Consciousness = learning? The role of recurrent processing in perceptual learning
Meuwese, J.D.I.

Citation for published version (APA):
Meuwese, J. D. I. (2014). Consciousness = learning? The role of recurrent processing in perceptual learning

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

Download date: 12 Dec 2018
Chapter 5. The role of ketamine in perceptual learning: mixed performance and reaction time effects

N-methyl-D-aspartate (NMDA) receptors are thought to play a role in inducing synaptic plasticity. However, not much is known about the involvement of NMDA receptors in human low-level perceptual learning. Therefore, we investigated whether the NMDA receptor antagonist ketamine would impair perceptual learning, using a texture discrimination task. During training, subjects were under administration of a subanesthetic dose of ketamine or a placebo. One day later learning was assessed: subjects had to perform the same texture discrimination task, followed by a version during which feedback was provided. Indeed, in the placebo condition subjects performed significantly better one day after training, whereas performance was not improved in the ketamine condition (except for the feedback version of the task). However, these learning effects did not differ significantly between drug conditions: compared to the ketamine condition, performance improvement in the placebo condition was not significantly enhanced. We therefore cannot definitely conclude that more learning has taken place in the placebo condition than in the ketamine condition. Interestingly, reaction times were significantly slower in the ketamine condition compared to the placebo condition. This is remarkable, as during the training session (when subjects were under ketamine or placebo administration) reaction times did not differ. Whether the findings are due to a ceiling effect or other factors is discussed.

INTRODUCTION

Perceptual learning is the increased ability to extract information from the environment, through experience and practice with sensory stimulation (Gibson, 1969). Perceptual learning effects often are long lasting and stimulus-specific, leading to long-term neural changes in early visual areas (for a review, see Gilbert, Sigman, & Crist, 2001). It is thought that these experience-dependent changes in visual cortex require activation of NMDA receptors (Bear, 1996). Namely, NMDA channels possess a unique property: their gating is both ligand- and voltage-dependent. The channel only opens up when both glutamate binds to the NMDA receptor and the neuron is sufficiently depolarized by concomitant pre-synaptic activation of its AMPA receptors (Collingridge & Bliss, 1987). Prolonged activation will open up the NMDA channel and allow calcium entry into the postsynaptic neuron, inducing synaptic plasticity through upregulation of AMPA receptors (Barry & Ziff, 2002; Bredt & Nicoll, 2003; Malinow & Malenka, 2002; Sheng & Kim, 2002; Shi, 1999). This way, the NMDA receptor acts as a Hebbian coincidence detector, strengthening the synapse contingent upon concurrent pre- and post-synaptic activity (Cotman & Monaghan, 1988; Flohr et al, 1998; Mori & Mishina, 1995; Morris, 1989).

One way to study the role of NMDA receptors in learning is blocking the receptor using pharmacological interventions. Using NMDA receptor blockers such as D,L-2-amino-5-phosphonovaleric acid (APV), NMDA receptors have been shown to play an important role in mediating synaptic plasticity during learning and development of rat and kitten visual cortex (Artola & Singer, 1987; Kleinschmidt, Bear, & Singer, 1987; Morris, 1989). In humans, the NMDA receptor antagonist ketamine has been found to affect memory-related functions: the acquisition of new memories (verbal or object recall) (Malhotra et al, 1996; Oye, Paulsen, & Maursel, 1992; Parwani et al., 2005) and more transient memory functions such as the retention of visual information across time in a delayed match-to-sample task (Taffe, Davis, Gutierrez, & Gold, 2002) (see Morgan & Curran (2006) for a review). However, not much is known about the involvement of NMDA receptors in human low-level perceptual learning.

The current study investigated whether manipulating NMDA receptors with the NMDA receptor antagonist ketamine would impair perceptual learning. We used a texture discrimination task originally designed by Karni and Sagi (1991), which has often been used to study perceptual learning (Censor & Sagi, 2009; Ofen, Moran, & Sagi, 2007; Sagi & Tanne, 1994; Schwartz et al., 2002). In a recent article (Meuwese et al., 2013, see Chapter 6), we showed that a subanesthetic dose of ketamine significantly impaired performance on this texture discrimination task, compared to a placebo condition. In the current study, we added a perceptual learning component to the experimental design of Meuwese et al. (2013, see Chapter 6), by retesting every subject on the texture discrimination task one day after this task had been performed under a subanesthetic dose of ketamine or placebo administration. We expected that ketamine administration would abolish perceptual learning effects one day after administration because of the ketamine-induced NMDA receptor blockade, prohibiting synaptic plasticity.
METHODS

Subjects
Twenty subjects (11 males, 9 females) participated in the experiment for financial compensation. The experiment was approved by the Medical Ethical Review Committee of the Academic Medical Center of Amsterdam. Written informed consent was obtained from each subject before experimentation. Subjects were screened by a psychiatrist for conditions that may cause complications upon ketamine administration, such as psychiatric disorders and drug addiction. Subjects had normal or corrected-to-normal vision, two were left-handed. Subjects were required to refrain from recreational drug usage for 30 days prior to participation and to have had no prior experience with ketamine. Four subjects were excluded because of incorrect task order administration and technical failure. All analyses are based on the remaining sixteen subjects (10 males, 6 females, $M = 23.21$ years of age, $SD = 1.17$ years).

General Procedure
The experiment was a within-subject double blind, placebo-controlled design. Each subject participated in two training sessions, taking place two weeks apart: one during which ketamine was administered and one where a placebo was administered. The order of the drug conditions (ketamine or placebo) was counterbalanced across subjects. One week prior to the to start of the experiment a practice session took place to familiarize subjects with the task. In both sessions, subjects performed a texture discrimination task in which they had to discriminate the orientation (horizontal or vertical) of a peripheral target texture that was masked at a decreasing stimulus onset asynchrony (SOA). The quadrant in which the target texture appeared (upper left or right) was counterbalanced across conditions and sessions.

One day after each training session, a testing session took place (during which no ketamine or placebo was administered). During these testing sessions, perceptual learning was assessed using the same texture discrimination task that subjects performed during the training session the day before. Perceptual learning was defined as an improvement of percentage correct on the texture discrimination task during testing the next day, compared to the placebo condition during training (as an improvement compared to the ketamine training condition would not necessarily mean that subjects have learned, just that subjects perform better when no longer being under the influence of ketamine). After the first test, they performed the same task again, but this time they received performance feedback on the texture discrimination task as well (instead of only on the fixation task), to see if this would improve any learning effects.
Task Design

On each trial, subjects performed a dual task, first designed by Karni and Sagi (1991). Subjects had to identify a central letter (a randomly rotated T or L) (‘fixation task’, first button press), whilst discriminating the orientation of a masked peripheral target texture (horizontally or vertically aligned line segments) (‘texture discrimination task’). SOA between stimulus and mask decreased from 467 to 66 ms. Immediate auditory feedback was provided for the fixation task. Figure and task were adapted with permission from Schwartz et al. (2002).

Figure 5.1. Schematic illustration of a single trial. On each trial, subjects performed a central letter identification task (a randomly rotated T or L) to ensure fixation (‘fixation task’) and identified the orientation of a peripheral target texture (horizontal or vertically aligned line segments) (‘texture discrimination task’). SOA between stimulus and mask decreased from 467 to 66 ms. Immediate auditory feedback was provided for the fixation task. Figure and task were adapted with permission from Schwartz et al. (2002).
steady decrease of performance with these decreasing SOA’s. Immediate auditory feedback was provided for the fixation task, to ensure high task performance (and thus fixation). No feedback was given for the texture discrimination task. The feedback version was administered after the standard version. This time, feedback on the texture discrimination task was provided in addition to the auditory feedback on the fixation task. On every trial, a green or red bar containing the text ‘correct’ or ‘incorrect’ (in Dutch) respectively was presented for 500 ms immediately after the response was made.

For each drug condition (ketamine or placebo), the target texture was always presented in the same quadrant (upper left or right (Pourtois et al., 2008), counterbalanced across subjects), for both the training and testing session. As improvements in task performance do not transfer across quadrants (Karni and Sagi, 1991; Schwartz et al, 2002; Yotsumoto and Watanabe, 2008), this enabled us to assess texture discrimination in both conditions whilst limiting within-subject transfer effects of task performance.

Drug administration
Only during the training sessions drugs were administered (placebo or ketamine). Drugs were administered by an anesthesiologist unblinded to group allocation for safety reasons. Experimenters and subjects were blind to the drug condition. Venous access was established using a 20G intravenous catheter (Vasofix, B Braun, Melsungen, Germany). Subsequently, in the ketamine condition, a subanesthetic dose of S-ketamine (Eurocept BV, Ankeveen, The Netherlands) was administered intravenously. First a slow bolus of 0.15 mg/kg was administered, followed by continuous infusion of 0.1 mg/kg/h using an infusion pump (Perfusor fm, B Braun, Melsungen, Germany) to keep plasma ketamine levels constant throughout the experiment. In the placebo condition, saline (NaCl 0.9% (B Braun, Melsungen, Germany)) was administered via the same procedure.

Data analysis
Trials with a reaction time deviating more than two SD from the average on the fixation task or the texture discrimination task were excluded from analysis. SOA curves were constructed for performance and reaction time by averaging over subjects per drug condition per SOA. For SOA’s that were used for two consecutive blocks (when the SOA was set at 133, 117, 100, 83 and 66 ms), values were averaged across blocks, resulting in one value per SOA.

Between drug conditions, performance and reaction time curves were compared using a repeated measures ANOVA for drug condition of the training session (ketamine, placebo) x SOA (467, 367, 267, 167, 133, 117, 100, 83 and 66 ms). Drug order (whether subjects received ketamine during the first or the second training session) was included as a between-subjects factor, to exclude possible effects of drug order on perceptual learning and task performance. Perceptual learning was measured as the increase of texture discrimination performance during the testing session, compared to the subjects’ performance during the placebo training session. This placebo baseline was used for both
drug conditions, because in the ketamine condition, an improvement of the testing session compared to the ketamine training session would not necessarily mean that subjects have learned, just that subjects perform better when no longer under the influence of ketamine. We also performed paired t-tests on the average performance across SOA’s, as an overall measure of learning. Within condition, we also compared overall learning effects using paired t-tests. Statistical analysis was performed using SPSS 17.0 (IBM, Armonk, USA).

RESULTS

Training session
For detailed results of the training session we refer to Meuwese et al. (2013, Chapter 6). Here, it suffices to summarize that ketamine significantly impaired performance on the texture discrimination task compared to the placebo condition. This was not merely due to task difficulty or a difference in sedation levels. Importantly, there were no reaction time differences between conditions, indicating that the found effects were not caused by a non-specific effect of ketamine.

Performance
During the testing session, one day after the training session during which a placebo was administered, overall percentage correct was significantly increased ($t_{(1,15)} = 3.079, p = .008$) (Figure 5.2E). Subjects who were under ketamine administration during training did not show a significant improvement one day later, compared to their placebo training baseline ($t_{(1,15)} = 1.097, p = .29$) (Figure 5.2E). However, when comparing learning effects for the placebo versus ketamine condition, no differences between drug conditions were observed in terms of overall learning effect ($t_{(1,15)} = -0.319, p = .75$) and comparing performance on all SOA’s using a repeated measures ANOVA ($F_{(1,4)} = 1.096, p = .31$) (Figure 5.2C). This means that we cannot conclude that there is more learning in the placebo condition compared to the ketamine condition, even though we observed a within-condition learning effect only for the placebo condition.

A similar pattern of performance enhancement was found for the feedback version of the task compared to the standard version (Figure 5.2G). The placebo condition showed a marginally significant increased performance on the feedback version of the texture discrimination task, compared to the standard version the same day ($t_{(1,15)} = 2.120, p = .051$). No performance enhancement was found in the Ketamine condition ($t_{(1,15)} = 1.480, p = .16$). But again, we cannot conclude that there was more improvement in the placebo condition than the ketamine condition, as no between drug conditions difference was found ($t_{(1,15)} = -.319, p = .75$; ANOVA: $F_{(1,14)} = .123, p = .73$). Compared to the placebo training session baseline however, both the placebo and ketamine condition showed increased performance on the feedback texture discrimination task (placebo: $t_{(1,15)} = 3.466, p = .003$; ketamine: $t_{(1,15)} = 2.905, p = .011$; Figure 5.2F), but again no differences in learning effect were found between the placebo and
The role of ketamine in perceptual learning

Ketamine condition ($t(1,15) = 1.029, p = .32$; ANOVA: $F_{(1,14)} = .990, p = .34$) (Figure 5.2D and 5.2F).

For both versions of the task, there was no effect of SOA on learning effects (all $F_{(8,7)} < .938$, all $p > .54$), nor any interactions of drug condition and SOA (all $F_{(8,7)} < .955$, all $p > .53$), indicating that learning effects did not differ across SOA’s. Drug order and drug condition did however interact significantly for the standard version ($F_{(1,14)} = 4.859, p = .045$); ketamine had a stronger effect on performance when administered during the first session (feedback version: ($F_{(1,14)} = .022, p = .88$). Performance on the fixation task was equal between conditions, for both the standard version ($F_{(1,14)} = 2.114, p = .17$) and the feedback version ($F_{(1,14)} = .184, p = .68$) of the task (all percentage correct $M \geq 95\%$, all SD < 4.3).

**Figure 5.2.** Perceptual learning effects of performance on the texture discrimination task. Perceptual learning was assessed one day after training under ketamine or placebo administration with the standard version and providing feedback. (A) and (B) depict raw performance scores, performance of the placebo condition during training was used as a baseline (see ‘Methods’ section). Learning effects ((C) and (D)) reflect the amount of performance improvement per SOA, compared to each subjects’ placebo training baseline. Overall learning effects (average performance improvement across SOA’s) ((E) and (F)) were observed within- but not between-conditions. (G) depicts the overall difference between the feedback version and the standard version of the task; only the placebo condition shows a marginally significant improvement on the feedback version.
Reaction time

Subjects in the placebo condition were faster in responding to the target in the texture discrimination task, compared to the training session the day before ($t_{(1,15)} = -4.141, p = .0009$). In contrast, reaction times did not decrease in the ketamine condition compared to the placebo training baseline ($t_{(1,15)} = -.944, p = .36$) (see Figure 5.3E). However, again no differences between drug conditions were observed ($t_{(1,15)} = -1.138, p = .27$, ANOVA: $F_{(1,14)} = 2.859, p = .11$), so the reaction time decrease in the placebo condition was not significantly larger than that of the ketamine condition (Figure 5.3C and 5.3E).

For the feedback version of the task, the same pattern of results was observed, yet more pronounced. Reaction time in the placebo condition was significantly decreased compared to the placebo training session baseline ($t_{(1,15)} = -4.897, p = .0002$), whereas in the ketamine condition it was not ($t_{(1,15)} = -1.490, p = .16$) (Figure 5.3F). The paired t-test revealed no between-condition

![Figure 5.3](image-url)

*Figure 5.3. Perceptual learning effects of reaction time on the texture discrimination task. Perceptual learning was assessed one day after training under ketamine or placebo administration with the standard version and providing feedback. (A) and (B) depict raw reaction times, reaction time of the placebo condition during training was used as a baseline (see ‘Methods’ section). Learning effects ((C) and (D)) reflect the amount of reaction time difference per SOA, compared to each subject’s placebo training baseline. An ANOVA (drug condition x SOA) revealed a significant difference between the ketamine and placebo condition for the feedback version (D) ($F_{(1,14)} = 5.668, p = .03$). Overall reaction times (average reaction time differences across SOA’s) ((E) and (F)) were improved only in the placebo condition, but there were no significant differences between drug conditions. (G) shows the overall difference between the feedback version and the standard version of the task; no significant improvements were observed.*
difference \((t_{(1,15)} = -1.507, p = .15)\), but the repeated measures ANOVA did (correcting for the effects of drug order by including this as a between-subjects factor) \((F_{(1,14)} = 5.668, p = .03)\) (see Figure 5.3D). Thus, one day after placebo administration, subjects were significantly faster than one day after ketamine administration, when drug order (whether subjects received ketamine during their first or second training session) was taken into account. This reaction time effect is especially notable since no reaction time differences between drug conditions were observed during the training session, while subjects were under placebo or ketamine administration (see Meuwese et al., 2013, Chapter 6).

For the feedback version, there was an effect of SOA; the longer (or ‘easier’) the SOA, the larger the reaction time improvement for both drug conditions \((F_{(8,7)} = 8.109, p = .006;\) standard version: \(F_{(8,7)} = 2.344, p = .14\); no interactions of drug condition and SOA (all \(F_{(8,7)} < 1.382, all p > .34\)). Interactions of drug condition and drug order were found for both versions of the task (standard version: \(F_{(1,14)} = 19.127, p = .001;\) feedback version: \(F_{(1,14)} = 23.455, p = .00026\); ketamine had a much stronger effect on RT when it was administered during the first session, when subjects were not yet experienced on the task. This strong interaction, especially for the feedback version, explains why between condition differences are only revealed when drug order is taken into account with an ANOVA.

Both conditions did not show any reaction time differences on the feedback version compared to the standard version the same day (placebo: \(t_{(1,15)} = -.558, p = .59;\) ketamine \(t_{(1,15)} = -.351, p = .73\); between conditions: \(t_{(1,15)} = -.037, p = .97, ANOVA: F_{(1,14)} = .001, p = .97\) (Figure 5.3G). For the fixation task, reaction time in the placebo condition was shorter than in the ketamine condition, for both the standard version \((F_{(1,14)} = 6.244, p = .03)\) and the feedback version \((F_{(1,14)} = 8.994, p = .01)\) of the task.

DISCUSSION

We investigated whether the NMDA receptor antagonist ketamine impairs perceptual learning, as NMDA receptors manipulated by this drug are thought to be involved in synaptic plasticity (Flohr et al., 1998; Mori & Mishina, 1995; Morris, 1989). We measured performance on a texture discrimination task one day after the same task had been performed under administration of a subanesthetic dose of ketamine or a placebo. There was however no difference in performance between the ketamine and placebo condition, for both versions of the task (standard and feedback). Within-condition learning effects were present for both tasks in the placebo condition, and in the ketamine condition only for the feedback version. Interestingly however, for the feedback version, reaction times were significantly slower in the ketamine condition compared to the placebo condition. This is remarkable because no reaction time differences were observed during the training session, when subjects were under drug administration. Yet one day after ketamine administration, subjects are significantly slower than one day after placebo administration.
The current within-subject design is vulnerable to effects of the order in which drugs were administered and general practice effects. For instance, if a subject performs better during the second session, in which he receives a placebo, is this improvement due to the placebo or practice? We tried to minimize practice effects by keeping the training sessions two weeks apart, and by letting the target appear in different quadrants between sessions (as performance improvements on the texture discrimination task have been shown not to transfer between quadrants (Karni and Sagi, 1991; Schwartz et al, 2002; Yotsumoto and Watanabe, 2008)). In addition, we counterbalanced the order in which drugs were administered across subjects, and included 'drug order' as a between-subjects factor in our ANOVA's. Indeed, significant drug condition X drug order interactions can be observed in our ANOVA's (especially for RT), as the effect of ketamine was stronger when subjects received it during their first session, as opposed to receiving it during their second session, when they were already familiar with the task. That is also why the ANOVA for the feedback version RT (correcting for drug order as a between-subjects factor) revealed a significant difference between drug conditions, whereas t-tests (not taking this into account) did not. These findings stress the impact of order effects in within-subject drug studies, and the importance of correcting for it in an ANOVA.

In many other studies, ketamine has been found to affect memory-related functions (see Morgan & Curran (2006) for a review). There are several possible explanations for the fact that we do not find any strong learning effects in the current study. Possible factors could be the short training period (20 minutes) or a lack of statistical power due to the small number of subjects. Furthermore, it is important to note that our dose (0.1 mg/kg/h) is very low, and may not be sufficient to prohibit perceptual learning. This idea is supported by Taffe et al. (2002) who found ketamine-induced impairments on two perceptual memory tasks (delayed match-to-sample and a spatial working memory task) only for a dose of 1.0 mg/kg and higher. Their lowest dose – at 0.3 mg/kg still higher than the current dose – did not affect performance on those two tasks. It would be interesting to investigate whether higher doses of ketamine would gradually enhance learning impairments (for instance, see Oye 1992 and Newcomer 1999).

Moreover, the lack of learning effects in performance could be due to some kind of ceiling effect. Even though percentage correct was not 100%, the task may have had not much room for performance improvement. Although there may have been a ceiling effect present for performance, there was more room for improvement as far as reaction times are concerned. Subjects were able to speed up their decisions one day after placebo administration, whereas this was not the case one day after ketamine administration. This is also reflected by larger reaction time improvements for 'easier' SOA's in both drug conditions. Perhaps an analysis somehow integrating performance and reaction time measures would reveal larger between drug condition differences. Such an analysis could take into account a speed-accuracy tradeoff, which may have been present in the placebo condition in particular, impeding further performance enhancements.

In sum, we did not find strong supporting evidence for ketamine-induced perceptual learning impairments. The lack of performance differences between
the ketamine and placebo condition may be due to several factors, such as order effects of our within-subjects design, a too short training period, the small number of subjects, a too low dose of ketamine or a ceiling effect. Notably, we did observe faster reaction times for the placebo compared to the ketamine condition (for the feedback version), whilst no reaction time differences were present during the training session (when subjects were under ketamine or placebo administration). This suggests that even though performance may have been at ceiling, subjects in the ketamine condition experienced greater difficulty performing the task one day later than in the placebo condition.