Association of abnormal semantic processing with delusion-like ideation in frequent cannabis users: an electrophysiological study

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Abstract

Rationale—Frequent cannabis use is a risk marker for schizophrenia and delusions, but the neurocognitive mechanisms of this relationship remain unclear.

Objectives—We sought evidence that cannabis users have deficits in processing relationships between meaningful stimuli, similar to abnormalities reported in schizophrenia, and that these deficits are associated with delusion-like ideation. We used the N400 event-related brain potential (ERP) waveform as a neurophysiological probe of activation of concepts in semantic memory. We hypothesized that cannabis users would exhibit larger (more negative) than normal N400 amplitudes in response to stimuli meaningfully related to a preceding prime—reflecting deficient activation of concepts related to the prime. We further hypothesized that the magnitude of this abnormality would correlate with severity of delusion-like ideation.

Methods—We recorded ERPs in 24 frequent cannabis users and 24 non-using comparison participants who viewed prime words followed by targets which were either words related or unrelated to the prime or pronounceable non-words. The participants' task was to indicate whether the target was a word. Delusion-like ideation was measured via the Schizotypal Personality Questionnaire.

Results—Contrary to our hypothesis, cannabis users exhibited smaller than normal N400s to both related and unrelated targets. These abnormalities correlated with delusion-like ideation in cannabis users only.

Conclusions—The results are consistent with a generalized abnormality of activation within semantic memory neural networks in cannabis users. Further research is needed to investigate whether such an abnormality plays a role in the development of delusion-like ideation in cannabis users.

Keywords

Cannabis; Semantics; Language; Cognition; Humans; Delusions; Psychosis; Paranoid behavior; Event-related potentials; Electrophysiology

Introduction

Frequent cannabis use is a risk marker for development of schizophrenia and related psychotic disorders. Longitudinal studies suggest that this relationship may be a causal one, with cannabis use increasing risk in a dose-dependent manner (Arseneault et al. 2002; Moore et al. 2007; van Os et al. 2002). According to a meta-analysis of such studies, frequent (at least weekly) cannabis use more than doubles the odds of developing psychotic symptoms (Moore et al. 2007). Overall, 13 % of new schizophrenia cases have been estimated to be attributable to cannabis use (Zammit et al. 2002). Cannabis use in healthy individuals also predicts subsequent higher levels of psychosis-like experiences that do not meet the threshold for diagnosis of schizophrenia, including unusual ideation or perceptual experiences that are less fixed than delusions or hallucinations, respectively (Rossler et al. 2007; van Os et al. 2002). Moreover, in persons who have developed schizophrenia, ongoing cannabis use increases psychotic symptoms (Foti et al. 2010) and relapse risk (Zammit et al. 2008). However, the specific neurocognitive mechanisms whereby cannabis exerts its effect on the development of psychotic symptoms remain unclear.

Previous research forms the background for a causal model of frequent cannabis use and psychosis by establishing that cannabis interferes with the function of inhibitory GABAergic interneurons in the brain. By binding to CB1 receptors, which are located on GABAergic interneurons and widely distributed in the brain (Cohen et al. 2008; Eggen and Lewis 2007), the cannabis constituent Δ^9 -THC reduces GABA release, and hence attenuates the inhibitory effect, of these interneurons (Cohen et al. 2008; Fernandez-Espejo et al. 2009). Reduced GABAergic inhibition, in turn, leads to reduced synchrony of firing of groups of pyramidal neurons (Hajos et al. 2008; Hajos et al. 2000). Such synchrony is thought to be necessary for a variety of cognitive functions (Miltner et al. 1999; Sarnthein et al. 1998; Soltesz and Staley 2006; Varela et al. 2001), and its demonstrated deficiency in schizophrenia has been proposed as an underlying cause of cognitive deficits and psychosis in this disorder (Benes and Berretta 2001; Ford et al. 2007; Uhlhaas and Singer 2010). Regular cannabis use in otherwise healthy individuals is also associated with neural synchrony deficits, whose magnitude is correlated with levels of schizotypal personality traits, which qualitatively resemble schizophrenia symptoms (Skosnik et al. 2006).

In the present study, we hypothesized that frequent cannabis use predisposes individuals to delusion-like ideation by interfering with semantic priming, i.e., the normal preferential activation, following meaningful stimuli, of related concepts in semantic long-term memory. This impairment could plausibly be mediated by reduced interneuronal GABAergic function and, in turn, deficient neural synchrony in brain areas responsible for the activation of stored conceptual representations. Recent findings suggest that activation of concepts stored in semantic memory is associated with increased theta (3–7 Hz) synchrony (Bastiaansen et al.

2008; Bastiaansen et al. 2005; Salisbury and Taylor 2012). Therefore, by interfering with neural synchrony, cannabis use would impede the ability to use meaningful context to prime related concepts normally.

Deficits in activating contextually related concepts might produce subjective perceptions that the corresponding stimuli, when they occur, are out of place or unusually salient (Hemsley 2005)—as in psychotic individuals' descriptions of their everyday experiences: "Things seem to be in different places when I get home," "I have had the feeling that someone's place has been taken by a look-alike," (Eckblad and Chapman 1983) or "Objects seemed altered from the usual...they did not stand in overall context" (Parnas 1999). According to theories linking aberrant salience of environmental stimuli to delusion formation (Hemsley 2005; Kapur 2003; Maher 1974), delusions could be a "top-down" cognitive explanation that the individual imposes on such perceptions in an effort to make sense of them—e.g., someone is breaking into the person's home and moving things around, loved ones have been replaced by impostors, or objects are fakes containing monitoring devices.

In the present study, we used the N400 event-related brain potential (ERP) component as a neurophysiological probe to seek evidence for the hypothesis that frequent cannabis use predisposes individuals to delusion-like ideation by interfering with activation of normative associations in semantic memory. ERPs measure voltage changes at the scalp associated with cognitive stimuli and are thought to reflect synchronous firing of cortical pyramidal neurons. N400 is a negative ERP waveform occurring around 400 ms after any meaningful stimulus, such as a word or picture (Nobre and McCarthy 1995). Normally, N400 amplitude is reduced (less negative) when its eliciting stimulus is related to preceding context (Holcomb and Neville 1990; 1991; Kutas and Federmeier 2000; Kutas and Hillyard 1980; 1984; Stelmack and Miles 1990). Thus, following the prime word *CAT*, the related target word *MOUSE* elicits a smaller N400 than the unrelated word *ARROW*. These N400 amplitude reductions (or *N400 semantic priming effects*) are thought to reflect individuals' use of context to pre-activate associated items and thereby facilitate their processing (DeLong et al. 2005; Kutas and Federmeier 2000).

We expected that our results would parallel previous ERP evidence of deficient neural processing of relationships between meaningful concepts among persons with schizophrenia. Numerous studies have found evidence for larger (more negative) than normal N400 amplitudes in response to contextually related items, and smaller than normal N400 semantic priming effects, in schizophrenia (Condray et al. 2003; Condray et al. 2010; Ditman and Kuperberg 2007; Kiang et al. 2011; Kiang et al. 2008; Kostova et al. 2005; Kostova et al. 2003; Laurent et al. 2010; Mathalon et al. 2010; Ohta et al. 1999; Salisbury 2010; Salisbury 2008; Strandburg et al. 1997). In contrast, a few other schizophrenia studies have found smaller than normal N400 amplitudes to contextually related targets and increased N400 relatedness priming effects (Kreher et al. 2009; Kreher et al. 2008; Mathalon et al. 2002; Salisbury 2008). However, these latter data appear to be specific to short prime-target stimulus-onset asynchronies (SOAs; i.e., the time interval between the onsets of the two stimuli) of <300 ms, weakly related targets, and patients with disorganized speech and are thus suggestive of rapid automatic priming of weakly associated concepts in this subset of patients (Ditman and Kuperberg 2007; Kreher et al. 2009; Salisbury 2008). On balance,

however, N400 studies of schizophrenia patients provide evidence of a general reduction in semantic priming, at least at SOAs of approximately 300 ms or greater, during which more controlled or strategic cognitive processing is normally thought to occur. Furthermore, in line with our hypothesis, larger N400s to related targets, and smaller N400 relatedness priming effects, have been found to correlate with severity of delusions (Kiang et al. 2007; 2008).

By extension, we hypothesized that if frequent cannabis use acts as a risk for delusion-like ideation by preventing activation of related concepts in semantic memory following meaningful stimuli, then frequent cannabis users, compared to non-users, would exhibit reduced levels of semantic priming (as indexed by larger N400 amplitudes to contextually related stimuli and consequently decreased N400 relatedness priming effects). Furthermore, we hypothesized that this abnormality would be associated with higher levels of delusion-like ideation.

To test this hypothesis, we recorded ERPs in frequent cannabis users and a non-user comparison group, who viewed prime-target pairs presented at a 750-ms SOA, in which targets were either words related or unrelated to the prime word or pronounceable nonwords. The participants' task was to indicate via button press whether or not the target was a real word. We predicted that, at least in non-users, N400 would be larger to unrelated than to related targets, consistent with previous findings (Kutas and Hillyard 1989). We also predicted that, consistent with previous data (Skosnik et al. 2001), frequent cannabis users would exhibit higher levels of delusion-like ideation than non-users. Furthermore, we hypothesized that if cannabis use is associated with impaired activation of contextually related targets which contributes in turn to delusion-like ideation, then prime words would activate related targets less strongly in cannabis users than in non-users, resulting in abnormally large N400s to related targets, along with consequently smaller N400 relatedness priming effects. Moreover, we hypothesized that these abnormalities in cannabis users would correlate with severity of delusion-like ideation.

Methods

Participants

Frequent cannabis users ($n=24$) and non-users ($n=24$), 18 to 35 years of age, were recruited from the community via newspaper and Internet advertisements. Frequent use was defined as smoking an average of at least one joint of cannabis weekly over the last 6 months. Non-use was defined as not having used cannabis within the past year. The participants gave written informed consent and were compensated with cash (\$11/h). The study procedure was approved by the St. Joseph's Healthcare (Hamilton) Research Ethics Board.

Exclusion criteria for both groups included: (a) past or present DSM-IV Axis I disorder, including substance abuse or dependence (except cannabis abuse or dependence in the cannabis-using group), as determined by the Mini International Neuropsychiatric Interview (Sheehan et al. 1998); (b) left-handedness, as assessed by the Edinburgh Inventory (Oldfield 1971); (c) self-reported history of drug use other than cannabis in the past year; (d) exposure to a language other than English before age 5; (e) self-reported reading difficulties; (f) self-

reported visual impairment; (g) self-reported current or past neurological disorder; and (h) current use of neurological or psychotropic medications.

The Timeline Followback Method (TLFB) questionnaire (Sobell et al. 1996) was administered to cannabis users to assess the mean number of cannabis joints smoked per week in the past 6 months and to confirm that each member of this group had averaged at least one joint per week. A rapid urine toxicology screen for amphetamine, barbiturates, benzodiazepines, cocaine, MDMA, methamphetamine, methadone, opiate, PCP, and Δ^9 -THC (Tox/See, Bio-Rad Laboratories, Hercules, CA, USA) was administered to all participants. Individuals were excluded if they tested positive for any substance (with the exception of Δ^9 -THC in the cannabis-using group).

We aimed to exclude any cannabis users exhibiting the cannabis withdrawal syndrome, which has been identified in a subset of very frequent (i.e., daily) cannabis users, beginning as early as 5 to 6 h after last use and lasting up to several weeks in the presence of abstinence (Budney et al. 2004). Participants identified as daily cannabis users on the TLFB, and who last used cannabis more than 5 h previously, were administered a modified, interviewer-rated version of the Cannabis Withdrawal Checklist (Budney et al. 1999) to rule out the presence of cannabis withdrawal syndrome. No participants met criteria for cannabis withdrawal syndrome.

The TLFB method for assessing alcohol consumption (Sobell and Sobell 1992) was used to estimate each participant's mean number of alcoholic drinks consumed per day in the past 6 months.

Demographic characteristics of cannabis users and non-users, including cannabis users' mean number of joints smoked per week, are shown in Table 1. The two groups did not differ significantly in age, sex distribution, or years of education.

Psychological assessments

The participants completed the Schizotypal Personality Questionnaire (SPQ), a 72-item validated self-rating instrument with nine subscales corresponding to each of the nine DSM-IV schizotypal traits, including odd behavior, odd speech, ideas of reference, odd beliefs, unusual perceptual experiences, suspiciousness, social anxiety, lack of close friends, and constricted affect (Raine 1991). As an index of delusion-like ideation, each participant's subscale scores for ideas of reference, odd beliefs, and suspiciousness were summed to obtain a "delusion-like ideation" score. The participants also completed the Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn 1997) as a measure of receptive vocabulary.

N400 ERP procedure

Stimuli—Stimuli included 80 related (e.g., *METAL-STEEL*) and 80 unrelated (*DONKEY-PURSE*) prime-target word pairs. For each related pair, the target was among the words most commonly given as associates to the prime by participants in the University of South Florida word association norms (Nelson et al. 1999); mean response probability of related targets (i.e., proportion of individuals producing that word in response to the prime) was 0.42 (SD=0.23). For each unrelated pair, prime and target were not associates in the norms.

Across related and unrelated conditions, targets were matched for mean length and log-transformed frequency (Francis and Kucera 1982), and primes were also matched on these characteristics. Stimuli also included 160 word–nonword prime–target pairs (*DRESS-ZORES*), whose targets were pronounceable nonwords. No word occurred more than once among the stimuli. The 320-trial stimulus list included all prime–target pairs in a fixed randomized order, in four blocks of 80 trials each.

Task—In an electrically shielded, sound-attenuated chamber, the participants were seated at 100 cm in front of a video monitor on which stimuli were visually presented, with each letter subtending on average 0.36° of visual angle horizontally and up to 0.55° vertically. Words were displayed in yellow letters on a black background.

Each participant was presented with the stimulus list, with short rest breaks between blocks. Each trial consisted of: (a) a row of preparatory fixation crosses for 500 ms, (b) blank screen for 250 ms, (c) prime word for 175 ms, (d) blank screen for 575 ms, resulting in a 750-ms prime–target SOA, (e) target for 250 ms, (f) blank screen for 1,250 ms, (g) the prompt *Yes or No?* until participants responded via a button press, and (h) blank screen for 3,000 ms until onset of the next trial. All stimuli were centrally presented.

At a prompt, the participants were required to press one of two buttons, positioned under their right and left thumbs, respectively, to indicate whether or not the target was a word. One button (labeled “Yes”) signaled that the target was a word, while the other button (labeled “No”) signaled that it was a nonword; assignment of buttons was counterbalanced across participants. This response was delayed to minimize motor effects on the ERP.

Electroencephalographic data collection and analysis—During the experimental task, the electroencephalogram (EEG) was recorded using an ActiveTwo system (BioSemi BV, Amsterdam) from 32 sites approximately equally spaced across the scalp, positioned according to a modified International 10–20 System (Fp1–Fp2–AF3–AF4–F7–F3–Fz–F4–F8–FC5–FC1–FC2–FC6–T7–T8–C3–Cz–C4–CP5–CP1–CP2–CP6–P7–P3–Pz–P4–P8–PO3–PO4–O1–Oz–O2). The EEG was referenced to a left parietal common mode sense active electrode and a right parietal driven right leg passive electrode, which form a feedback loop driving the average potential across the montage as close as possible to the amplifier zero. The EEG was continuously digitized at 512 Hz and low-pass-filtered at 128 Hz. Blinks and eye movements were monitored via electrodes on the supraorbital and infraorbital ridges and on the outer canthi of both eyes. The EEG was re-referenced offline to the algebraic mean of the mastoids and bandpassed at 0.01–100 Hz. Continuous data were algorithmically corrected for eyeblink artifact (Jung et al. 2000). ERPs were computed for epochs from 100 ms pre-stimulus to 900 ms post-stimulus. Individual trials containing artifacts due to eye movement, excessive muscle activity, or amplifier blocking were rejected offline by visual inspection before time domain averaging; the participants’ mean percentage of trials lost to such artifacts was 17 % for cannabis users and 12 % for non-users.

For each participant, separate ERP averages were obtained for trials with related and unrelated target words. N400 amplitude was defined as the mean voltage from 300 to 500 ms post-stimulus.

Difference waveforms were obtained by subtracting the ERP average for related targets from the average for unrelated targets (*semantic priming effect*). Amplitude of N400 semantic priming effects was defined as their mean voltage from 300 to 500 ms post-stimulus.

Statistical analyses

P-values in analyses of variance (ANOVAs) with within-subject factors are reported after Greenhouse–Geisser Epsilon correction. Repeated-measures ANOVAs were calculated using the general linear model. For significant effects in the ANOVAs, the effect size, generalized ω^2 (Olejnik and Algina 2003), was calculated. Pairwise comparisons of factor-level means were made with Tukey simultaneous comparisons, with a family confidence coefficient of 0.95. All *P*-values are two-tailed.

Percentage of correct responses was analyzed by repeated-measures ANOVA, with *group* (cannabis-using vs. non-using) as between-subject variable and *target* (related vs. unrelated vs. nonword) as within-subject variable.

N400 mean amplitude was analyzed with a repeated-measures ANOVA, with *group* (cannabis-using vs. non-using) as between-subject variable and *target* (related vs. unrelated vs. nonword) and *electrode* (19 levels, corresponding to a contiguous array of bilateral sites centered on the centroparietal region, where N400 effects are typically most prominent (Kutas and Federmeier 2000): FC1, FC2, Cz, C3, C4, CP1, CP2, CP5, CP6, Pz, P3, P4, P7, P8, PO3, PO4, Oz, O1, and O2) as within-subject variables. Amplitude of the N400 semantic priming effect was analyzed in a repeated-measures ANOVA with *group* (cannabis-using vs. non-using) as between-subject variable and *electrode* (19 levels, corresponding to the sites listed above) as within-subject variable.

Because visual inspection suggested that amplitude of the post-N400 positivity might differ between groups, mean amplitude from 500 to 700 ms was analyzed post hoc in a repeated-measures ANOVA with *group* (cannabis-using vs. non-using) as between-subject variable and *target* (related vs. unrelated vs. nonword) and *electrode* (19 levels, corresponding to the sites listed above) as within-subject variables.

To test for an association between semantic priming and delusion-like ideation, Spearman's pairwise nonparametric correlation coefficients ρ were calculated for N400 semantic priming effects at site Cz vs. SPQ delusion-like ideation scores for each participant group. A nonparametric correlation coefficient was used because SPQ delusion-like ideation scores were non-normally distributed.

Results

Neuropsychological assessments

Mean scores for cannabis users and non-users on the SPQ and PPVT are shown in Table 1. Cannabis users had significantly higher SPQ total and delusion-like ideation scores compared to non-users. The groups did not differ significantly from one another on PPVT scores.

Behavioral data

The participants' mean correct response rates in the lexical-decision task are shown in Table 2. Overall, the high correct response rates indicate that the participants were attending to the stimuli and task. There was no *group* effect [$F(1,46)=1.73$, $P=0.20$]. There was a *target* effect [$F(2,92)=5.27$, $P=0.02$, $\omega^2=0.04$], indicating that, across both groups, the correct response rate was higher for related targets than for nonword targets. There was no *group*×*target* interaction [$F(2,92)=1.66$, $P=0.20$].

ERPs

To illustrate the difference between groups, grand average ERPs for related and unrelated word targets and nonword targets (at the midline central electrode site Cz) are shown for both groups in Fig. 1.

Mean N400 amplitudes and semantic priming effects for both groups and target types are shown in Table 3. Across both groups, mean N400 amplitudes were smaller (relatively less negative) for related targets than unrelated and nonword targets [*target* effect: $F(2,92)=39.74$, $P<0.0001$, $\omega^2=0.07$]. There was also a *group* effect [$F(1,46)=4.13$, $P<0.05$, $\omega^2=0.04$], indicating that, across all target conditions, mean N400 amplitudes were smaller (less negative) in the cannabis-using group compared to the non-using group. There was no *group*×*target* interaction [$F(2,92)=0.44$, $P=0.64$]. There was no effect of *group* on N400 semantic priming effects [$F(1,46)=0.41$, $P=0.53$].

Mean amplitude from 500 to 700 ms showed a trend for a *group* effect in which amplitude was more positive across target conditions for cannabis users compared to non-users [$F(1,46)=2.90$, $P=0.10$].

Correlation of N400 ERP measures with delusion-like ideation

Spearman's pairwise nonparametric correlation coefficients ρ for N400 semantic priming effects at site Cz vs. SPQ delusion-like ideation scores are shown in Table 4 for both groups.

Because the cannabis-using group exhibited smaller N400 amplitudes than the non-cannabis-using group in response to both related and unrelated targets, we explored whether there was an association between these abnormalities and delusion-like ideation. Spearman's pairwise non-parametric correlation coefficients ρ for N400 mean amplitudes for each target condition at site Cz vs. SPQ delusion-like ideation scores are shown in Table 4 for both groups. The significant positive correlation between N400 mean amplitudes for each target condition and SPQ delusion-like ideation scores in the cannabis-using group indicates that smaller (less negative) N400 amplitudes were associated with higher levels of delusion-like ideation (Fig. 2).

Discussion

In this study, we used the N400 ERP component as a neurophysiological probe of semantic activation to seek evidence for the hypotheses that frequent cannabis users exhibit subnormal activation of contextually related versus unrelated stimuli (i.e., less than normal semantic priming) and that this abnormality is associated with greater levels of delusion-like ideation

– consistent with a causal role for semantic priming deficits in the development of such ideation. We predicted that these semantic priming deficits would be reflected in larger (more negative) than normal N400 amplitudes in response to contextually related stimuli and consequently decreased N400 semantic priming effects (N400 amplitude differences between unrelated and related stimuli).

Our results, however, did not support this hypothesis. As expected, and consistent with previous data, frequent cannabis users exhibited higher levels of delusion-like ideation than non-users, and N400 amplitudes were smaller (less negative) for related compared to unrelated targets in the non-users. However, frequent cannabis users exhibited smaller N400 amplitudes than non-users did to both related and unrelated targets, such that cannabis users' N400 semantic priming effects did not differ significantly from that of non-users. Moreover, within the cannabis-using group, smaller N400 amplitudes to both related and unrelated targets were associated with higher levels of delusion-like ideation.

Thus, our results did not parallel existing N400 semantic priming abnormalities reported in schizophrenia at similarly long prime-target SOAs (>300 ms), a time course over which relatively strategic or controlled processing is normally thought to occur. The preponderance of previous studies using these SOAs has suggested less than normal activation of concepts related to the prime in patients with schizophrenia as reflected in larger than normal N400 amplitudes in response to related targets and smaller than normal N400 semantic priming effects (Condray et al. 2003; Condray et al. 2010; Ditman and Kuperberg 2007; Kiang et al. 2011; Kiang et al. 2008; Kostova et al. 2005; Kostova et al. 2003; Laurent et al. 2010; Mathalon et al. 2010; Ohta et al. 1999; Salisbury 2010; Salisbury 2008; Strandburg et al. 1997). In contrast, our results—namely, smaller than normal N400 amplitudes to both related and unrelated targets—were consistent with heightened activation within semantic memory of concepts both related and unrelated to the prime.

In our data, N400s elicited by the nonword targets in the lexical-decision task were, like those elicited by both types of word targets, also smaller in frequent cannabis users than in non-users. The precise functional significance of the N400 elicited by nonwords is incompletely understood but may reflect continuing attempts to extract meaning from the nonword (Deacon et al. 2004). According to one model, the nonword activates orthographically similar real words (“orthographic neighbors”), which then feed back to modulate the N400 amplitude elicited by the nonword, accounting for the finding that this amplitude is reduced in proportion to the nonword's number of orthographic neighbors (Laszlo et al. 2012). Thus, if cannabis use produces a generalized increase in activation within the semantic network, this might reduce N400 amplitudes elicited by nonwords by increasing the activation of concepts whose word representations are orthographic neighbors of these nonwords.

Our finding that N400 amplitude was less negative in cannabis users than non-users across all target types could also be consistent with a generalized increase in the amplitude of post-N400 positivity if this increase began early enough to overlap with the N400 time window. Such late positivities have been hypothesized to reflect attempts at re-analysis when linguistic stimuli differ from what was predicted, with the amplitude of the positivity being

proportional to the strength of the initial expectation and the degree to which the actual stimulus differs from it (Davenport and Coulson 2011). In our data, there was a trend for this post-N400 positivity to be larger (more positive) across target types for cannabis users versus non-users. If, based on the prime word, cannabis users made relatively strong and/or unusual predictions for the target word, then this might account for greater than normal late positivities when targets did not conform to the predictions. This difference in strategic or controlled processing could plausibly manifest at the relatively long prime-target SOA (750 ms) that we used, over which this type of processing is thought to play a role.

All of the cannabis users we tested had used cannabis within the previous week, and most had used it in the past 48 h. Thus, a limitation of our study design was that it did not allow us to distinguish whether the observed N400 abnormalities are associated specifically with recent cannabis use or are present in chronic cannabis users even in the absence of recent use. To isolate correlates of chronic cannabis use that persist in the absence of recent use, we would have had to exclude frequent cannabis users who had used it recently; however, in this naturalistic study, we chose not to do so as this would have excluded a large proportion of frequent cannabis users.

Our results are consistent with the hypothesis that increased activation of concepts related to meaningful stimuli, or decreased inhibition of unrelated concepts, plays a causal role in the development of delusion-like ideation in frequent cannabis users. Specifically, in frequent cannabis users, we found that smaller N400 amplitudes for targets both related and unrelated to a preceding prime were correlated with higher levels of delusion-like ideation. Importantly, however, although these correlations are consistent with a causal link, they do not prove causation. Additional studies are needed to corroborate and further characterize N400 semantic priming abnormalities in cannabis users and to investigate whether and, if so, how GABAergic dysfunction plays a role in their development. Further work is also necessary to understand the relation between our findings of abnormal semantic processing in cannabis users at the neurophysiological level and the previous observation that this group exhibits abnormal behavioral semantic priming in the form of larger reaction time advantages for related vs. unrelated targets at the same prime-target SOA of 750 ms (Morgan et al. 2010). Future research (e.g., longitudinal studies on pre-and post-cannabis use) can also test for further evidence that semantic processing abnormalities observed at the neurophysiological level in cannabis users mediate the development of delusion-like ideation.

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Fig. 1.

Grand average ERPs to related word targets (*solid line*), unrelated word targets (*dotted line*), and nonword targets (*dashed line*) for **a** cannabis users and **b** non-users at the midline central electrode site Cz. Mean N400 amplitude was less negative across all target types in cannabis users compared to non-users

Fig. 2. Scatterplots of N400 amplitudes elicited by **a** related and **b** unrelated targets vs. SPQ delusion-like ideation scores in the cannabis-using group

Table 1Demographic and psychological characteristics of the study sample (means $\pm$ SD given where applicable)

	Cannabis users (<i>n</i> =24)	Non-users (<i>n</i> =24)
Age (years)	23.1 $\pm$ 4.0	22.1 $\pm$ 2.9
Sex	9 female, 15 male	15 female, 9 male
Years of education	13.8 $\pm$ 2.2	14.4 $\pm$ 2.3
Cannabis joints smoked per week in the last 6 months	9.2 $\pm$ 9.1	–
Time since last cannabis use (h)	32.5 $\pm$ 37.6	–
Age of first cannabis use (years)	16.2 $\pm$ 1.8	–
Alcoholic drinks per day in the last 6 months	0.7 $\pm$ 0.7	0.7 $\pm$ 1.1
SPQ		
Total score ^a	16.5 (11.8)	9.8 (10.6)
Delusion-like ideation score ^b	5.1 (5.8)	2.3 (2.4)
PPVT	179.4 (8.7)	180.7 (6.5)

^a Cannabis users differed significantly from non-users, $t(46)=2.26$, $P=0.04$ ^b Cannabis users differed significantly from non-users, $t(46)=2.22$, $P=0.03$

Table 2

Percentage of correct lexical-decision responses by group and target condition (mean values, with SD in parentheses)

	Cannabis users (<i>n</i>=24)	Non-users (<i>n</i>=24)
Related	99.5 (0.9)	99.5 (1.1)
Unrelated	98.0 (2.5)	99.5 (0.7)
Nonwords	97.8 (4.4)	98.4 (3.0)

Table 3Mean N400 amplitude (μV) by participant group and target condition

	<u>Cannabis users ($n=24$)</u>		<u>Non-users ($n=24$)</u>	
	Mean	SD	Mean	SD
Related	3.64	3.78	1.84	3.19
Unrelated	1.34	3.86	-0.13	3.37
Nonword	1.31	3.78	0.04	3.05
Semantic priming effect (unrelated minus related)	-2.30	2.30	-1.97	1.92

Table 4

Spearman's pairwise nonparametric correlation coefficients ρ of N400 measures (at Cz) vs. SPQ delusion-like ideation scores

	Mean N400 amplitude, related targets	Mean N400 amplitude, unrelated targets	Mean amplitude, N400 priming effect
Cannabis users ($n=24$)	0.65 **	0.48 *	-0.16
Non-users ($n=24$)	-0.21	-0.07	0.28

*
 $P=0.02$

**
 $P=0.0006$