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 nonwords. 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 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 remains 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; Eggan and Lewis 2007), the cannabic 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). Likewise, 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 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 in press). 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 thought normally 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 nonusers, 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.

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 six months. Non-use was defined as not having used cannabis within the past year. Participants gave written informed consent and were compensated with cash ($11/hour). 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; (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 six 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) 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 hours 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 hours 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 six months.

Demographic characteristics of cannabis users and nonusers, 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

Participants completed the Schizotypal Personality Questionnaire (SPQ), a 72-item validated self-rating instrument, with 9 subscales corresponding to each of the 9 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. 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, participants were seated 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 1250 ms; (g) the prompt *Yes or No?* until participants responded via a button-press; and (h) blank screen for 3000 ms until onset of the next trial. All stimuli were centrally presented.

At the prompt, 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 (CMS) active electrode and a right parietal Driven Right Leg (DRL) 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. Offline, the EEG was re-referenced 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 off-line by visual inspection before time-domain averaging; 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 centred 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 nonusers. The groups did not differ significantly from one another on PPVT scores.

Behavioral data

Participants' mean correct-response rates in the lexical-decision task are shown in Table 2. Overall, the high correct-response rates indicate that 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 x 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. 2.

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 x 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-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 nonparametric 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 did non-users 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 thought normally 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 activation of concepts whose word representations are orthographic neighbours 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 the 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 hours. 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 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 behavioural 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 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.

References

Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt T (2002) Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ 325: 1212-1213

Bastiaansen MC, Oostenveld R, Jensen O, Hagoort P (2008) I see what you mean: Theta power increases are involved in the retrieval of lexical semantic information. Brain Lang 106: 15-28

Bastiaansen MC, van der Linden M, Ter Keurs M, Dijkstra T, Hagoort P (2005) Theta responses are involved in lexical-semantic retrieval during language processing. J Cogn Neurosci 17: 530-41

Benes FM, Berretta S (2001) GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. Neuropsychopharmacology 25: 1-27

Budney AJ, Hughes JR, Moore BA, Vandrey R (2004) Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry 161: 1967-77

Budney AJ, Novy PL, Hughes JR (1999) Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction 94: 1311-22

Cohen M, Solowij N, Carr V (2008) Cannabis, cannabinoids and schizophrenia: integration of the evidence. Aust N Z J Psychiatry 42: 357-68

Condray R, Siegle GJ, Cohen JD, van Kammen DP, Steinhauer SR (2003) Automatic activation of the semantic network in schizophrenia: evidence from event-related brain potentials. Biol Psychiatry 54: 1134-48

Condray R, Siegle GJ, Keshavan MS, Steinhauer SR (2010) Effects of word frequency on semantic memory in schizophrenia: electrophysiological evidence for a deficit in linguistic access. Int J Psychophysiol 75: 141-56

Davenport T, Coulson S (2011) Predictability and novelty in literal language comprehension: an ERP study. Brain Res 1418: 70-82

Deacon D, Dynowska A, Ritter W, Grose-Fifer J (2004) Repetition and semantic priming of nonwords: implications for theories of N400 and word recognition. Psychophysiology 41: 60-74

DeLong KA, Urbach TP, Kutas M (2005) Probabilistic word pre-activation during language comprehension inferred from electrical brain activity. Nat Neurosci 8: 1117-21

Ditman T, Kuperberg GR (2007) The time course of building discourse coherence in schizophrenia: an ERP investigation. Psychophysiology 44: 991-1001

Dunn LM, Dunn LM (1997) Peabody Picture Vocabulary Test, 3rd edn. American Guidance Service, American Guidance Service

Eckblad M, Chapman LJ (1983) Magical ideation as an indicator of schizotypy. J Consult Clin Psychol 51: 215-25

Eggan SM, Lewis DA (2007) Immunocytochemical distribution of the cannabinoid CB1 receptor in the primate neocortex: a regional and laminar analysis. Cereb Cortex 17: 175-91

Fernandez-Espejo E, Viveros MP, Nunez L, Ellenbroek BA, Rodriguez de Fonseca F (2009) Role of cannabis and endocannabinoids in the genesis of schizophrenia. Psychopharmacology (Berl) 206: 531-49

Ford JM, Krystal JH, Mathalon DH (2007) Neural synchrony in schizophrenia: from networks to new treatments. Schizophr Bull 33: 848-52

Foti DJ, Kotov R, Guey LT, Bromet EJ (2010) Cannabis Use and the Course of Schizophrenia: 10-Year Follow-Up After First Hospitalization. Am J Psychiatry 167: 987-993

Francis WN, Kucera H (1982) Frequency of Analysis of English Usage. Houghton Mifflin, Houghton Mifflin

Hajos M, Hoffmann WE, Kocsis B (2008) Activation of cannabinoid-1 receptors disrupts sensory gating and neuronal oscillation: relevance to schizophrenia. Biol Psychiatry 63: 1075-83

Hajos N, Katona I, Naiem SS, MacKie K, Ledent C, Mody I, Freund TF (2000) Cannabinoids inhibit hippocampal GABAergic transmission and network oscillations. Eur J Neurosci 12: 3239-49

Hemsley DR (2005) The schizophrenic experience: taken out of context? Schizophr Bull 31: 43-53

Holcomb PJ, Neville HJ (1990) Auditory and visual semantic priming in lexical decision: a comparison using event-related brain potentials. Lang Cognitive Processes 5: 281-312

Holcomb PJ, Neville HJ (1991) Natural speech processing: an analysis using event-related brain potentials. Psychobiol 19: 286-300

Jung TP, Makeig S, Humphries C, Lee TW, McKeown MJ, Iragui V, Sejnowski TJ (2000) Removing electroencephalographic artifacts by blind source separation. Psychophysiology 37: 163-78

Kapur S (2003) Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160: 13-23

Kiang M, Christensen BK, Zipursky RB (2011) Depth-of-processing effects on semantic activation deficits in schizophrenia: An electrophysiological investigation. Schizophr Res 133: 91-98

Kiang M, Kutas M, Light GA, Braff DL (2007) Electrophysiological insights into conceptual disorganization in schizophrenia. Schizophr Res 92: 225-236

Kiang M, Kutas M, Light GA, Braff DL (2008) An event-related brain potential study of direct and indirect semantic priming in schizophrenia. Am J Psychiatry 165: 74-81

Kostova M, Passerieux C, Laurent JP, Hardy-Bayle MC (2005) N400 anomalies in schizophrenia are correlated with the severity of formal thought disorder. Schizophr Res 78: 285-91

Kostova M, Passerieux C, Laurent JP, Saint-Georges C, Hardy-Bayle MC (2003) Functional analysis of the deficit in semantic context processes in schizophrenic patients: an event-related potentials study. Neurophysiol Clin 33: 11-22

Kreher DA, Goff D, Kuperberg GR (2009) Why all the confusion? Experimental task explains discrepant semantic priming effects in schizophrenia under "automatic" conditions: evidence from Event-Related Potentials. Schizophr Res 111: 174-81

Kreher DA, Holcomb PJ, Goff D, Kuperberg GR (2008) Neural Evidence for Faster and Further Automatic Spreading Activation in Schizophrenic Thought Disorder. Schizophr Bull 34: 473-482

Kutas M, Federmeier KD (2000) Electrophysiology reveals semantic memory use in language comprehension. Trends Cogn Sci 4: 463-470

Kutas M, Hillyard SA (1980) Reading senseless sentences: brain potentials reflect semantic incongruity. Science 207: 203-5

Kutas M, Hillyard SA (1984) Brain potentials during reading reflect word expectancy and semantic association. Nature 307: 161-3

Kutas M, Hillyard SA (1989) An electrophysiological probe of incidental semantic association. J Cogn Neurosci 1: 38-49

Laszlo S, Stites M, Federmeier KD (2012) Won't get fooled again: An event-related potential study of task and repetition effects on the semantic processing of items without semantics. Lang Cogn Process 27: 257-274

Laurent JP, Kostova M, Passerieux C (2010) N400 and P300 modulation as functions of processing level in schizophrenia patients exhibiting formal thought disorder. Int J Psychophysiol 75: 177-82

Maher BA (1974) Delusional thinking and perceptual disorder. J Individ Psychol 30: 98-113

Mathalon DH, Faustman WO, Ford JM (2002) N400 and automatic semantic processing abnormalities in patients with schizophrenia. Arch Gen Psychiatry 59: 641-8

Mathalon DH, Roach BJ, Ford JM (2010) Automatic semantic priming abnormalities in schizophrenia. Int J Psychophysiol 75: 157-66

Miltner WH, Braun C, Arnold M, Witte H, Taub E (1999) Coherence of gamma-band EEG activity as a basis for associative learning. Nature 397: 434-6

Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2007) Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet 370: 319-28

Morgan CJ, Rothwell E, Atkinson H, Mason O, Curran HV (2010) Hyper-priming in cannabis users: a naturalistic study of the effects of cannabis on semantic memory function. Psychiatry Res 176: 213-8

Nelson DL, McEvoy CL, Schreiber TA (1999) The University of South Florida word association norms.

Nobre AC, McCarthy G (1995) Language-related field potentials in the anterior-medial temporal lobe: II. Effects of word type and semantic priming. J Neurosci 15: 1090-1098

Ohta K, Uchiyama M, Matsushima E, Toru M (1999) An event-related potential study in schizophrenia using Japanese sentences. Schizophr Res 40: 159-70

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9: 97-113

Olejnik S, Algina J (2003) Generalized eta and omega squared statistics: measures of effect size for some common research designs. Psychol Methods 8: 434-47

Parnas J (1999) From predisposition to psychosis: progression of symptoms in schizophrenia. Acta Psychiatr Scand Suppl 395: 20-9

Raine A (1991) The SPQ: a scale for the assessment of schizotypal personality based on DSM-III-R criteria. Schizophr Bull 17: 555-64

Rossler W, Riecher-Rossler A, Angst J, Murray R, Gamma A, Eich D, van Os J, Gross VA (2007) Psychotic experiences in the general population: a twenty-year prospective community study. Schizophr Res 92: 1-14

Salisbury D (2010) N400 to lexical ambiguity and semantic incongruity in schizophrenia. Int J Psychophysiol 75: 127-32

Salisbury DF (2008) Semantic activation and verbal working memory maintenance in schizophrenic thought disorder: insights from electrophysiology and lexical ambiguity. Clin EEG Neurosci 39: 103-7

Salisbury DF, Taylor G (in press) Semantic priming increases left hemisphere theta power and intertrial phase synchrony. Psychophysiology

Sarnthein J, Petsche H, Rappelsberger P, Shaw GL, von Stein A (1998) Synchronization between prefrontal and posterior association cortex during human working memory. Proc Natl Acad Sci 95: 7092-6

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC (1998) The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59 Suppl 20: 22-33

Skosnik PD, Krishnan GP, Aydt EE, Kuhlenshmidt HA, O'Donnell BF (2006) Psychophysiological evidence of altered neural synchronization in cannabis use: relationship to schizotypy. Am J Psychiatry 163: 1798-805

Skosnik PD, Spatz-Glenn L, Park S (2001) Cannabis use is associated with schizotypy and attentional disinhibition. Schizophr Res 48: 83-92

Sobell LC, Sobell MB (1992) Timeline followback: a technique for assessing self-reported alcohol consumption. In: Litten RZ, Allen J (eds) Measuring alcohol consumption: psychosocial and biological methods. Humana Press, Totowa, NJ, pp 41-72

Sobell LC, Sobell MB, Buchan G, Cleland PA, Fedoroff I, Leo GI (1996) The reliability of the Timeline Followback method applied to drug, cigarette, and cannabis use. 30th Annual Meeting of the Association for Advancement of Behavior Therapy, New York

Soltesz I, Staley K (2006) High times for memory: cannabis disrupts temporal coordination among hippocampal neurons. Nat Neurosci 9: 1461-3

Stelmack RM, Miles J (1990) The effect of picture priming on event-related potentials of normal and disabled readers during a word recognition memory task. J Clin Exp Neuropsychol 12: 887-903

Strandburg RJ, Marsh JT, Brown WS, Asarnow RF, Guthrie D, Harper R, Yee CM, Nuechterlein KH (1997) Event-related potential correlates of linguistic information processing in schizophrenics. Biol Psychiatry 42: 596-608

Uhlhaas PJ, Singer W (2010) Abnormal neural oscillations and synchrony in schizophrenia. Nat Rev Neurosci 11: 100-13

van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H (2002) Cannabis use and psychosis: a longitudinal population-based study. Am J Epidemiol 156: 319-27

Varela F, Lachaux JP, Rodriguez E, Martinerie J (2001) The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2: 229-39

Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G (2002) Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ 325: 1199

Zammit S, Moore TH, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G (2008) Effects of cannabis use on outcomes of psychotic disorders: systematic review. Br J Psychiatry 193: 357-63

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

	Cannabis users (n=24)	**Non-users (n=24)**
Age (years)	23.1±4.0	22.1±2.9
Sex	9 female, 15 male	15 female, 9 male
Years of education	13.8±2.2	14.4±2.3
Cannabis joints smoked per week in the last 6 months	9.2±9.1	-
Time since last cannabis use (hours)	32.5±37.6	-
Age of first cannabis use (years)	16.2±1.8	-
Alcoholic drinks per day in the last 6 months	0.7±0.7	0.7±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 nonusers, $t(46)=2.26$, $P=0.04$

[b]Cannabis users differed significantly from nonusers, $t(46)=2.22$, $P=0.03$

Table 2 Percentage of correct lexical-decision responses, by group and target condition (mean values, with SD in parentheses)

	Cannabis users (n=24)	**Non-users (n=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 3 Mean N400 amplitude (μV), by participant group and target condition

	Cannabis users (n=24)		**Non-users (n=24)**	
	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
Nonusers (*n*=24)	-0.21	-0.07	0.28

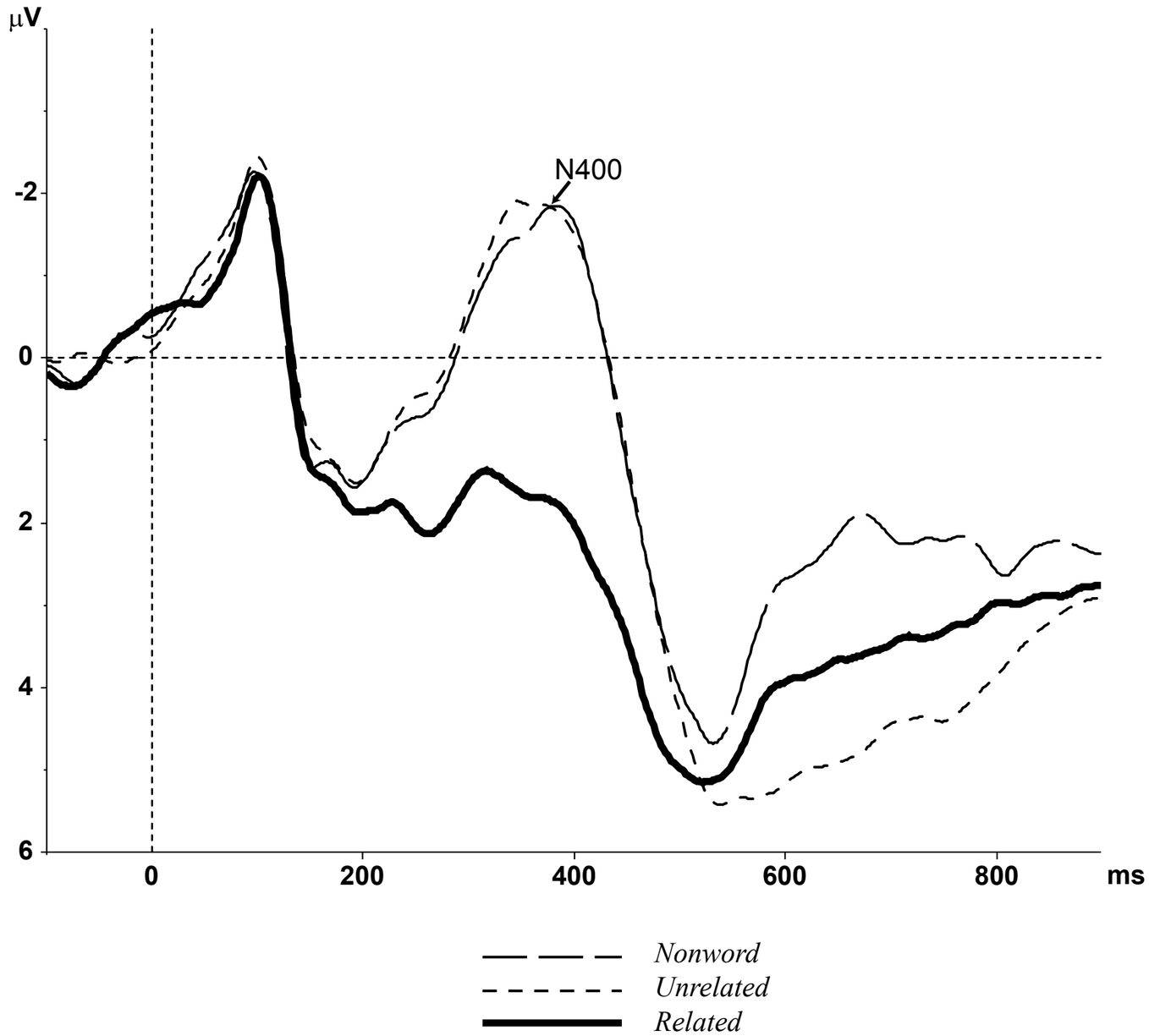
**P*=0.02

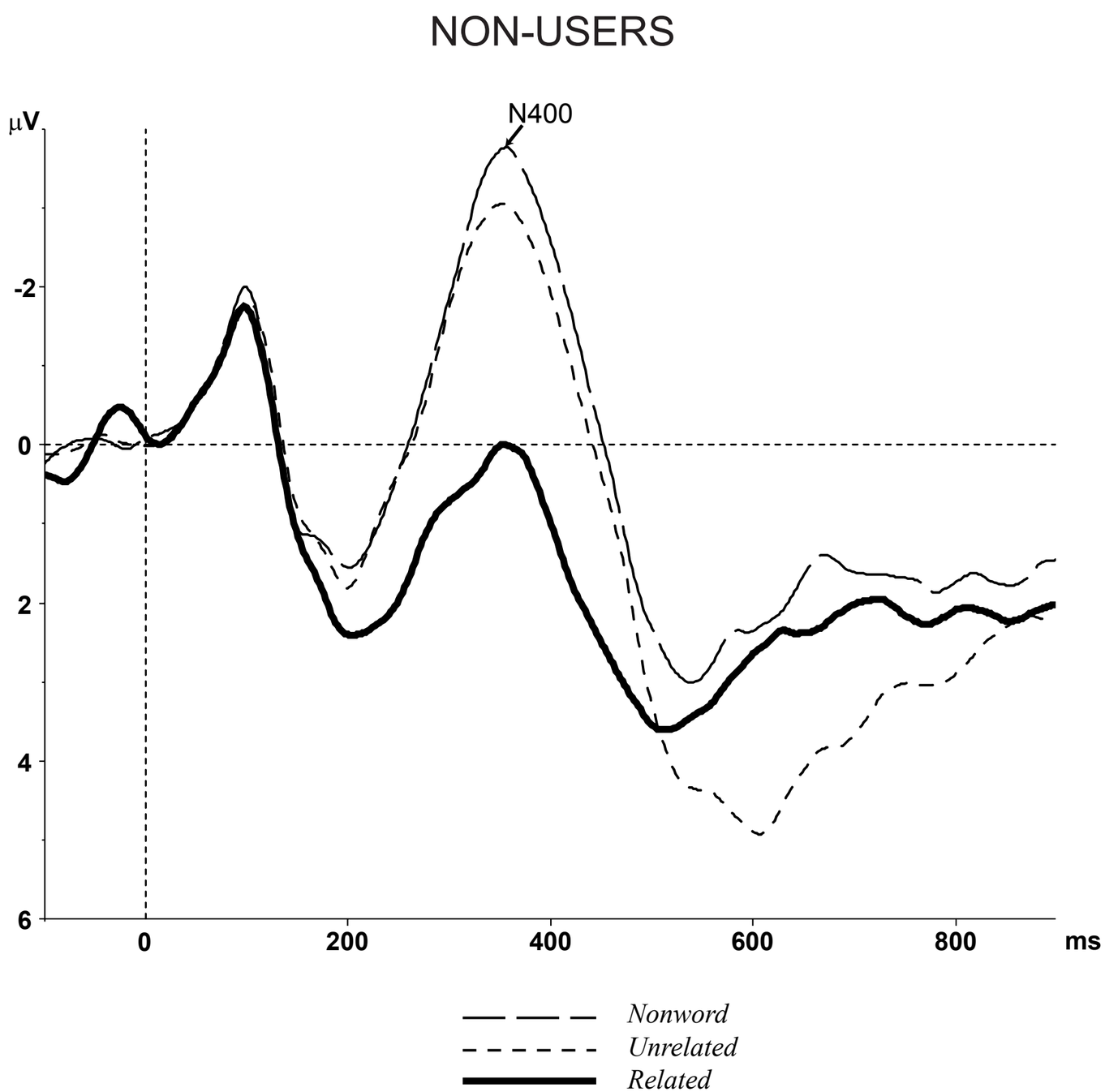
***P*=0.0006

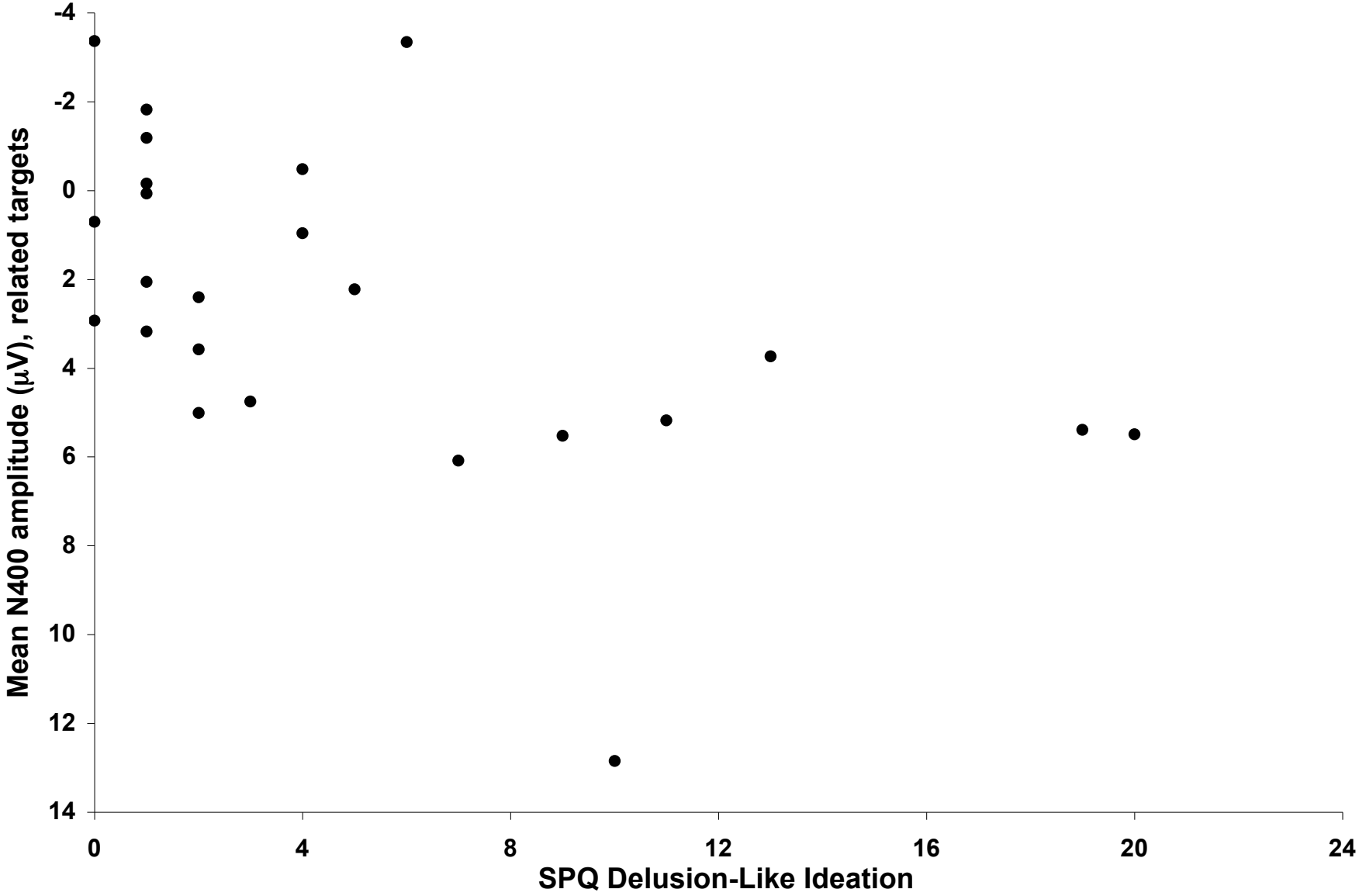
Fig. 1 Grand average ERPs to related word targets (solid line), unrelated word targets (dotted line), and nonword targets (dashed line), for (a) cannabis users and (b) non-users, at the midline central electrode site Cz. Mean N400 amplitude was less negative across all target types in cannabis users compared to non-users.

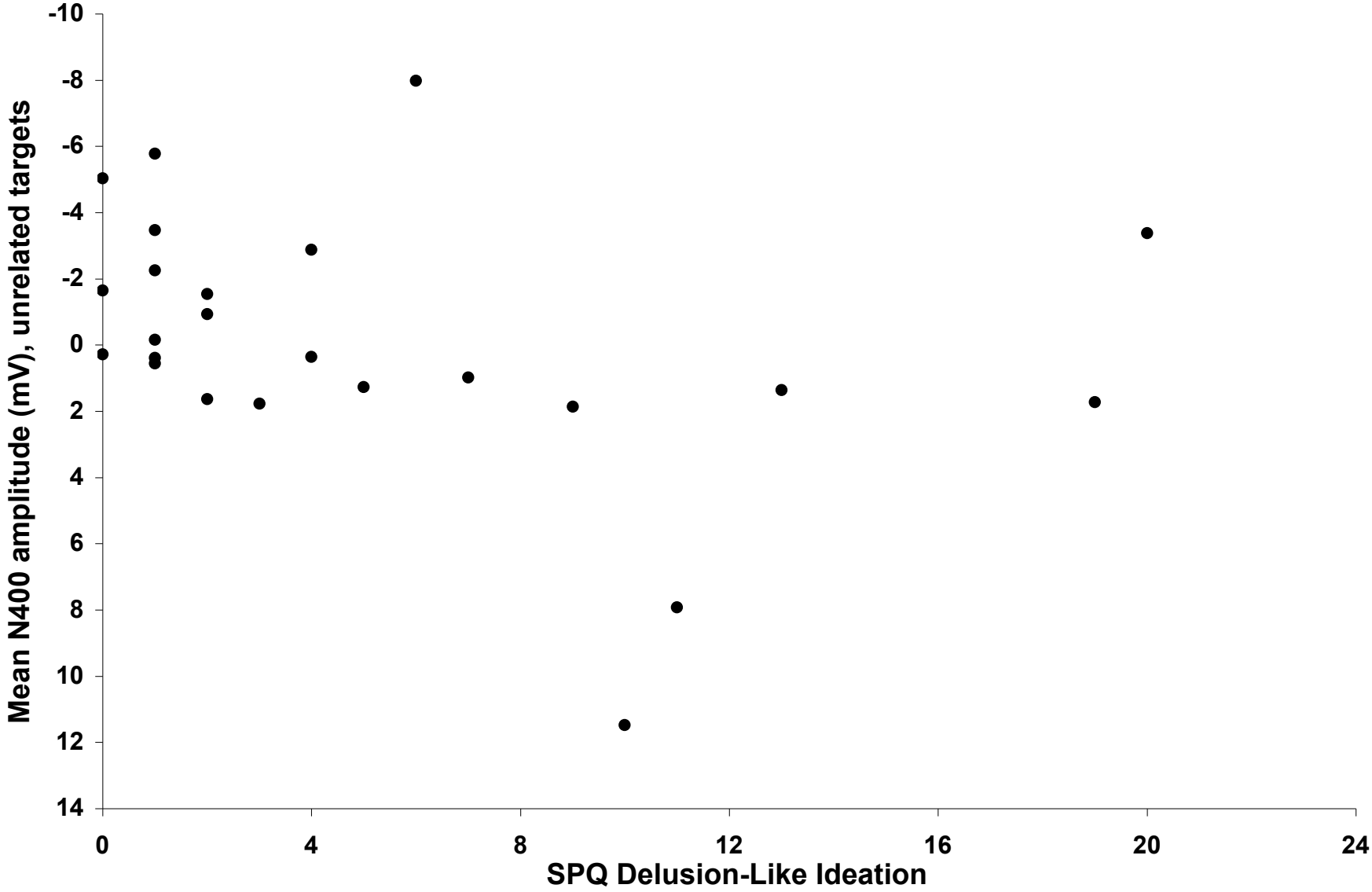
Fig. 2 Scatterplots of N400 amplitudes elicited by (a) related and (b) unrelated targets vs. SPQ Delusion-like Ideation scores in the cannabis-using group.

CANNABIS USERS




NON-USERS
N400
μV
-2
0
2
4
6
0
200
400
600
800
ms
Nonword
Unrelated
Related


Mean N400 amplitude (μV), related targets
-4
-2
0
2
4
6
8
10
12
14
0
4
8
12
16
20
24
SPQ Delusion-Like Ideation


-10
-8
-6
-4
-2
0
2
4
6
8
10
12
14
Mean N400 amplitude (mV), unrelated targets
0
4
8
12
16
20
24
SPQ Delusion-Like Ideation