Reduction of Auditory P50 Gating Response in Marihuana Users: Further Supporting Data

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Auditory P50 Suppression
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INTRODUCTION

In the auditory sensory gating paradigm two stimuli are presented close together with the result that the P50 evoked potential amplitude elicited by the second ("test") stimulus is normally reduced or attenuated by the effects of the first ("conditioned") stimulus.[1] The sensory gating response is expressed as a ratio of the P50 amplitudes produced by the conditioned and test stimuli. A robust inhibitory gating mechanism can completely suppress the response to the test stimulus resulting in a gating ratio of zero, whereas a total absence of sensory gating would result in identical P50 amplitudes to both conditioning and test stimuli and a ratio of 100%.

Recently we reported[2] that the auditory P50 sensory gating response was significantly reduced in medically and psychiatrically normal adult chronic marihuana (THC) users as contrasted with nonuser controls. This communication provides further support for our earlier finding by applying the same methodology used before to a new sample of mixed adolescent and adult heavy THC users and nonuser controls.

SUBJECTS

Normal adult and adolescent subjects using THC exclusively ≥ 3 times per week (THC Group) and those with no history of abuse drug use (Controls) were recruited. Exclusion criteria included current or past medical illness affecting the central nervous system, current or past Axis 1 psychiatric diagnosis, use of prescribed medications, history of closed head injury regardless of presence or absence of reported sequelae, history of EEG testing or computed tomography scan regardless of results or stated purpose, any current use of non-THC abuse drugs (THC users) or abuse drugs of any kind (control subjects), and any generalized and/or focal slowing or spike-wave activity in the current testing EEG. Because paired auditory P50 sensory gating is known to be defective (i.e., reduced suppression) in both positive and negative symptom schizophrenics[3-9] and, to a lesser extent, in first degree relatives of schizophrenics,[10-12] we also decided to exclude any subject with a 1st degree relative with a diagnosis of psychosis. Seventeen nonuser controls and 12 THC users were screened following informed consent. Three potential controls were excluded because of current or past use of THC and 1 THC user was excluded because of reported total abstinence from THC for a period of 8 months prior to testing. An *a priori* decision was made that the "conditioning" click P50 amplitude must be > 1 μV to allow meaningful computation of a gating ratio. One THC user and 1 nonuser control subject were excluded because this condition was not met. A second *a priori* requirement for computing a gating ratio was that the P50 response latency to the second, or "test" click, must be within ± 15 msec. of the P50 latency for the "conditioning" click. One control subject failed to meet this condition and was excluded. Finally, 1 control subject was excluded because of neurocognitive problems and data from 1 control could not be used because of ambiguity of P50 peak identification. The final sample of 10 THC users and 10 nonuser controls did not differ on age (THC mean age = 21.4; Control mean age = 17.5; t = 0.993, p = ns) or gender composition (Fisher's Exact Test, p = ns). The mean duration of THC exposure for users was 7.1 years (median = 4.0) with a mean use frequency of 23 "joints" per week (median = 18, range = 3 to 56). Subjects abstained from THC use for a minimum of 24 hours prior to testing and all urine drug screens collected prior to testing were negative.

Recording Procedures

The methodology was identical to that used in our previous study.[2] Twenty-one scalp electrodes plus ocular

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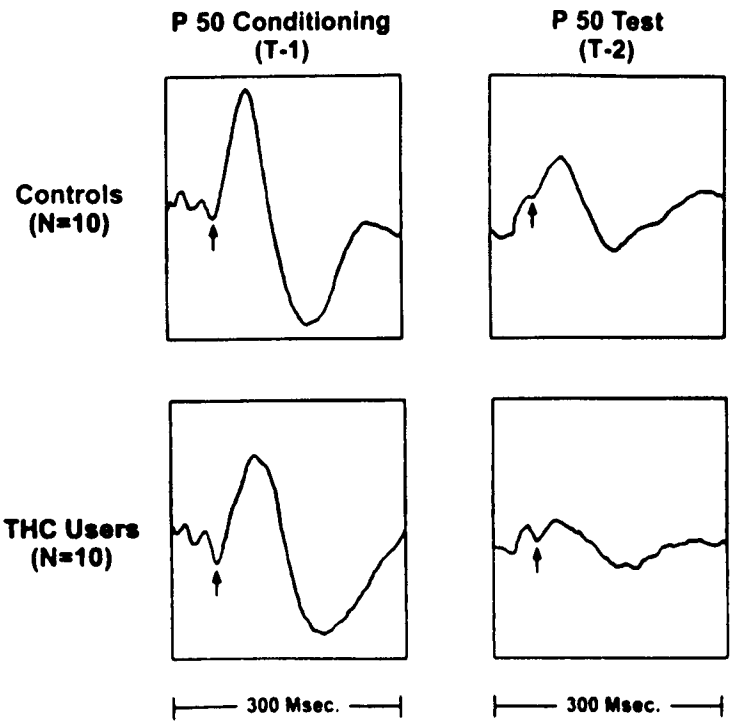

Figure 1.
Group average auditory evoked potential response for control subjects and THC users. P50 peaks are marked by arrows. Positive polarity is downward. See text for explanation.

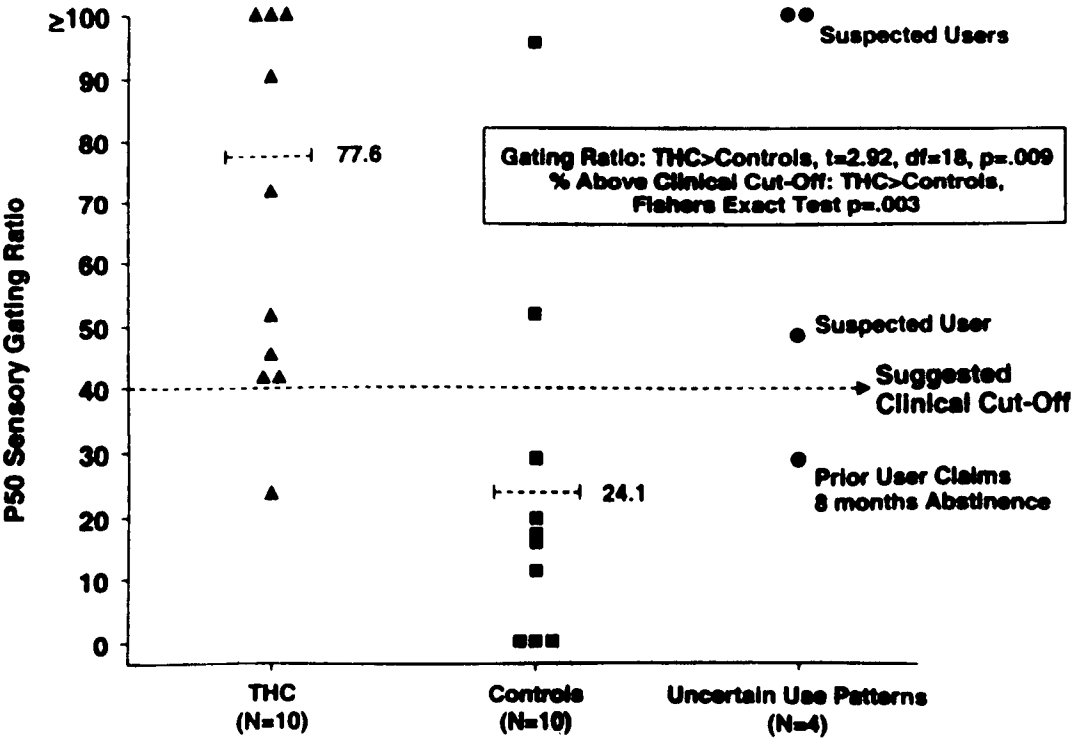

Figure 2.
Paired auditory P50 ratios in heavy THC users and nonuser control subjects.

monitoring leads were applied using the International 10/20 System.[13] A monopolar linked ear (A1 - A2) reference was employed and impedances were kept ≤ 3000 ohm. Subjects reclined with eyes closed in a sound-attenuated and electromagnetically shielded room and provided assurance that they could easily hear the auditory stimulus to be used. Waveform acquisition was monitored online with a 21 channel topographic display, and if contaminating ocular potentials occurred the sweep was canceled and restarted. P50 acquisition was obtained by delivering 50 identical pairs of 80-dB auditory clicks (500 msec interclick separation) to the subject bilaterally through electrically shielded earphones with one pair of clicks presented every 10 sec. High and low frequency filters were 70 Hz and 0.1 Hz, digitization rate was 800 Hz, and the measurement sweep was 300 msec with responses averaged over 50 presentations of the paired stimuli. A Cadwell Spectrum 32 recording instrument was used for data collection and analyses. Although high filter settings similar to ours have been used by others, settings of 100 to 500 Hz are more frequently encountered in the literature. In our previous report,[2] we summarized data showing that auditory P50 evoked amplitudes were identical to two decimal places for a series of subjects tested during the same experimental session, using high filter settings of both 70 Hz and 500 Hz (mean amplitude with 70 Hz filter = 3.91 μV, σ = 1.8; mean amplitude with 500 Hz filter = 3.91 μV; σ = 2.3; tests for normality and equal variance satisfied, t = 0.0000, df = 50, p = ns).

Auditory P50 Measurement and Gating Ratio

The conditioning and test P50 responses were displayed topographically at all 21 scalp electrode locations. Inspection indicated that contamination by spread of prefrontal ocular potentials to posterior leads did not occur. P50 amplitudes (N40 to P50 peak-to-peak measure) and latencies were measured at the vertex (Cz) electrode. The response at Cz was enlarged making peak identification easier, and the N40 and P50 peaks were identified visually by two experienced raters blind to the subject's group status. Latency and amplitude measures were generated electronically by cursor placement on the appropriate peak locations. The sensory gating ratio was defined as the P50 amplitude for the test stimuli (second click) divided by the P50 amplitude to the conditioning stimuli with the result multiplied by 100.

RESULTS

The results paralleled our previous findings.[2] THC use had no effect on the P50 response to the conditioning click (THC: mean latency = 59.6 msec, Controls: mean latency = 58.7 msec, t = 0.627, p = ns; THC: mean amplitude = 4.86 μV, Controls: mean amplitude = 3.88 μV, t = 1.12, p = ns) indicating that marihuana users and nonuser controls were comparable on the primary auditory P50 response.

The mean conditioning and test P50 waveforms (peaks marked by arrows) for THC users and controls are shown in Figure 1. A substantial reduction of the P50 response to the test stimulus occurs for controls while a much lesser degree of suppression is evident for THC users. The distributions of P50 sensory gating ratios for THC users and controls are shown in Figure 2. THC users had a significantly higher mean sensory gating ratio than did controls (THC: mean ratio = 77.6%, Controls: mean ratio = 24.1%, $t = 2.92$, df = 18, p = .009) suggesting a THC-associated reduction in the sensory gating response. Some authors have suggested[9,12,14] that sensory gating ratios of 40% or less fall within normal limits while those above 40% are "abnormal." With only one exception,[15] mean sensory gating ratios for published samples of normals have all been under 40% (range = 13.9% to 39.3%).[2,5,9,12,16-19] Because of this, Figure 2 includes a clinical cut-off point at a ratio of 40%. Ninety percent of the THC users have gating ratios higher than 40% whereas only 20% of the controls have ratios exceeding this level (Fisher's Exact Test: p = .003).

Figure 2 also plots sensory gating ratio scores for 4 subjects omitted from final analyses subsequent to detection of exclusion criteria. Three presumptive nonuser controls excluded because of suspected THC use had sensory gating ratios above 40% (1 at 48.5% and 2 at 100%), while a THC user excluded because of an 8 month period of total THC abstinence prior to testing had a sensory gating ratio of 28.9%, which is within the normal range.

DISCUSSION

This study supports our earlier observation[2] that chronic THC use adversely affects the auditory P50 sensory gating response and thus strengthens our confidence that impaired sensory gating may be a sequela of cumulative THC exposure. Furthermore, the current study includes adolescents (THC: n = 5, mean age = 15.8, gating ratios = 41.7% to 118%; Controls: n = 6, mean age = 13.8, gating ratios = 0% to 51.6%) and suggests that the relationship between impaired gating and THC use extends to younger people (THC adolescents: mean gating ratio = 68.7%, Control adolescents Mean gating ratio = 16.1%, $t = 3.25$, df = 9, p = .01; relationship between THC use and gating ratio above 40%, Fisher's Exact Test p = .015).

In our previous study[2] correlations between patterns of THC use and sensory gating ratios were nonsignificant. Because these analyses involved small numbers of THC users they were repeated using the combined sample of THC users from both our previous report[2] and the present report. When this was done there continued to be no association between impaired sensory gating and duration (in years) of THC exposure (r = -0.056, n = 28, p = ns). However, impaired sensory gating was significantly correlated with the average number of "joints" smoked per week (r = 0.54, n = 28, p = .003) and the number of "joint-years"

exposure defined as number of "joints" per day times duration in years ($r = 0.487$, $n = 28$, $p = .008$).

In our previous review[20] of neurophysiological methods in human marihuana research, we found only a few studies employing evoked potential methods and among them the results were variable with no replicable findings emerging. Our previous attempts to isolate evoked potential effects of chronic THC exposure using rigorously screened medically and psychiatrically normal subjects have been disappointing and we were unable to demonstrate associations between chronic THC use and brain stem auditory evoked response,[21] a variety of early and middle latency visual, auditory, and somatosensory evoked responses,[22] and P300 cognitive responses using auditory and visual modalities.[23] However, Solowij and her associates have shown[24-26] that if one goes beyond the simple "odd-ball" P300 paradigm and makes the evoked potential acquisition task more complex and cognitively demanding, it may be possible to demonstrate the adverse effects of chronic THC exposure.

Previously we were able to demonstrate[27-29] a significant association between chronic daily THC use and a topographic quantitative EEG pattern of persistent "alpha hyperfrontality" (i.e., elevations of alpha absolute power, relative power, and coherence over frontal cortex) as well as significantly reduced mean alpha frequency. In addition, a transient "alpha hyperfrontality" and decreased alpha frequency lasting about 4 hours could be produced by having infrequent THC users smoke active marihuana (two dose levels) in the laboratory under placebo controlled blind conditions.[30] When we combined data from our current and previous report,[2] we were unable to demonstrate an association between impaired sensory gating and the three components of EEG alpha hyperfrontality among 23 chronic marihuana users (Total alpha hyperfrontality: $r = .20$, p = ns; Absolute Power Component: $r = .12$, p = ns; Relative Power Component: $r = .08$, p = ns, Coherence Component: $r = .37$, p = ns). Recently we reported[31] that a topographic EEG pattern of "theta hyperfrontality" also characterized THC users, and that this pattern correlated significantly with the cumulative duration of THC use in years. However, this topographic quantitative EEG feature also failed to correlate significantly with sensory gating ratio scores among the 23 THC users. It thus appears that both the topographic EEG and the impaired sensory gating sequelae of chronic THC use are independent responses to THC exposure and as such may rest on differing THC induced pathophysiological processes.

Although the exact pathophysiology underlying the association between THC exposure and impaired sensory gating is not yet known, it may involve the influence of THC on hippocampal function. The auditory P50 evoked response in humans has been recorded from depth electrodes within the hippocampus[32] and is diminished by lesions extending into this area,[33] while the corresponding sensory gating response in the rat may also be dependent upon hippocampal integrity.[34-37] Furthermore, THC concentrations appear to be particularly elevated in hippocampal areas in numerous species including humans.[38-44]

Based on the present and previous[2] results further study with larger sample sizes directed at establishing impaired auditory P50 sensory gating as a CNS consequence of THC abuse seems warranted. It would be useful to conduct serial sensory gating measurements following various periods of THC abstinence in order to assess the degree of persistence of this phenomenon. The causal role of THC in producing impaired sensory gating could be further strengthened by conducting placebo controlled acute THC smoking studies using casual infrequent THC users with base line normal gating ratios. The production of a transient THC induced reduction of the gating response (i.e., decreased suppression) in such subjects would support the primary effect of THC as the active agent. In our judgment future studies of the sensory gating -marihuana association should continue to focus on well screened normals free of current or past medical or psychiatric disorders in order to avoid the many confounds bound to exist when using clinical populations. Furthermore, because P50 sensory gating is known to be impaired in schizophrenics[3-9] and their 1st degree relatives,[10-12] the exclusion of subjects with a family history positive for schizophrenia or other psychosis should be encouraged. To our knowledge P50 sensory gating has not been applied in studies of the wide range of abuse substances. Fein and associates[45] have reported a failure of P50 suppression in recent cocaine users but not in alcoholics.

SUMMARY

This report attempts to replicate our recent finding[2] of a significantly reduced sensory gating response in medically and psychiatrically normal chronic marihuana users. After exclusions, 10 normal heavy marihuana users ($\geq$ 3 times per week) and 10 normal non-user controls were tested with the paired auditory P50 sensory gating procedure. Sensory gating ratios were significantly higher (i.e., impaired suppression) for THC users as compared to controls. Using combined data from the current and previous report,[2] the degree of sensory gating impairment among THC users was significantly correlated with the frequency of marihuana use per week. Suggestions for further research are offered.

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