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ORIGINAL INVESTIGATION

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Effects of synthetic Δ^9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man

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Abstract Binocular depth inversion represents an illusion of visual perception that is sensitive to various behavioural and psychiatric conditions. It is affected by cannabinoids, reflecting associated changes in perception. The present study investigated the differences in binocular depth inversion of different classes of natural and artificial objects and the effect of synthetic Δ^9-tetrahydrocannabinol (Dronabinol) on these illusionary perceptions. Using this model, the effects of orally administered Dronabinol on binocular depth inversion were investigated in 17 healthy male volunteers. Pictures from natural and artificial objects were presented stereoscopically and the depth perception of the volunteers was scored in an operationalized way. The time-course of the effects of Dronabinol on binocular depth inversion was analyzed with regard to the stimulus classes (natural and synthetic objects). Significant differences in binocular depth inversion of the different groups of stimuli were revealed. Objects with a higher degree of everyday familiarity were generally seen as more illusionary than those with a lower degree of everyday familiarity. A strong impairment of binocular depth inversion due to Dronabinol was found in most classes of objects. Analysis of different stimulus classes provides further information on the underlying perceptual processing of binocular depth inversion. An impairment of top-down processing of visual sensory data by Dronabinol is suggested. The anandamidergic system seems to be involved in areas of visual information processing.

Key words Cannabinoids · THC · Dronabinol · Binocular depth inversion · Human

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Introduction

Since the identification of Δ^9-tetrahydrocannabinol (Δ^9-THC) as the major psychoactive compound of cannabis resin (Gaoni and Mechoulam 1964), various effects of Δ^9-THC have been investigated over the last decades. The recent identification of a central nervous cannabinoid receptor (Devane et al. 1988) and of the first endogenous cannabinoid receptor ligands, anandamide and 2-arachidonylglycerol (Devane et al. 1992; Stella et al. 1997), gave rise to investigations of the specific actions of naturally and synthetically obtained cannabinoids (for review, see Howlett 1995). Previous studies of the effects of cannabis on visual perception in humans mainly used cannabis resin with specified concentrations of Δ^9-THC. However, from a psychopharmacological point of view, administration of a mixture of different genuine cannabinoids may cause a variety of neuropsychological effects that may not necessarily be associated with the action of Δ^9-THC. We therefore selected a synthetic Δ^9-THC, Dronabinol (Marinol), which has been approved for medical purposes in the United States of America. While the physiological and pathophysiological role of the anandamidergic system still remains widely unknown in humans, this system has been implicated in the pathogenesis of psychoses (Emrich et al. 1997). So far, most of the clinical observations regarding the latter topic, as well as our experimental studies in this field (Emrich et al. 1991, 1997), did not exclude possible interactions with non-psychotropic cannabinoids like cannabidiol

(Petitet et al. 1998). Recently, cannabidiol has been proposed to have antipsychotic properties as well (Zuardi and Guimaraes 1997). We therefore used a less contaminated source of Δ^9-THC here, to prove and extend our previous findings on the perceptual effects of cannabinoids.

Binocular depth inversion represents a well-known model of illusionary perception. It has been shown that binocular depth perception is influenced by various factors. Wheatstone (1838) found that binocular disparity is the most effective one. He also discovered that interchanging the view of the left and the right eye using a stereoscope leads to a reversed depth experience of most objects ("pseudoscopic vision") (Wheatstone 1852). Other cues influencing depth perception were identified as lighting direction, texture gradients, retinal rivalry, contour lines, and motion parallax (Ramachandran 1988; Parker et al. 1995).

Under certain circumstances, the individual perception of a pseudoscopically presented three-dimensional object may differ from the physical information of an object. Current theories on visual perception suggest an interaction of bottom-up and top-down processing resulting in the conscious experience of an object. Binocular depth inversion has been understood as a process of generating hypotheses on the three-dimensional shape of objects by interpreting the bottom-up signals from the eyes using conceptual and perceptual knowledge (top-down) as well as general rules of perception, such as Gestalt laws of organization and perspective (Yellott Jr 1981; Hill and Bruce 1993; Gregory 1998). Referring to this concept, binocular depth inversion results from a domination of top-down object knowledge over bottom-up signals. We previously suggested that the disturbance of binocular depth inversion is due to an impairment of the top-down processing of the presented objects (Emrich 1989; Schneider et al. 1996). Thus, a reduction or reversal of binocular depth inversion by Δ^9-THC would be due to an impairment of the top-down processing, and this would be strongest for the stimuli which use the most top-down processing.

To investigate this hypothesis, binocular depth inversion for different natural and artificial objects was assessed in 17 healthy volunteers before and after administration of Δ^9-THC. The present study was part of a larger electrophysiological and neuropsychological investigation on the effects of synthetic Δ^9-THC in man (see also Leweke et al. 1998).

Materials and methods

The appropriate ethics committee and the German Federal Institute for Drugs and Medical Devices – Federal Opium Agency approved the study-protocol as outlined below.

Seventeen healthy male volunteers participated in the study. They signed an informed consent form and were allowed to withdraw from the study at any time without disclosure of their reasons. The subjects were aged between 20 and 47 years, with a mean age of 28.8. All subjects reported normal health, normal or corrected to normal vision and were found to have an entirely normal general and neurological status before entry into the study. Stereoscopic vision was tested using the TNO test (Lameris, Utrecht, Netherlands). Furthermore, urine drug screening was performed before entry into the study. Subjects with a history of recurrent abuse of illicit drugs other than cannabinoids or other psychiatric, neurological, and medical diseases were not included into the study. No positive proof of opiates, cocaine, amphetamines, phencyclidine, and cannabinoids in a urine drug screening was tolerated. To minimize the risk of an idiosyncratic psychotic reaction on first use of Δ^9-THC (Negrete 1989) and to avoid first contact experience, only subjects with past experience but no recent consumption of cannabinoids (at least for the previous 12 weeks) were included. The overall lifetime consumption of cannabinoids was limited to ten times to prevent long-term influences of previous cannabis use. Subjects were requested not to take any other medication for a period of at least 10 days before the study was performed.

All subjects received a standardized breakfast 1 h prior to the start of the experiments. They performed baseline tests for binocular illusionary perception as described below. Afterwards, Dronabinol (Marinol) was administered orally at dosages of 10, 12.5 or 15 mg, depending on the body weight of each volunteer (~120 μg Dronabinol per kg body weight). This dosing was within the range of the recommended dosing as an appetite stimulant (maximum dosage: 20 mg/day) and as an antiemetic (maximum dosage 30 mg/day, maximum single dosage 15 mg/m^2). Volunteers were told that they might receive a placebo or active drug. Binocular depth inversion was then tested three times starting 70, 140 and 250 min after administration of Dronabinol.

For testing binocular depth inversion, the following technique was used. Stereoscopic pictures were taken from four groups of different natural objects: flowers, some other ordinary objects (e.g. a chair), teddy-bear masks, and faces of middle-aged males. Faces were photographed as frontal views (Fig. 1A). Groups of stimuli thus differed in their everyday familiarity (Hill and Bruce 1994). The pictures of the teddy-bear masks were taken from the backside of the mask looking into the concave shape of it (primary concave view). This results in a hollow face illusion that is not only based on the manipulation of the binocular disparity. Therefore, depth information of these pictures represented a concave shape with respect to all depth perception cues mentioned above counting for stronger support of the bottom-up processes involved. The stereoscopic pictures were scanned and transferred to an Apple Macintosh computer. Depth information of most pictures was manipulated by exchanging the left and the right picture taken, thus resulting in a change in disparity indicating an inverted object ("pseudoscopic vision"). The teddy-bear masks were presented in a non-pseudoscopic way because of their primary concave view.

Artificial objects were designed by use of a three-dimensional modeling and rendering software (Strata Studio Pro for Mac OS). Each object consisted of a combination of different bisected basic geometric figures and had an overall concave shape. An identical gray scale surface texture and lighting orientation was chosen for all objects. Three-dimensional models were then rendered with a viewing angle between different perspectives of 4° (Fig. 1B) and 8° (not shown).

The corresponding pictures were presented on a computer monitor with high resolution (overall stimulus size 800 × 600 points, 30.0 × 22.5 cm) and color depth (16 bits) for a maximum of 60 s. A Wheatstone stereoscope (Wheatstone 1838) was used to achieve stereoscopic vision. The mirror stereoscope used four semisilvered trapezoid mirrors with two central right and left eye display mirrors (25 cm^2), and two larger lateral right and left mirrors (160 cm^2) each with a vertical axis of rotation. The distance between the presentation unit and the mirror stereoscope in front of it was about 50 cm. The lateral mirrors reflected the corresponding part of the stereoscopic to the corresponding central mirror. The ability to

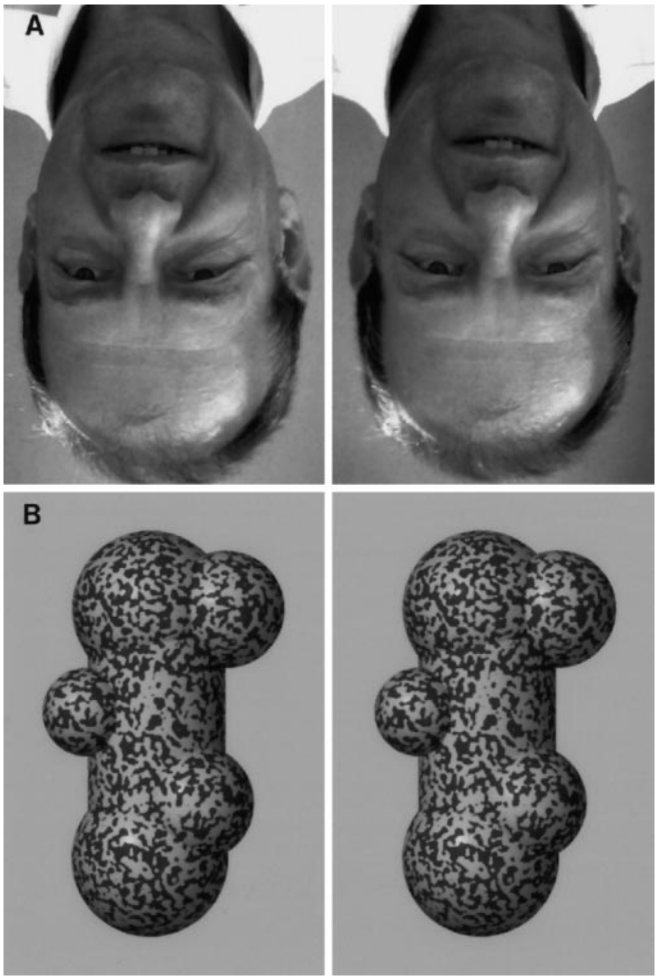

Fig. 1A,B Stereoscopic pictures of objects related to different object classes. **A** Depth inverted stereoscopic picture of a male human face in upside-down orientation. **B** Stereoscopic presentation of an artifical object created by use of a three-dimensional rendering software. Viewing angle between perspectives is 4°

rotate the lateral mirrors enabled the adjustment of the stereoscope to the individual interocular distance of each volunteer.

The volunteers were told that the presented objects might either have a more convex or a more concave shape. Each inverted image displayed was preceded by the same non-inverted image. Images without binocular depth information or without a corresponding inverted image were randomly presented as distracting stimuli. The volunteers were instructed that depth perception of each object might vary or not. Using an operationalized description, they described their visual perception of the overall shape of the object and of a selected part of each object as very concave, concave, flat, convex, and very convex. This was expressed using a five-step rating scale. When depth perception was totally inverted, a score of zero points was given and a complete matching between depth perception and the veridical view of the object was scored as four points. Each time three objects of a class were presented and the ratings for the overall shape of the object and for a selected part of each object were averaged and divided through the maximum possible score. Thus a maximum of one point was applicable for each class of objects. This score is referred to as "inversion score".

Statistical analysis of the data was performed using SPSS (Statistical Package for the Social Sciences). A Friedman two-way ANOVA was used for analyzing group effects. Subsequently, paired Wilcoxon-tests were performed where applicable.

Results

General observations

All volunteers were able to tell if they had received the active drug. Their subjective reactions ranged from mild euphoria to more pronounced reactions. A feeling of loss of self-control was reported by most of the subjects. Discrete body distortions occurred as well. One subject went through a 2 h episode of productive paranoid psychotic state with persecutory delusions, delusions of thought insertion, attentional irritability, fear, and – to some extent – verbal aggressive behavior. The subject was talked through this episode and did not contribute data to the study.

Binocular depth inversion

The depth inversion scores for each class of objects are illustrated in Fig. 2. Initial scores before administration of Dronabinol showed marked differences between the different classes. A lower score indicates a more pronounced depth inversion. The initial scores for flowers and artificial objects as well as for natural objects and faces upside down showed no significant paired differences. All other paired comparisons revealed highly significant differences between the corresponding classes of objects ($P \leq 0.01$, Wilcoxon test). Interestingly, faces presented upside down were seen significantly different from those presented right way up ($P \leq 0.01$), which was a consistent finding also under the influence of Δ^9-THC ($P \leq 0.01$ at 70 and 140 min and $P \leq 0.001$ at 250 min). As could be expected, depth inversion scores for teddy-bear masks were initially significantly different from both presentations of faces ($P \leq 0.001$ each) and of natural objects, indicating the influence of further depth perception cues other than binocular disparity. The perception of the control objects that were presented in a non-inverted fashion as mentioned above was not altered in any case.

The influence of Δ^9-THC on binocular depth inversion can also be derived from Fig. 2. Compared to the initial values, subsequent depth inversion scores were increased for the perception of artificial objects, natural objects, teddy-bear masks and all face stimuli presented. Depth inversion of flowers was not significantly altered by Δ^9-THC. Although the initial inversion score for artificial objects started at 0.77 ± 0.14, there was a further increase to a maximum of 0.94 ± 0.06 ($P \leq 0.01$) 250 min after intake of Δ^9-THC. Nevertheless, it is most likely that these results are affected by a ceiling effect that might cause an underestimation of the drug effect on binocular depth inversion of artificial objects both within and between groups in this study.

The maximum inversion scores were found 140–250 min after drug application. This is very much

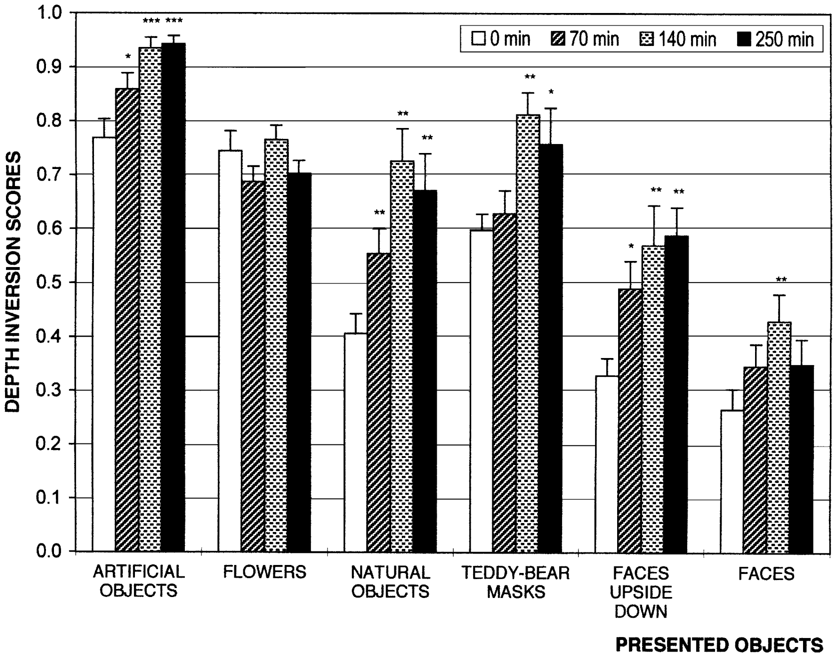

Fig. 2 Depth inversion scores for each different class of objects presented. The mean values of the inversion scores (± standard error of the mean, n = 16) are shown for the following classes of objects presented: artificial objects, flowers, natural objects, teddy-bear masks (primary concave), faces presented upside down, and faces presented upside. For each class of objects the initial inversion score before drug administration (0 min) as well as subsequent inversion scores after oral drug administration (70 min, 140 min, 250 min) are illustrated. A Friedman two-way ANOVA was performed for each group of objects. *Asterisks* indicate the error probability revealed by respective Wilcoxon tests comparing the subsequent values with the initial value where applicable due to the ANOVA (*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$)

in line with Δ^9-THC plasma levels revealed previously by our group where a plasma peak concentration was seen about 120 min after oral administration of Dronabinol (Leweke et al. 1998). Therefore, most of the inversion scores showed a moderate decline 250 min after drug administration, indicating a dose-dependent effect of Δ^9-THC on binocular depth inversion.

The sensitivity of the different classes of objects to Δ^9-THC effects during the experiment is reflected by the average of the scores taken at each time after drug application for each class of objects. Comparison of the initial values with these averages of the scores reveals a maximum increase in average scores for natural objects (+ 0.24 ± 0.19; $P \leq 0.01$) and faces upside down (+ 0.22 ± 0.19; $P \leq 0.01$).

Discussion

Illusionary perceptions have been a matter of interest for several hundred years. More recently, the underlying mechanisms of binocular depth inversion have been revealed in more detail (Yellott Jr 1981; Hill and Bruce 1993; Gregory 1998). So far, there is no indication for an underlying general disturbance of binocular depth perception (Yellott Jr 1981). The perceptual experiences of the different classes of objects found in our study are in agreement with previous observations: objects with a higher degree of everyday familiarity, i.e. faces, chairs or a house, tend to evoke a more pronounced binocular depth inversion (Yellott Jr 1981; van den Enden and Spekreijse 1989; Hill and Bruce 1994). This is reflected by the initial scores of the different object classes found in our study as well. Interestingly, natural objects and faces upside down as well as flowers and artificial objects show similar initial depth inversion scores, indicating comparable initial degrees of everyday familiarity. The everyday familiarity of natural objects should be taken into account to gain a more differentiated view of impaired binocular depth inversion associated with behavioral or psychiatric disturbances. Artificial or synthetic images seem to provide additional information on disturbances of perceptual processes, as they have a low degree of familiarity.

As already mentioned in the introduction, appealing models and hypotheses regarding the mechanisms involved in binocular depth inversion have been proposed. For example, Gray and Rawlins (1986) suggested a comparator system that gauges incoming sensory data (bottom-up) against conceptual knowledge (top-down). The comparator determines the ultimate conscious experience of the outer world. They suggest hippocampal structures as a possible site of the comparator mechanism. Gregory (1998) has recently presented a further elaboration of this hypothesis. It has been proposed that internal correcting and adaptive systems may be deficient in psychotic states and that an imbalance in systems responsible for concept formation occurs (Malenka et al. 1982; Frith and Done 1989). It is still controversially discussed if other structures of the temporal lobes and/or prefrontal cortical areas are involved in these processes (Crick and Koch 1992; Haxby et al. 1994). At present, the basic neural mechanism of binocular depth inversion remains an object of further research.

However, our baseline data for different types of objects support the proposed view on internal correcting and adaptive systems. The influence of top-down processing on the depth inversion of objects with a higher degree of everyday familiarity seems to be more pronounced than of objects with a lower degree of everyday familiarity. Furthermore, the top-down processing in the sense of correcting mechanism is apparently weakened by the influence of Δ^9-THC, resulting in an increase in veridicality for the depth recognition of the most objects. As expected, this effect depends on the initial degree of correction of the conscious experience and the type of objects presented. Interestingly, in the case of artificial objects, even the very low level of initial correction is further decreased by application of Δ^9-THC. On the other hand, the objects with the highest degree of familiarity – faces presented right way up – do not show the relatively largest change in veridicality. This might be due to the fact that a strong influence of top-down processing in the recognition of these stimuli is relatively less reduced by Δ^9-THC at the applied dosage. Further experiments with better-controlled ways of administration of Δ^9-THC, allowing more sophisticated dose-response control, may contribute to a further understanding of this phenomenon.

Although the neural mechanism of binocular depth inversion is still not clarified, there is evidence from patients with focal epilepsy that temporal lobe neuronal circuits may be involved in binocular depth inversion (unpublished data). Furthermore, the temporolimbic system is proposed to have a part in the manifestation of positive schizophrenic symptoms (Bogerts 1997). Concerning our model of impaired binocular depth inversion in productive psychotic syndromes (Emrich 1989; Schneider et al. 1996), these findings are in line with the data presented here and point to a possible involvement of the temporal lobe in these perceptual processes.

Interestingly, autoradiographic investigations of cannabinoid receptor distribution revealed high densities of cannabinoid receptors in human limbic structures like the dentate gyrus, the hippocampus CA1 region, and the amygdala (Herkenham et al. 1990). These findings suggest a physiological and possibly also pathophysiological role of the anandamidergic system in these structures. This is further supported by data from rhesus monkeys showing an impairment of visual recognition memory by Δ^9-THC similar to those evoked by limbic lesions (Aigner 1988).

An alternative hypothesis explaining the effects of Δ^9-THC might be that the alterations found here are attributable to cannabinoid receptors in the visual system itself thus resulting in an affection of the bottom-up processes of perception. In fact, studies in humans report several instances of heightened sensory awareness during cannabinoid intoxication (Hollister 1986). So far, studies in monkeys indicate no serious effects of Δ^9-THC on simple visual discrimination tasks (Schulze et al. 1988). With regard to binocular depth inversion, this possible explanation should be further investigated.

Our data support the hypothesis that the anandamidergic system is involved in perceptual processes on a higher level of information processing. There was no evidence that more general effects of cannabinoids like slowed processing speed, as suggested by others (Braff et al. 1981), have to be considered in the interpretation of our data (Leweke et al. 1998). This might be related to the fact that a synthetic Δ^9-THC has been used at a moderate dosage compared to other studies in this field (for review see Miller and Branconnier 1983).

The data presented here strengthen our previous findings on the effects of cannabis resin on binocular depth inversion with respect to the less contaminated source of Δ^9-THC and the elimination of possible interactions with other cannabinoid compounds of the cannabis resin (Emrich et al. 1997). The analysis of different stimulus classes provides further information on the underlying perceptual processing of binocular depth inversion. The underlying mechanisms of binocular depth inversion and the effects of Δ^9-THC herein remain speculative at that point. As soon as in-vivo methods for the functional imaging of the endogenous cannabinoid system become available, these should be evaluated with regard to the depth inversion effect to substantiate further the search for the underlying mechanism.

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