further complicated by differences between species and strains, acute versus chronic drug administration, and different testing protocol used. In this study we therefore tested the effect of acute and chronic clomipramine treatment on short-term habituation and prepulse inhibition of startle in dominant versus subordinate rats in order to account for differences in anxiety levels before treatment. We also used different prepulse levels and prepulse/pulse intervals. We found no significant differences in baseline startle or PPI between dominant and subordinate rats under control conditions, but significantly reduced short-term habituation in subordinate animals. Clomipramine treatment had no effect on baseline startle responses, but significantly improved habituation in subordinate rats upon chronic treatment. PPI was slightly improved upon chronic treatment in subordinate animals, especially at short ISIs.

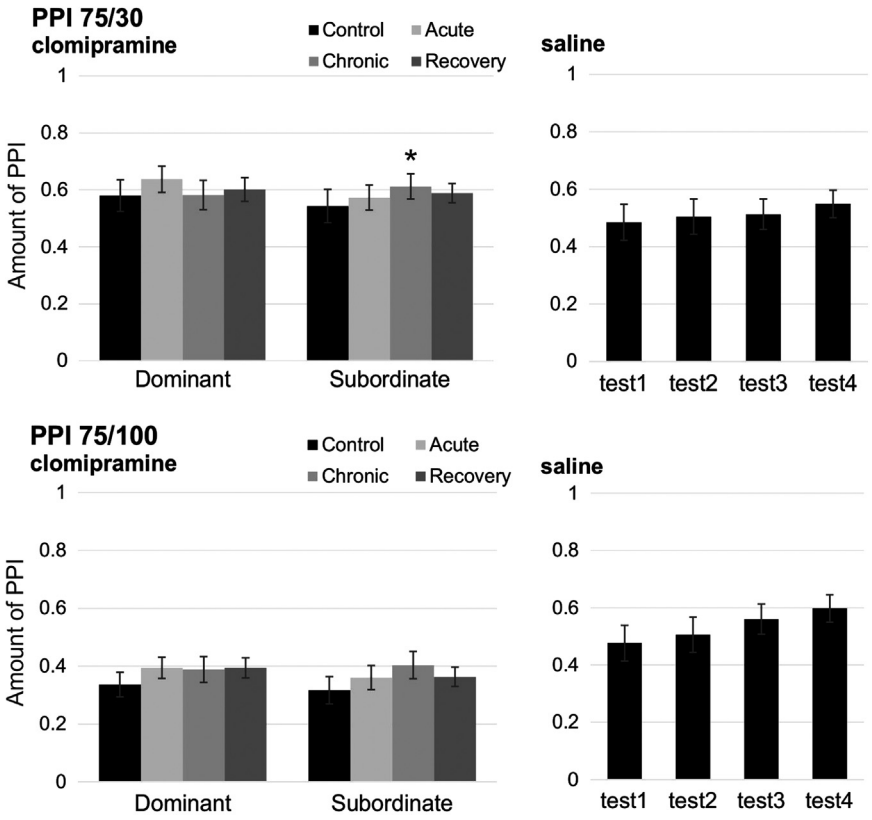

Figure 3 Prepulse inhibition with 75 dB prepulse intensity. *Top:* PPI in animals using a low prepulse intensity of 75 dB at 30 ms ISI. The amount of inhibition (normalised to baseline startle of each animal) is plotted for different drug treatments. The prepulse inhibited startle by around 50–60% and there was no difference between dominant and subordinate animals, however, subordinate animals showed a small but significant improvement in PPI upon chronic treatment when compared to initial PPI under saline treatment (*, $n=22$ per group). Saline injected animals did not show any changes in PPI. *Bottom*: PPI in animals using a prepulse intensity of 75 dB at 100 ms ISI was smaller with around 40% inhibition. There were no differences between dominant and subordinate animals, nor did the drug treatment significantly affect PPI, although a similar trend than observed above can be seen ($n=22$ animals per group). Saline injected animals did also not show significant changes in PPI ($n=6$). Error bars show SEM.

4.1. Baseline startle

Fear-potentiated startle is a common paradigm for measuring fear elicited by a conditioned stimulus presented in combination with the startle eliciting stimulus (Davis et al., 1993). Anxiety is considered to be a more general, unconditioned, form of discomfort and apprehension that is not related to a certain stimulus and therefore generally increases startle responses (for review see Davis, 1984; Koch, 1999). We try to mimic differences in baseline anxiety and stress levels by grouping male rats into dominant versus subordinate animals. We had expected to see higher baseline startle amplitudes in subordinate rats due to higher anxiety levels. Indeed, we saw a trend towards higher startle in subordinate animals; however, it failed to reach statistical significance. The baseline level of startle varies immensely between individual animals in this outbred rat strain, and this huge general variability could have masked a subtle difference due to the social status. Also, baseline startle response measurements are affected by weight – a higher weight leads to a stronger startle signal on the movement sensitive platform that was used to measure the startle response. Subordinate rats may gain weight at a slower pace than dominant rats which may counteract a higher startle response, albeit we do not see a statistically significant weight difference between our animal groups (data not shown). We also only tested a startle stimulus of 110 dB, which elicits maximum startle responses in most animals. We cannot exclude the possibility that there are differences in baseline startle between dominant and subordinate rats at lower stimulus intensities due to a lower startle threshold in subordinate animals or a steeper input/output function. Unfortunately, we could not measure startle to different startle stimulus amplitudes since this would have interfered with measurements of habituation.

Baseline startle increased in both groups throughout the experiment. Previous studies have seen either no change in baseline startle by serotonergic modulation in rats (Geyer and Tapson, 1988; Martinez and Geyer, 1997) or an increase of baseline startle in humans after acute modulations (Liechti et al., 2001; Browning et al., 2007; Grillon et al., 2007). Quednow et al. (2004) also found a trend for an increase in baseline startle in humans after two weeks of SSRI administration, however, studies on chronic SSRI administration in rats showed a reduced startle response (Bosker et al., 2010; Homberg et al., 2011). Serotonergic raphe neurons have been shown to directly project to startle neurons in the caudal pontine reticular formation (PnC) (Steinbusch, 1981; Kolta

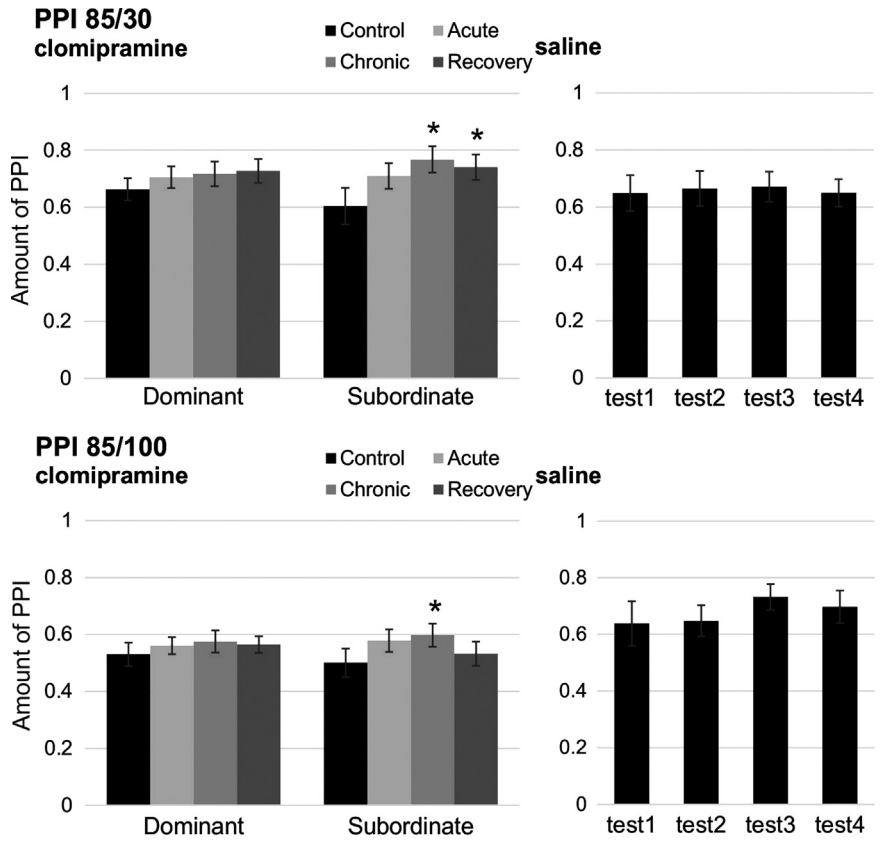

Figure 4 Prepulse inhibition with 85 dB prepulse intensity: the amount of inhibition (normalised to baseline startle of each animal) is plotted for different drug treatments. Under control conditions the startle response is reduced by around 65% (30 ms ISI, *top*) or 55% (100 ms ISI, *bottom*) of the baseline response. PPI slightly increased during treatment in subordinate animals, and significantly enhanced PPI upon chronic treatment (*, $n=$ 22 animals per group). PPI did not change in saline treated animals throughout the experiment *(right)*. Error bars show SEM.

et al., 1993). In the presence of serotonin, pH-sensitive potassium channels (TASK-3) that are expressed in startle mediating giant neurons in the PnC, are inactivated by 5-HT_{2C} receptor activation, which could theoretically cause an increase in baseline startle response (Davis et al., 1986; Weber et al., 2008). A similar serotonergic effect was also reported in the startle pathway of the goldfish (Curtin et al., 2013). Also, acute norepinephrine increases arousal and thereby potentially the startle reactivity. Indeed, epinephrine knock-out mice and rats with lesions in the locus coeruleus show reduced startle reactivity (Adams and Geyer, 1981) and fear potentiated startle (Toth et al., 2013). However, it is difficult to assess to what extent the increase in baseline startle in our study was due to clomipramine administration versus just a gain in weight. Startle amplitudes also increased in saline injected control animals, and our statistical analysis failed to detect any significant difference between saline and clomipramine injected groups, indicating that weight gain was the major factor driving the increase in startle amplitude.

4.2. Clomipramine effects on habituation

Although dominant and subordinate rats did not show statistically significant differences in initial startle response under control conditions, this is the first report showing that they significantly differ in the ability to habituate to repeated startle stimuli. This is consistent with the theory that a high anxiety level increases startle and leads to sensitization rather than habituation upon repeated stimulation (Groves and Thompson, 1970; Prescott, 1998). Acute administration of the selective serotonin re-uptake inhibitor (SSRI) escitalopram has shown a slowing effect on habituation in humans, which is consistent with the initial increase in anxiety level during SSRI intake (Jensen et al., 2007; Oranje et al., 2011), thus anxiety levels might be one factor influencing the difference between dominant and subordinate rats. Chronic administration of the SSRI sertraline decreased habituation in patients with major depression (Quednow et al., 2004). Accordingly, studies on chronic SSRI administration in rats showed a reduced startle response, and reduced habituation (Bosker et al., 2010; Homberg et al., 2011). Norepinephrine has also been suggested to oppose habituation by increasing sensitization (Adams and Geyer, 1981). In contrast, we did not observe any disruptions of habituation after clomipramine treatment, but an improvement in habituation in subordinate rats after chronic administration and no change (although a trend to less habituation) in dominant animals. Interestingly, animals tended to change the rank order through clomipramine treatment as well, indicating that especially the subordinate rats benefit from the anxiolytic effect of clomipramine after adaptive changes occurred.

Previous studies in humans have demonstrated that patients with higher baseline startle amplitudes had a stronger improvement of depressive symptoms when taking SSRIs; thus it was suggested that the strength of the startle at baseline could be used as a predictor for the efficacy of antidepressant therapy. Changes in baseline startle amplitude were not significantly correlated to improvement, though (Quednow et al., 2004). Results of our study suggest that the ability to habituate to startle stimuli, rather than the baseline startle response amplitude itself, might be predictive of the susceptibility to monoamine re-uptake inhibitors.

4.3. Prepulse inhibition

The monoamine re-uptake inhibitor imipramine reduced PPI (Hammer et al., 2007) which suggests a detrimental effect of either serotonin or norepinephrine on PPI. Indeed, it has been found consistently and repeatedly that stimulation of α1 and β norepinephrine receptors results in PPI disruption, and that PPI deficits can be reversed by α1 and β receptor antagonists (Bakshi and Geyer, 1998; Carasso et al., 1998; Shilling et al., 2004; Alsene et al., 2006; Swerdlow et al., 2006a; Alsene et al., 2010, 2011). Chronic administration of the SSRI sertraline had no effect on PPI in patients with major depression (Quednow et al., 2004). Accordingly, studies on chronic SSRI in rats have shown no effect on PPI (Bosker et al., 2010; Homberg et al., 2011).

MDMA has been reported to increase PPI without affecting habituation in humans, whereas it was reported to disrupt PPI and habituation in rodents. Effects in both models could be reversed by serotonin re-uptake inhibitors (Vollenweider et al., 1999; Liechti et al., 2001). In general, agonists for the 5HT-1A receptors and antagonists to 5HT-2A seem to enhance PPI or restore disrupted PPI (McFarland et al., 2011; Price et al., 2012; Uchiumi et al., 2013) whereas 5HT-1A antagonists and 5HT-2A agonists reduce PPI (Mansbach and Geyer, 1989; Rigdon and Weatherspoon, 1992; Sipes and Geyer, 1994; Fletcher et al., 2001; Prinssen et al., 2002; Brosda et al., 2011; Wischhof et al., 2012). However, it was also suggested that the attenuation in PPI through serotonin depletion is also partially due a decrease in serotonin and norepinephrine levels in the prefrontal cortex (Kusljic et al., 2003). Accordingly, epinephrine deficient mice also show a higher degree of prepulse inhibition (Toth et al., 2013). This is important in light of clomipramine displaying its effects on both serotonergic and norepinephrinergic activity (Dell'Osso et al., 2006). We found a significant enhancement of PPI with clomipramine that was more pronounced at short ISI of 30 ms as compared to 100 ms ISIs. In line with our findings, other studies have also found serotonergic effects on PPI specifically with short ISIs (Vollenweider et al., 2007).

4.4. Potential mechanisms of chronic clomipramine

It was suggested that the effect of serotonin on PPI at short ISIs is due to 5HT-2A receptor modulation in lower brain regions that directly modulate startle, whereas at long ISIs a simultaneous and potentially counteracting stimulation of 5HT-1A on cortical pyramidal cells come into play (Martin-Ruiz et al., 2001; Martin-Ruiz and Ugedo, 2001; Vollenweider et al., 2007). Thus, an adaptive down-regulation of 5HT-2A upon chronic treatment could explain the habituation and PPI enhancement specifically at short ISI. The difference in baseline serotonergic signalling between dominant and subordinate animals might explain the difference in sensitivity to this effect.

Recent studies suggest that the regulation of neurogenesis might also play a role in chronic effects of antidepressants. It has been shown that neurogenesis is decreased by depression (Santarelli et al., 2003), as well as by chronic stress (Lagace et al., 2010). Chronic social defeat has been shown to induce stress and reduce neurogenesis by 50%, which could be reversed by chronic antidepressant treatment (Jiang et al., 2015), and the serotonin and norepinephrine re-uptake inhibitor venlafaxine has shown to increase neurogenesis in the hippocampus (Zhang et al., 2015). It was suggested that neurogenesis specifically in the ventral portion of the hippocampus (homologous to the anterior hippocampus in humans) is relevant for anxiety and mood regulation (for review see O'Leary and Cryan, 2014). Activity in the ventral hippocampus, however, has also been shown to greatly influence sensorimotor gating, most importantly PPI (Swerdlow et al., 1995; Zhang et al., 2002; Adams et al., 2008; Rhein et al., 2013; Nguyen et al., 2014). An increase in neurogenesis in the ventral hippocampus could therefore potentially be responsible for changes in sensorimotor gating at longer ISIs in subordinate rats upon chronic treatment with anti-depressants. Future studies will have to address this hypothesis and further explore the mechanisms underlying chronic effects of antidepressants on sensorimotor gating.

5. Conclusion

Our study suggests that the social status in rats has an influence on the effect of chronic clomipramine on sensorimotor gating, especially on habituation, and that the amount of habituation under control condition might be a good predictor of the effect of clomipramine. Given that the social status of a rat is indicative of anxiety and stress levels, it would imply that clomipramine has different effects in depressed patients than in human volunteers.

Our data further indicate that both habituation and/or PPI are not disrupted, but can potentially be improved through clomipramine. This is important when clomipramine or similar drugs are applied to humans with schizophrenia or other comorbidities associated with sensorimotor deficits, since it is critical not to exacerbate sensorimotor gating deficiencies.

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Contributors

Susanne Schmid designed the study, wrote the final manuscript and handled it. Alvin Yang contributed to the study design and acquired some of the data, analysed it, and did statistical analysis. Karen Carlton and Tahira Daya acquired some of the data, analysed it, and wrote a first draft of the manuscript. Jin Hui helped acquiring the data. All authors contributed to and have approved the final manuscript. None of the authors have any conflict of interest.

Conflict of interest

None of the authors have any conflict of interest.

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