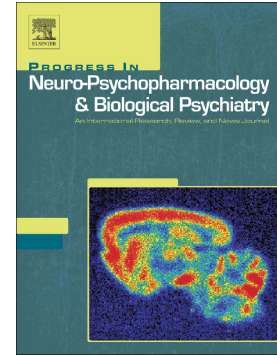


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Inhibition of return (IOR) in patients with schizophrenia and cannabis use

Thomas Schnell^a, Karsten Heekeren^b, Jörg Daumann^c, Euphrosyne Gouzoulis-Mayfrank^d

^a Medical School Hamburg, University of applied Science and Medical University, Department of Clinical Psychology and Psychotherapy, Am Kaiserkai 1, 20457 Hamburg, Germany

^b Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland

^c Department of Psychiatry and Psychotherapy, University Hospital of Cologne, Kerpener Str. 62, 50937 Cologne, Germany

^d Department of Psychiatry and Psychotherapy, LVR-Hospital Cologne, Wilhelm-Griesinger Str. 23, 51109 Cologne, Germany

Corresponding author: Prof. Dr. Dr. Thomas Schnell, Tel: 0049 177 2671089, Mail: thomas.schnell@medicalschooll-hamburg.de

Abstract

Research concerning the spatial orientation in patients with schizophrenia has demonstrated a state independent deficit in inhibition of return (IOR), which has been discussed as a vulnerability marker for schizophrenia. Other recent investigations on brain structure and cognitive processing have revealed less deficits in schizophrenia patients with comorbid cannabis use (SCH+CUD) compared to abstinent schizophrenia patients (SCH). It was hypothesized that these results may reflect a premorbid lower vulnerability in at least a subgroup of comorbid patients. The aim of the present study is to extend previous work by investigating IOR functioning in patients with schizophrenia and cannabis use. This in turn should supplement the existing studies on the vulnerability of this patient group. Therefore, we compared IOR functioning in four groups: 62 patients with schizophrenia and 46 healthy controls, both with and without cannabis use. Participants underwent a covert orienting of attention task (COVAT) with peripheral cues and three stimulus onset asynchronies (SOAs: 200 ms, 400 ms and 800 ms). Both schizophrenia groups displayed delayed IOR with a more pronounced IOR effect in SCH+CUD compared to SCH. In healthy controls, IOR did not seem to be significantly affected by cannabis use. Significant IOR-differences between groups were only seen between SCH patients without cannabis use and both healthy groups at SOA 400 ms. Patterns of cannabis use as well as clinical parameters of psychoses did not affect IOR. Our results may support the hypothesis of IOR as a vulnerability marker for schizophrenia and of a lower biological vulnerability in at least a subgroup of SCH+CUD.

Keywords: Cannabis, Comorbidity, Inhibition of Return (IOR), Schizophrenia, Vulnerability

1. Introduction

Neurocognition and preattentive cognitive functioning in cannabis users and in schizophrenia

Cannabis use is associated with neurocognitive impairments (e.g. memory, attention and executive functioning) in healthy users. These deficits persist over the period of acute cannabis administration and in adolescent onset users, even life-long persistence seems probable (Solovij and Michie, 2007). Interestingly, impairments in healthy cannabis users are similar to those in schizophrenia patients not using cannabis (Lorenzetti et al., 2013; Yücel et al., 2008). Deficits appear in prodromal and first-episode patients, in patients with chronic schizophrenia and have also been identified in first-degree relatives (Antonova et al., 2005). Age of onset of schizophrenia was found to be inversely proportional to deficits, but the progression of deficits is not related to the number of psychotic episodes, contradicting state-dependency of cognition (Krug and Kircher, 2017; Van Assche et al., 2017). Hence, impairments are thought to represent trait markers of schizophrenia, reflecting neurobiological vulnerability.

A recent review further describes preattentive processes and cognitive inhibition as neurobiological vulnerability markers of psychoses, underlying state-independent characteristics (Krug and Kircher, 2017). And similar to above mentioned findings, schizophrenia patients and healthy cannabis users commonly display deficits at prepulse inhibition (PPI) of the startle reflex (Kedzior et al., 2016; Morales-Muñoz et al., 2015), at P50 sensory gating, a neurobiological determined inhibitory mechanism (Rentzsch et al., 2011), and at mismatch negativity (MMN) (Impey et al., 2015).

Superior performance in comorbid patients with schizophrenia and cannabis use

Cannabis use is highly prevalent among patients with schizophrenia and some negative effects of consumption on people with psychotic disorders are well established (Hamilton,

2017). Schizophrenia patients using cannabis (SCH+CUD) present an earlier onset of psychoses (Hermle et al., 2013) and overall poor long-term outcomes (Hamilton, 2017; Schnell, 2014). Based on these findings, we would expect additive negative effects on cognition. But surprisingly, schizophrenia patients (with onset of cannabis use prior to the first psychotic episode) demonstrate similar or even better cognitive performance compared to abstinent patients (Hanna et al., 2016; Mallet et al., 2017; Schnell et al., 2012). Consistent with these findings, SCH+CUD was associated with less severe deficits compared to abstinent patients with regard to PPI (Morales-Muñoz et al., 2015), MMN (Rentzsch et al., 2011) and P50 sensory gating (Broyd et al., 2013; Rentzsch et al., 2007). On one hand, such counterintuitive findings may reflect a beneficial impact of cannabis on cognition and on preattentive functioning in SCH+CUD (e.g. Morales-Muñoz et al., 2015). An explanation refers to possible neuroprotective effects of cannabis which will counteract a putative neurotoxic process related to schizophrenia (Potvin et al., 2008). Neuroprotective properties of cannabinoids at the cellular level were established in a variety of models explaining neuronal injury and toxicity (Sarne and Mechoulam, 2005). On the other hand, although neuroprotection cannot be ruled out, some experts prefer an alternative interpretation, because it offers a slightly better justification for the above mentioned negative associations between cannabis use and development of schizophrenia. The findings of higher functioning in average SCH+CUD may be explained through complex interaction effects between cannabinoids and the neurobiological vulnerability for schizophrenia (Schnell et al., 2012; Yücel et al., 2012). With cannabinoids probably interfering or interacting with vulnerability for psychoses, cannabis use may be an important factor in the etiology of schizophrenia (Hamilton, 2017). Correspondingly, longitudinal studies point to an up to 40% greater risk of psychosis in individuals who have ever used cannabis (Davis et al., 2016; Gage et al., 2016). Especially adolescent cannabis use is associated with enhanced risk for psychosis (Mané et al., 2017; Shalvoy et al., 2016).

Moreover, the pro-psychotic properties of cannabis may trigger psychoses in less vulnerable individuals and some of SCH+CUD may not have become psychotic if they had not used cannabis. And since cognitive deficits are thought to be related to the neurobiological vulnerability for psychosis (Snitz et al., 2006), higher functioning in SCH+CUD may reflect a moderately lower vulnerability for psychoses compared to abstinent patients who developed schizophrenia without the additional impact of cannabis (Schnell et al., 2012). Correspondingly, superior cognitive functioning in SCH+CUD was even more pronounced when regular consumption started before the age of 17 (Jockers-Scherübl et al., 2007). Summarized, cannabis does not cause superior functioning in schizophrenia, but it triggers schizophrenia in high functioning individuals with low vulnerability. Ergo, instead of improving cognition in schizophrenia, consumption may cause the same adverse effects both in comorbid patients and otherwise healthy users.

Schizophrenia, cannabis use and Inhibition of Return (IOR)

Inhibitory processes of attention in schizophrenia, such as spatial orienting of visual attention, complement the above mentioned studies. In a typical covert orienting task, subjects have to maintain fixation on a central cross and respond as quickly as possible to a target, which appears in a peripheral box following a cue that summons attention to the direction where the target is going to appear (valid cueing) or to the contralateral direction (invalid cueing). When the cues are non-predictive, the response characteristics critically depend on stimulus-onset asynchrony (SOA). With short SOAs (<300 ms), valid cues result in a reaction time advantage over invalid trials, which is due to a reflexive shift of attention towards the source of stimulation. In contrast, with longer SOAs, valid cues result in longer reaction times to the subsequent target. There is still extensive debate about the underlying mechanism of this phenomenon and its potential functionality (De Vries et al., 2016). Nonetheless, this is mostly thought to reflect an automatic inhibitory mechanism,

protecting the organism from redirecting attention to previously scanned insignificant locations. This concept is described by the term “Inhibition of Return” (IOR; Posner and Cohen, 1984). Besides IOR, alertness and facilitation reflect more basal functions of attention, which are typically included in complex paradigms as covert orienting of attention task (COVAT). Interestingly, schizophrenia patients normally present a facilitation in trials with spatially neutral cues over uncued trials, called altering effect which is more pronounced in conditions with longer SOAs. Patients normally display similar alerting effects compared to healthy controls. Given the normal alerting effects in patient groups, the finding of deficient IOR cannot be explained by a general deficit in the processing or memory trace of cues. Instead, it may reflect a specific abnormality in the mechanism underlying the IOR system. Nevertheless, research on IOR in schizophrenia has generated mixed and seemingly conflicting results that range from profoundly disturbed to an intact IOR (Kalogeropoulou et al., 2015; Tang et al., 2015). Some researchers identified deficient IOR in chronic but not in first-episode patients with schizophrenia. They state that a deficit in IOR may begin during the course of psychoses and deteriorate with further episodes (Liu et al., 2010). Some authors even contemplate that differences between the studies may arise due to the use of differing methods and paradigms, and that IOR effects are task contingent (Prasad et al., 2015). Others highlight confounding influences, such as psychomotor slowness or lack of motivation in patients with schizophrenia, which may result in poorer secondary IOR performance (Moritz and Laudan, 2007; Moritz et al., 2017). However, the majority of published studies revealed deficient or delayed IOR, which appears to be state-independent (Kebir et al., 2010; Mushquash et al., 2012). In line with these findings, previous studies of our group indicate that IOR in schizophrenia is unrelated to psychopathology, number of psychotic episodes and type of medication. A common interpretation (relevant to the present issue) is to refer to IOR as a vulnerability marker of psychoses (Gouzoulis-Mayfrank et al., 2004, 2006).

This squares with the fact that endocannabinoid brain activity is related to vulnerability for psychoses, since putative mechanisms involving the endocannabinoid system are discussed in an attempt to explain IOR deficits in schizophrenia (Gallinat et al., 2012). Finally, there is little empirical evidence concerning the impact of cannabis use on Inhibition of Return (IOR), providing that cannabis use in otherwise healthy users does not disturb IOR (Colzato and Hommel, 2008) or enhance IOR (Vivas et al., 2012). We found no corresponding studies on IOR in SCH+CUD patients.

For this reason, the present investigation is the first known IOR-study that compares schizophrenic patients and healthy controls, each with and without cannabis use. No IOR-deficits were assumed in healthy controls irrespective of cannabis use, suggesting no specific deteriorating effect of cannabis on IOR, with respect to the above mentioned findings of Colzato and Hommel (2008) and Vivas et al. (2012). According to recent discussions concerning lower vulnerability for psychosis in SCH+CUD patients, and IOR as a vulnerability marker of psychoses, we suggest less severe deficits in IOR in SCH+CUD patients compared to SCH patients. Group differences within the schizophrenia-condition may be explained by differences in (preexisting) vulnerability levels.

2. Materials and Methods

The study was carried out in compliance with the latest revision of the Declaration of Helsinki and was approved by the local ethics committee of the Medical Faculty of the University of Cologne. Following, a detailed study-description was handed out to each participant who in turn filled out a written informed consent form.

2.1. Subjects

Our sample consisted of 62 schizophrenic patients of the Psychiatric University Hospital and the LVR-Hospital of Cologne (n=32 with- and n=30 without cannabis use) and 46 healthy controls (n=16 with- and n=30 without cannabis use). Regarding the sample size, we followed the patients and tested as many of them as possible. Target dimension was a minimum of about 15 patients per group on the basis of previous studies on IOR in schizophrenia. Using the present COVAT paradigm, similar or even smaller sample sizes revealed enough power to reproduce significant group differences (i.e. Gouzoulis-Mayfrank et al., 2006: 32 schizophrenia patients, 16 controls). All patients were in a partly remitted state and were medicated depending on clinical requirements. They had to fulfill criteria of schizophrenia according to the DSM-5 (APA, 2013). Exclusion criteria were further Axis I psychiatric disorders or relevant neurologic disorders affecting brain function as well as acute positive symptoms interfering with the capability to give informed consent. The SCH+CUD subgroup had to comply with regular cannabis use (at least one cannabis-joint per month; in accordance with Schnell et al., 2012). Further, SCH+CUD patients with current cannabis use within at least two weeks prior to examination were excluded, in order to adjust data for acute and sub-acute cannabis-effects. To verify patients' corresponding statements, possible drug abuse was identified by a serum toxicology screening. At the time of the onset of cannabis use, SCH+CUD patients should not suffer from any neuro-psychiatric disorder (meaning no psychiatric diagnosis or treatment up until that time). The healthy controls with cannabis use (CUD group) had to comply with regular cannabis use (at least one cannabis-joint per month). Cannabis use within at least two weeks prior to examination was an exclusion criterion. Further exclusion criteria for all groups (patients and controls) were any additional illicit life-time substance abuse/use (except for cannabis in SCH+CUD and CUD), regular alcohol use (more than three drinks per week; in accordance with Jockers-Scherübl et al., 2007), any

further relevant neuropsychiatric disorders, non-compliance with the requirements of the study and incapability/refusal to give an informed consent.

2.2. Procedures and measures

All included participants performed a detailed interview on demographics. A structured interview with schizophrenic patients was conducted in order to verify a clinical diagnosis according to DSM-5 (APA, 2013) and an additional interview on data for psychiatric medications, age at onset of schizophrenia, number of psychotic episodes and inpatient treatments. Psychotic symptoms were assessed by means of the Brief Psychiatric Rating Scale (BPRS; Ventura et al., 1993). Psychotic patients using cannabis (SCH+CUD) as well as otherwise healthy users (CUD) were asked for patterns of consumption including age at onset of use, passed time since the last dose (number of days), average frequency of use (joints per month) and duration of regular cannabis use (number of months). Collected data of patients were verified by means of personal interviewing the attending medical doctor, and in case of any further questions, we also analyzed the patients' medical records. Finally, participants underwent a covert orienting of attention task (COVAT) with peripheral cues and three stimulus onset asynchronies (SOAs: 200 ms, 400 ms and 800 ms). Previous studies of our group typically revealed robust effects of the cue-target-interval (SOA) on reaction time with delayed IOR in schizophrenia. This measurement was found to be quite reliable at SOA 800 ms and it persisted at SOA 1050 ms. In the present study, we applied an additional mean latency with SOA 400 ms to identify the critical point in time that allows IOR to develop between SOAs 200 ms and 800 ms. Our aim is to compare present findings with our previous research. Throughout, the appearance and magnitude of IOR seems strongly responsive to different methods and paradigms (Prasad et al., 2015). Therefore, a comparison requires a similar COVAT paradigm. Except for the manipulation of SOAs, we had to keep stable task-specific parameters. For example, the

use of cue-back conditions is known to reinstate or speed up IOR (Larrison-Faucher et al., 2002). The COVAT paradigm was presented using the stimulus delivery- and experiment control program Presentation®. Subjects were seated about 60 cm in front of the computer monitor and were asked to maintain visual fixation on a centrally presented cross. The task was to respond as rapidly as possible to the target by pressing a single key with the index finger of the dominant hand which was allowed to rest on the key in anticipation of making a response. The main target was a star, which appeared on each trial within one of the two peripheral square boxes at about 5° right or left from the central fixation cross for 200 ms. A practice experiment consisting of 24 trials was performed prior to each session with no reaction times (RT) recorded. The experiment consisted of 272 trials. 32 trials were uncued: In these no-cue trials the target appeared in the center of one of the two boxes with equal probability following an interval of 1100 ms after the previous key was pressed. In another 48 trials both boxes were brightened (neutral cue) and the target followed either in the right or in the left box with equal probability. The time from onset of cue to onset of target was either 200 ms, or 400 ms, or 800 ms (SOA 200 ms, or 400 ms, or 800 ms). In the remaining 192 trials either the right or the left box was brightened with equal probability, and the target followed either in the brightened box or the opposite box (valid or invalid cue) with equal probability (SOA 200 ms, or 400 ms, or 800 ms). In all cued trials, the cue appeared always following an interval of 1000 ms after the previous key press (intertrial interval) and remained for 100 ms. For an exemplification of a trial with the target in the right visual field and an invalid (left) cue see figure 1.

- please insert figure 1 -

2.3. Statistical analyses

Four groups were compared regarding demographics using χ^2 -tests for categorical data and analysis of variance (ANOVA) for continuous data, including a post hoc test. Clinical parameters of SCH versus SCH+CUD and cannabis use patterns of SCH+CUD versus CUD were compared using χ^2 -tests for categorical data and independent t-tests for continuous data. Mann-Wittney U-Test was used, if requirements for parametric tests were not fulfilled.

COVAT trials with reaction times (RTs) less than 100 ms or exceeding 1000 ms were excluded, because they were considered either as an anticipatory response or brief periods of general inattention to the task. Subjects were excluded from further analyses if more than 10% of the trials had to be eliminated according to these criteria. Median RT values of the remaining trials were calculated for each subject and type of trial. Group performances were summarized as mean values of this data.

In order to obtain a measure for the general response readiness, we initially analysed RTs in no-cue trials by means of analysis of variance (ANOVA) with in form of a between-subjects design (SCH, SCH+CUD, CUD, healthy) and performed post hoc analyses when appropriate. Subsequently, we calculated alertness effects by subtracting the median RT of the neutral-cue trials from the median RT of the no-cue trials for every subject and type of trial (alertness effect in ms: $RT_{\text{no-cue}} - RT_{\text{neutral cue}}$). Similarly, we calculated validity effects by subtracting the median RT of the valid- from the median RT of the invalid trials (validity effect in ms: $RT_{\text{invalid}} - RT_{\text{valid}}$). Alertness and validity effects were analysed by means of repeated-measures ANOVAs with the between-subject factor group (SCH, SCH+CUD, CUD, healthy) and the within-subject factor time (SOA 200 ms, SOA 400 ms, SOA 800 ms). We integrated data of left and right VFs for all conditions, because previous analyses showed no significant lateralized effects. Main effects of group, time and interaction effects (group x time) were calculated. When necessary, significant group

effects were specified by means of multiple-comparison post-hoc analyses according to the conservative Bonferroni correction procedure. To explore associations between alertness and validity effects on the one hand, and demographics, clinical characteristics of schizophrenia, and patterns of cannabis use on the other hand, we performed Pearson correlations. In order to analyze confounding influence of psychomotor retardation on IOR, we correlated RTs of no-cue trials (general response readiness) with validity effects (SOA 400 ms). Finally, we examined the possible interactions of the type of medications with alertness and validity effects with a further analysis of variance (ANOVA), after dividing all schizophrenia patients (with and without cannabis use) into groups according to their medication (first group with second generation antipsychotics (SGAs) and a second group with a combination of SGAs, antidepressants and mood stabilizers).

Lastly, regarding the results of ANOVAs, we performed a computer based post hoc power analysis, using the program “G-Power 3.1.9.2” (Faul et al., 2009). The post hoc analysis computed statistical power ($1-\beta$ error probability) as a function of significance level, sample size, and population effect size. Values over 0.8 report sufficient power.

All p-values ≤ 0.05 were considered significant, except for the correlation analyses, where the significance level was set at $p \leq 0.01$ in order to avoid accumulation of type 1 error due to multiple correlations. All procedures were performed using SPSS version 21.

3. Results

3.1. Demographic data, clinical characteristics, psychiatric medication and patterns of cannabis use

The final sample consisted of 30 SCH patients, 32 SCH+CUD patients, 16 healthy individuals with- (CUD) and 30 without cannabis use. No participants had to be excluded due to high percentages of anticipatory or extremely slow responses ($\geq 10\%$ of the trials). However, one SCH patient dropped out because he did not finish the COVAT task due to

lack of motivation. This is taken into account in the previously mentioned sample size. Two SCH+CUD patients and three CUD participants were excluded just before COVAT-examination due to acute cannabis-intoxication. The mean percentage of excluded trials was 1.12% in SCH, 0.76% in SCH+CUD, 0.47 in CUD and 0.29 in abstinent controls. Groups were similar for all demographic data (differences below significance). The two groups with schizophrenia patients (SCH vs. SCH+CUD) were similar concerning clinical characteristics and there were no significant differences in medication. The two groups with cannabis use (SCH+CUD vs. CUD) presented similar patterns of consumption. Just age at onset of consumption differed significantly between groups with lower age in the schizophrenia group (below 16 years vs. 18 years within healthy users). SCH+CUD patients began using cannabis approximately seven years prior to the onset of psychosis. Furthermore, both groups with cannabis use smoked significantly more cigarettes per day than the SCH group and abstinent healthy controls.

A detailed presentation of data is given in table 1.

- *please insert table 1* -

3.2. Performance data

Reaction times (RTs) of all groups, displayed in milliseconds (ms), are visually presented in figure 2. Descriptive inspection of RTs between groups displayed overall shortest RTs in healthy controls and longest RTs in SCH patients. In reference to the cannabis use, data present the counterintuitive but typical pattern: Schizophrenia patients using cannabis reacted overall faster than abstinent patients, whereas healthy cannabis users were slower than abstinent controls.

- *please insert figure 2* -

RTs in no-cue trials are considered as a measure for general response readiness. Group differences were analysed by means of ANOVA. The combined calculations identified significant differences between the four groups ($F=6.013$; $p=.001$; $df=3/104$; partial $\eta^2=.148$). Specifying post hoc analyses revealed significant group differences between SCH and CUD ($p=.027$), and between SCH and healthy controls ($p=.001$), after correction according to Bonferroni. No further combination within the four groups reached statistical significance.

Alertness-Effects

The Greenhouse-Geisser correction was used to mitigate violations of the sphericity assumption. Repeated-measures ANOVAs of the alertness effects ($RT_{\text{no-cue}} - RT_{\text{neutral cue}}$) only revealed a significant main effect of time (SOA) ($F=99.4$; $p\leq.001$; $df=1.67/173.88$; partial $\eta^2=.489$). Inspection of the descriptive data suggest that this main effect reflects a stronger response facilitation with the two longer SOAs (400 ms and 800 ms) compared to the short SOA of 200 ms. Main effect of group ($F=.745$; $p=.528$; $df=3/104$; partial $\eta^2=.021$) and interaction effect of group x time (SOA) ($F=1.95$; $p=.088$; $df=5.01/173.88$; partial $\eta^2=.053$) were below statistical significance. The general alerting effect of spatially uninformative cues was similar in all groups. Neither schizophrenia nor cannabis use distinguished in a specific manner. Results of the statistical post hoc power analyses for F-tests revealed sufficient power ($1-\beta$ error probability) for all conditions of the ANOVA. All values ranged between 0.88-0.99 and exceeded the critical value of 0.80. For a graphic representation of alertness-effects see figure 3.

- please insert figure 3 -

Validity-Effects

The Greenhouse-Geisser correction was used to mitigate violations of the sphericity assumption. Repeated-measures ANOVAs of the validity effects revealed no significant main effect of group ($F=1.836$; $p=.145$; $df=3/104$; $\text{partial } \eta^2=.050$), but of time (SOA) ($F=53.498$; $p\leq.001$; $df=1.63/170.15$; $\text{partial } \eta^2=.340$), and a significant interaction effect (time x group) ($F=4.418$; $p\leq.001$; $df=4.90/170.15$; $\text{partial } \eta^2=.113$). With regard to significant interaction between SOAs and groups, inspection of the descriptive data suggests that the interaction effect reflects the obvious lack of IOR in SCH at SOA 400 ms, whereas it appeared in both healthy groups. Reaction times of SCH+CUD were quite similar between valid and invalid trials. Finally, at SOA 800 ms, all groups developed the typical IOR-effect, though the average reaction times of valid trials were slower compared to invalid trials (negative validity effect=IOR; compare figure 4). Post hoc ANOVAS for each SOA condition revealed significant group differences between SCH patients and healthy cannabis users (CUD) and between SCH patients and abstinent healthy controls at SOA 400 ms (SCH vs. CUD, $p=.017$; SCH vs. healthy, $p=.048$).

Results of the statistical post hoc power analyses for F-tests revealed sufficient power ($1-\beta$ error probability) for all conditions of the ANOVA. All values ranged between 0.91-0.98 and exceeded the critical value of 0.80.

Validity effects in the four groups are presented in figure 4.

- please insert figure 4 -

3.3. Effects of demographics, clinical characteristics, nicotine, medication, motor slowness and cannabis use on validity and alertness

No significant correlations emerged between COVAT data (validity and alertness effects) and demographics, clinical data such as age at onset of schizophrenia, number of psychotic

episodes or inpatient treatments, and psychotic symptoms. We also found no significant associations between validity- and alertness effects and nicotine use (daily number of cigarettes), or patterns of cannabis use (age at onset of use, passed time since last dose, average frequency of use and duration of regular consumption). Correlations ranged between $r = -0.3$ to 0.3 and were far from statistical significance. Regarding motor slowness, significant correlations emerged between reaction times on no-cue trials and IOR (SOA 400) for both SCH patients ($r=.531$, $p=.004$) and CUD healthy controls ($r=.630$, $p=.001$) at a medium effect size; long reaction times were associated with reduced IOR effect. We found no significant correlations in SCH+CUD patients ($r=.266$, $p=.141$) and abstinent healthy controls ($r=.143$, $p=.451$). Finally, we divided the groups of patients with schizophrenia (both SCH+CUD and SCH) into two new subgroups according to their medication (46 patients treated with second generation antipsychotics (SGAs) versus 16 patients treated with a combination of SGAs, antidepressants and mood stabilizers). Finally, ANOVAs displayed no significant differences between the groups (validity: $F=1.376$, $p=.245$, $df =1/60$, $\text{partial } \eta^2=.022$; alertness: $F=.233$, $p=.631$, $df =1/60$, $\text{partial } \eta^2=.004$).

4. Discussion

In our present study, schizophrenia patients without cannabis use (SCH) but not SCH+CUD displayed overall slower reaction times (RTs) compared to both healthy groups (CUD and abstinent healthy participants), signaling lower vigilance in abstinent schizophrenia patients. The usual response facilitation in trials with spatially neutral cues over uncued trials, called alertness effect, normally presents general response facilitation with longer SOAs, as a consequence of increased preparedness to respond to the target. Our data is consistent with common alertness effects. Actually, neither a specific effect of schizophrenia nor of cannabis use was found. All groups present similar results with group

differences below statistical significance. Normal alertness and deficient IOR refer to more specific abnormalities underlying inhibitory mechanisms of IOR, since alertness reflects basal functioning of attention. In accordance with previous findings, IOR in schizophrenia patients (SCH and SCH+CUD) was not disturbed, but appeared delayed. Whereas the validity effect was observed at SOA 400 ms in healthy participants with and without cannabis use, schizophrenia patients displayed IOR only at SOA 800 ms, also irrespective of cannabis use. Further, our data showed significant interaction effects between groups and SOAs due to marked reactivity of validity and IOR effects in SCH+CUD compared to SCH, depending on SOA condition. We found a less pronounced IOR-delay in SCH+CUD compared to abstinent patients. And at SOA 800, the validity effect was quite more pronounced in SCH+CUD compared to SCH. Similar marked reactivity was seen in CUD compared to abstinent controls. All in all, sub-acute cannabis use does not seem to disturb but even to enhance the validity-effect in schizophrenia cannabis users and in healthy users. At least, in line with several previous investigations, we identified the lack of associations between IOR deficit and demographics/clinical parameters (Gouzoulis-Mayfrank et al., 2004, 2006; Kebir et al., 2008, 2010). The stability of the IOR deficit, similar to neurocognitive deficits as memory functions or concentration may be viewed as a trait feature or vulnerability marker of schizophrenia.

Quite similar results were provided by Kebir et al. (2010) with occurring IOR effect in schizophrenia at SOA 700 ms and in healthy controls at SOA 300 ms. Also, a meta-analysis conducted by Mushquash et al. (2012) provides support for delayed IOR in schizophrenia. A recent study of Tang et al. (2015) postulated an intact IOR in schizophrenia, because they found no differences between patients and controls. But at second glance, we propose that the data of Tang and Colleagues in fact corresponds to our findings concerning delayed, but not preserved effect. Some authors argue for an intact IOR in schizophrenia because the effect was seen in patients and controls without group

differences. Albeit, researchers presented two quite long SOAs with 700 ms and 1200 ms, and no short SOA of 400 ms. While Tang and colleagues explain the missing group differences at 700 ms as preserved or intact IOR in patients, we assume a delayed effect. Tang and colleagues cannot rule out that shorter SOAs would have differentiated between groups according to group differences at SOA 400 ms in our sample of the present study. Anyhow, in line with Moritz et al. (2017), we cannot rule out confounding influence of secondary factors such as motor retardation regarding IOR deficit in SCH patients (SOA 400 ms).

With regard to cannabis use, previous studies on brain structure and cognitive functioning revealed the counterintuitive finding of higher functioning in schizophrenia patients, if they use cannabis (SCH+CUD) and if onset of cannabis use was prior to onset of schizophrenia (Schnell et al., 2012; Yücel et al., 2012). An increasingly spreading interpretation is that not cannabis but lower vulnerability is responsible for the finding: Since the endocannabinoid system (ECS) may be involved in the etiology of schizophrenia (Bossong and Niesink, 2010; Lubman et al., 2015), exogenous cannabinoids may interact with the neurobiological vulnerability and facilitate the manifestation of the disorder in low vulnerable individuals. Furthermore, low vulnerability is reflected by a higher functioning compared to patients with no cannabis use. Suggesting that IOR is a vulnerability marker of schizophrenia, our data concerning less pronounced IOR-deficits in SCH+CUD vs. SCH may comply with the initial hypotheses of an average lower vulnerability for psychoses in SCH+CUD patients. In line with that, all our SCH+CUD patients started to smoke cannabis several years before the onset of psychotic symptoms. Hence, no patient of the SCH+CUD group developed psychoses without the potential additional “load” of cannabis. Further, the young adolescent average age at onset of cannabis use within our SCH+CUD group (15.8 years) is in harmony with our hypothesis of low vulnerability for psychoses, compared to SCH patients without cannabis use. According to previous findings, early

onset of consumption is associated with enhanced risk for psychosis (Lubman et al., 2015). Specifically, cannabis use in adolescence has been proposed to induce the onset of psychosis up to 2.7 years earlier than in those who develop psychosis without a history of consumption (Davis et al., 2016). Thus, some of the early onset cannabis users within the SCH+CUD group would not have fallen ill if they had not used cannabis. Such individuals, whose psychoses depends on the additive “load” of cannabis, are on average less vulnerable and display higher functioning compared to individuals, who develop psychoses without additive cannabinoids.

However, keeping similar effects in the healthy population in mind, findings may also show that validity and attentional inhibition are enhanced through cannabis use. This is in line with Vivas et al. (2012). Nevertheless, it conflicts with our results that specific cannabis use patterns did not affect validity in healthy users, which was also the case in SCH+CUD. And finally, it is not clear if greater IOR represents an advantage or disadvantage for visual search performance. Conclusively, similar findings in SCH+CUD and CUD that are different from those in abstinent patients were also seen in startle reactivity and prepulse inhibition. Cannabis use in patients with schizophrenia was associated with a similar pattern of alterations in PPI when compared to healthy cannabis users. These results appeared to be different from patients with schizophrenia who do not use cannabis (Scholes-Balog and Martin-Iverson, 2011). It may be the case that similar mechanisms underlie IOR and PPI and that cannabinoids influenced specific processes different from other cognitive domains.

Finally, we prefer the interpretation of higher functioning in SCH+CUD as a consequence of an average low vulnerability, because it may have important implications for the clinical prognosis of SCH+CUD patients. Provided that they succeed in controlling their cannabis use, high functioning SCH+CUD patients with low vulnerability for psychoses could have a clinical course that may be more favorable than the course and long-term results of SCH

patients without drug-related comorbidities; relatively preserved cognition is associated with higher benefit from psychotherapeutic interventions. Unfortunately, sustained consumption of cannabis is highly prevalent within patients with schizophrenia and contributes to the unfavorable clinical course of this comorbid population.

Limitations: We must acknowledge some limitations of the present study: Even if studies of our own group showed that IOR was independent of the number of psychotic episodes, state dependent findings were also reported. For a more robust argumentation, studying IOR in first episode and high risk patients would differentiate between vulnerability markers that precede the onset of the disease and progressive alterations, if they exist. Further, schizophrenia is a highly heterogeneous psychiatric disorder with respect to etiology, long-term outcome of the disease and psychopathology. We just could match our groups for psychopathology and demographics. Nevertheless, we cannot guarantee the homogeneity of groups. Finally, a generalization of findings is limited through the task-prone character of IOR effects.

5. Conclusions

To our view, cannabis is not responsible for the higher functioning in SCH+CUD patients, but it triggers schizophrenia in high functioning individuals with low vulnerability for psychosis. Following, our study contains further reference to our initial hypotheses of an average low vulnerability in SCH+CUD patients. This in fact could have implications regarding a better course of the disease compared to abstinent patients with an average higher vulnerability, if comorbid patients succeed to reduce cannabis use. Nevertheless, some aspects remain speculative, especially regarding the role of cannabis in preattentive inhibitory mechanisms. Future studies should analyze IOR in subjects with high risk of schizophrenia, prodromal or schizotypal subjects, in order to clarify the role IOR plays as a vulnerability marker. With respect to the hypotheses of average lower vulnerability in

SCH+CUD patients, future research should take an additional group of SCH+CUD patients who develop cannabis use *after* the onset of schizophrenia into account. According to our hypotheses, such patients with late onset of cannabis use should not demonstrate higher functioning compared to abstinent patients with schizophrenia.

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Conflicts of interest

None

Authors contribution

Detailed author contributions:

- Study concept and design: Gouzoulis-Mayfrank, Schnell
- Acquisition of data: Schnell
- Analysis and interpretation of data: Gouzoulis-Mayfrank, Schnell, Daumann, Heekeren
- Drafting of the manuscript: Schnell
- Critical revision of the manuscript for important intellectual content: Gouzoulis-Mayfrank, Schnell, Daumann, Heekeren
- Statistical analysis: Schnell
- Administrative, technical, and material support: Daumann, Heekeren
- Study supervision: Gouzoulis-Mayfrank

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Ethical Statement

Authors agree upon standards of expected ethical behavior.

The study was carried out in compliance with the latest revision of the Declaration of Helsinki.

Written, informed consent was obtained from all participants.

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The authors declare no conflicts of interest.

Authors are aware of and comply with the publishing ethics policy of the journal.

Detailed author contributions:

- Study concept and design: Gouzoulis-Mayfrank, Schnell
- Acquisition of data: Schnell
- Analysis and interpretation of data: Gouzoulis-Mayfrank, Schnell, Daumann, Heekeren
- Drafting of the manuscript: Schnell
- Critical revision of the manuscript for important intellectual content: Gouzoulis-Mayfrank, Schnell, Daumann, Heekeren
- Statistical analysis: Schnell,
- Administrative, technical, and material support: Daumann, Heekeren
- Study supervision: Gouzoulis-Mayfrank

Highlights

- Schizophrenia (SCH) is associated with cognitive deficits, including IOR
- These deficits are discussed as vulnerability markers for psychoses
- Cannabis use in schizophrenia (SCH+CUD) is associated with less deficits
- Higher functioning may reflect beneficial (neuroprotective) effects of cannabis
- Alternatively, it reflects an average lower vulnerability for psychoses in SCH+CUD

Figure 1.

COVAT paradigm - example of a trial with the target in the right visual field and invalid (left) cue

Figure 2. Mean Reaction times (RTs) in milliseconds (ms) in the COVAT.

RT: Reaction times; SOA: stimulus onset asynchrony (in ms); No: nocue trial; N: neutral trial; I: invalid trial; V: valid trial

Figure presents the mean reaction times of all groups regarding the different trials of the COVAT paradigm. Visual inspection of RTs displays overall shortest RTs in healthy controls and longest RTs in SCH patients. ANOVA revealed significant differences between groups at all COVAT trials.

Figure 3. Alertness-Effects ($RT_{no-cue} - RT_{neutral\ cue}$)

Abbreviations: RT: Reaction times; SOA: stimulus onset asynchrony.

Repeated-measures ANOVA revealed a significant main effect of time (SOA). This main effect reflects a stronger response facilitation with the two longer SOAs (400 ms, 800 ms) compared to the short SOA (200 ms)

Figure 4. Validity Effects ($RT_{invalid} - RT_{valid}$)

Abbreviations: RT: Reaction times; SOA: stimulus onset asynchrony.

Repeated-measures ANOVA revealed a significant interaction-effect of group x time (SOA). It reflects the lack of IOR in schizophrenia patients without cannabis use (SCH) at SOA 400 ms.

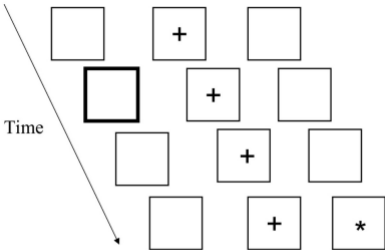


Figure 1

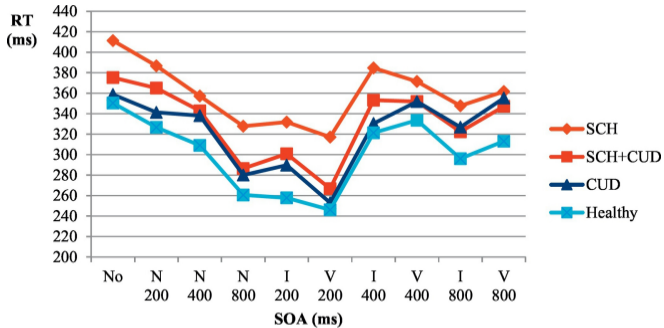


Figure 2

Alertness-Effects

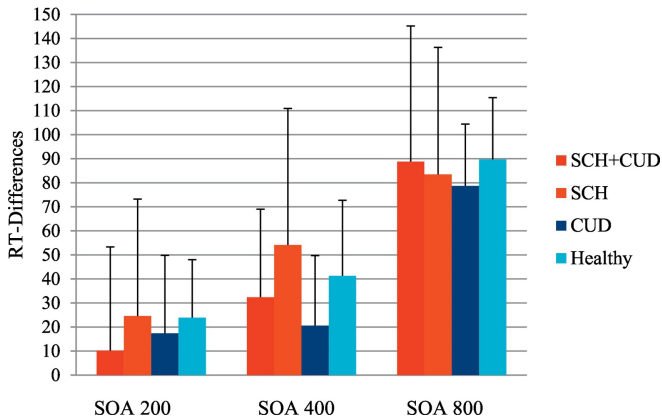


Figure 3

Validity-Effects

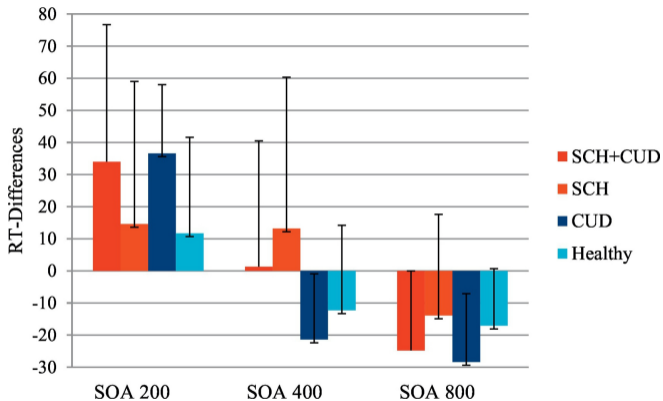


Figure 4