Abnormal brain activity in prefrontal brain regions in abstinent marijuana users

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We used PET 15O and a modified version of the Stroop task to determine if 25-day abstinent heavy marijuana (MJ) users have persistent deficits in executive cognitive functioning (ECF) and brain activity. Performance on a modified version of the Stroop task and brain activity was compared between 25-day abstinent, heavy marijuana users (n = 11), and a matched comparison group (n = 11). The 25-day abstinent marijuana users showed no deficits in performance on the modified version of the Stroop task when compared to the comparison group. Despite the lack of performance differences, the marijuana users showed hypoactivity in the left perigenual anterior cingulate cortex (ACC) and the left lateral prefrontal cortex (LPFC) and hyperactivity in the hippocampus bilaterally, when compared to the comparison group. These results suggest that marijuana users display persistent metabolic alterations in brain regions responsible for ECF. It may be that marijuana users recruit an alternative neural network as a compensatory mechanism during performance on a modified version of the Stroop task. These differences in brain activity may be a common denominator in the evolution of maladaptive behaviors such as substance abuse and other neuropsychiatric disorders.

Keywords: Psychoactive substance use disorder; Brain-imaging techniques; Neuropathology; Cognitive neuroscience

Introduction

Marijuana (MJ) is a drug of abuse which can elicit many acute psychoactive effects including euphoric effects, decreased anxiety, altered alertness, and intoxication (Webb et al., 1996). MJ may also impair cognitive and psychomotor performance weakening a person’s ability to operate a vehicle or make appropriate decisions (Liguori et al., 1998). These effects are thought to result from the psychoactive ingredient Δ-9 tetrahydrocannabinol (THC) which is found in higher concentrations in the MJ used today than the MJ used in the 1970s (WHO, 1997). Because of this increased potency and the estimated 12 million MJ users in the United States who use this drug alone or in combination with other drugs (NHSDA, 2002), it is imperative to investigate not only the immediate effects of MJ, but also its persistent effects.

Deficits in learning and memory and executive cognitive functioning (attention/planning/mental flexibility) are the most common acute effects of MJ observed when MJ users are evaluated after 12–72 h of abstinence (Fletcher et al., 1996; Pope and Yurgelun-Todd, 1996). Nevertheless, due to the long half-life of THC (4.1 ± 1.1 days) (Huestis and Cone, 1998), these effects might have resulted from drug residue in the brain or from drug withdrawal (Haney et al., 1999). To date, only two studies have investigated MJ over an extended, 28-day interval of abstinence (Bolla et al., 2002; Pope et al., 2001). Pope et al. (2001) report that cognitive deficits appear reversible after 7 days of abstinence and are related to recent cannabis use rather than to cumulative lifetime use. In contrast, even after 28 days of abstinence, we observed a persistent dose-related association between increasing number of joints used per week and greater decrements in neurocognitive performance (Bolla et al., 2002).

Neuroimaging studies investigating the acute effects of THC show increases in resting regional cerebral metabolic rate (rCMR) in the cerebellum, frontal, prefrontal, and temporal cortices compared to controls (Volkow et al., 1996). When THC was administered intravenously, there were dose-dependent increases in regional cerebral blood flow (rCBF) in the insula, cingulate gyrus, and subcortical structures, primarily in the right hemisphere (Mathew et al., 1997). After 26 h of abstinence, MJ users showed
lower resting rCBF (PET $H_2^{15}$O) in the posterior cerebellum, an area dense with cannabinoid receptors, and the bilateral ventral prefrontal cortex (Block et al., 2000). Only the right anterior cingulate cortex (ACC) showed an increase in rCBF in MJ users compared to controls (Block et al., 2000). When a verbal memory task was used in conjunction with PET $H_2^{15}$O in 26-h abstinent MJ users, a decrease in rCBF was seen in memory-related brain regions including the prefrontal cortex and the hippocampus (Block et al., 2002).

The Stroop task measures cognitive control and behavioral monitoring and is frequently used in substance abuse research (Bolla et al., 2002; Hooker and Jones, 1987; Solowij et al., 2002). Specifically, the Stroop task requires response inhibition (MacDonald et al., 2000; Pardo et al., 1990). This task reliably activates the anterior cingulate cortex (ACC) and the lateral prefrontal cortex (LPFC) in normal populations (Bench et al., 1993; MacDonald et al., 2000; Pardo et al., 1990). Attentional demands of the task are believed to be controlled by the LPFC, whereas the ACC is involved in conflict monitoring (MacDonald et al., 2000). The caudal-dorsal (perigenual) ACC has strong reciprocal interconnections with the LPFC creating a network responsible for executive cognitive functions (ECF) such as performance monitoring, conflict resolution, and response inhibition (Carter et al., 1998; MacDonald et al., 2000). The rostral-ventral (infragenual) ACC has interconnections with the amygdala, periaqueductal gray, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and the orbitofrontal cortex and is thought to be responsible for assessing emotional salience of information (Devinsky et al., 1995). Disruption to these networks could create deficits in ECF and the regulation of emotional responses and may lead to the development and persistence of maladaptive behaviors such as drug use (Bolla et al., in press).

The Stroop task appears to be a useful instrument in substance abuse research. Our neurobehavioral data from 28-day abstinent MJ users show that, as the number of joints per week increases, performance on the Stroop task declines in MJ users with lower estimated intellectual function (Bolla et al., 2002). In addition, acute administration of THC has been shown to increase the Stroop interference effect (Hooker and Jones, 1987). After a 17-h period of abstinence, there was no increase in the Stroop interference effect compared to controls (Solowij et al., 2002). However, only the MJ group showed a significant difference between the color–word condition and the color–read condition (Solowij et al., 2002), suggesting that MJ users have trouble meeting increased task demands. In our positron emission tomography (PET) data from 25-day abstinent cocaine abusers, no performance deficits were found during a modified version of the Stroop task; however, abnormalities in rCBF were observed in the ACC and the LPFC compared to a group of controls (Bolla et al., in press). Based on these findings, we decided to use the same modified Stroop task to examine performance and brain activity in 25-day abstinent MJ users.

We hypothesized that MJ users would show alterations in brain functioning in the ACC and the LPFC during performance on a modified Stroop task. In addition, we hypothesized that alterations could also be seen in the cerebellum and hippocampus because these regions are dense with cannabinoid receptors (Mailleux et al., 1992; Ong and Mackie, 1999) and were shown to be altered in previous neuroimaging studies of MJ users (Block et al., 2000, 2002; Mathew et al., 1997; Volkow et al., 1996).

**Methods**

**Participants**

All participants were recruited through newspaper and radio advertisements. The institutional review boards of the NIDA-IRP and the JHU Bayview Medical Center approved this study. All participants gave written informed consent and received remuneration. Selection was based on drug use history obtained using a structured interview, Drug Use Survey Questionnaire (DUSQ) (Smith, 1991), Addiction Severity Index (ASI) (McLellan et al., 1980), and the Diagnostic Interview Schedule (DIS) (Robins et al., 1981). All participants were men, right-handed, 24–45 years old, had IQs of 90 or greater (assessed by the Shipley Institute of Living Scale) (Zachary, 1991), and English was their native language.

**Comparison group**

This group consisted of 11 men who reported consuming less than 13 alcoholic drinks per week and reported no current or past use of any illicit drug based on self-reported drug use history. Urine toxicology results confirmed these reports.

**Marijuana group**

This group consisted of 11 men who claimed MJ as their drug of choice, smoked MJ for at least 2 years, currently used at least four times per week, had two positive urine toxicology screens for MJ and its metabolites during medical screening and day of admittance, and consumed less than 13 alcoholic drinks per week. The positive urine toxicology screens at the time of admittance ensured a relatively uniform period of abstinence. Participants were excluded if they met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for current or past dependence on any other psychoactive substance other than MJ, including alcohol, or if they had a urine toxicology screen positive for substances other than MJ.

**Exclusion criteria for all participants**

Volunteers were excluded for a past or current Axis I disorder other than nicotine dependence by DSM-IV criteria using the DIS (e.g., PTSD and major depressive disorder). Those reporting a history of neurological illness, use of psychoactive medication, an abnormal neurological examination, color blindness, or left-handedness were also excluded.

**Data collection**

Participants were medically screened at the Clinical Inpatient Research Unit (CIRU) at NIDA-IRP to qualify for the study. MJ users were then admitted to the CIRU for approximately 25 days, and the comparison group was admitted to the Johns Hopkins Bayview General Clinical Research Center (GCRC) for 3 days to ensure a homogeneous, controlled environment before testing. Random drug screens were given as an additional measure of abstinence. Urines were analyzed by gas chromatography/mass spectrometry (GC/MS) for THC, 11-OH-THC, and by THCCOOH and TDx (FPIA-fluorescence polarization immunoassay) for THCOOH. No metabolites of THC were detected at the time of the PET session. No treatment or medications for drug abuse were given over the 25-day stay.
Design

Use of cigarettes or caffeine was prohibited 3 h before the PET session. Subjects participated in one PET session approximately on day 23 for MJ users and day 3 for the comparison group. Three cognitive conditions were studied: Rest-R (eyes fixated on a target); Active Task-A (Conflict condition); and Control Task-C (sensorimotor No Conflict condition). Two scans were acquired for each of the three conditions (Rest, Conflict condition, No Conflict condition). The Rest condition occurred at the beginning and end of the session for all participants. Task order was counterbalanced within and between participants. Participants received an injection of H$_2^{15}$O water (10 mCi) before each 1-min acquisition scan. The tasks began 1 min before injection of the tracer to cognitively engage the participants in the task at the time of image acquisition. The task was self-paced and ended after 120 s. Before scan acquisition, participants performed a practice task to acclimate them to responding with the keypad while in the scanner. A molded facemask was created to minimize head movement during scan acquisition without hindering vision or manual responding. Stimuli were presented at the center of an LCD monitor, controlled by a Toshiba laptop computer. The monitor was mounted approximately 1 m above and in front of the participant, tilted approximately 40° from the bed so that the participant could view the screen from inside the scanner while wearing the facemask. All participants reported no difficulty viewing the screen.

Modified Stroop task

A modified version of the computer-administered Automated Neuropsychological Assessment Metrics (ANAM) version of the Stroop task was used (Golden, 1978). As in the clinical version of the Stroop task (Golden, 1978), the participants were required to correct each mistake before proceeding to the next stimulus (self-paced). Unlike Golden’s version, the modified task required a manual rather than vocal response, and stimuli were presented as a single trial rather than as an array. Responses were recorded using a “3-key button box” (KPX-17 Parallel keypad, ALPS electronic), with separate buttons corresponding to RED, GREEN, and BLUE. All responses were made with the first three fingers of the right hand. Modifications were also made to the congruent condition of the classic Stroop task to enhance the differences in conflict between both conditions.

Conflict (color naming with word interference-incongruent stimulus dimensions)

This condition consisted of conflicting stimulus dimensions, and the task demand was to suppress a typical response. The Conflict condition displayed the words RED, GREEN, or BLUE in colors that did not match the meanings of the words (i.e., RED displayed in the color blue). Subjects were asked to respond to the color the word was printed in. For example, a correct response was a press of the BLUE key when viewing the word RED written in the color blue.

No conflict (word naming without word interference-congruent stimulus dimensions)

This condition presented no conflict in the dimensions of the stimulus. The No Conflict condition displayed the words RED, GREEN, or BLUE in colors that matched the written words (RED displayed in the color red). Therefore, this task was matched with the Conflict condition for response type (button press) and stimulus types (color, word meaning, and number of letters) making the visuomotor task demands identical to those of the Conflict condition. We designed this No Conflict condition to be less cognitively demanding than the Conflict condition. Unlike the classic Stroop task and the Conflict condition, subjects were asked to respond to the written word rather than the color of the stimulus. Therefore, this modification enhanced the response differences between the Conflict and No Conflict conditions. The No Conflict condition was very easy because the word (RED) matched the color (red), and subjects were asked to respond to the written word, which is the dominant tendency. However, the Conflict condition was more difficult because the stimulus dimension was incongruent requiring inhibition of the impulse to read the word (RED) while naming the incongruent color stimuli (e.g., the word RED presented in the color blue). Our pilot work in a group of controls showed that the mean average response time for the Conflict condition was significantly slower [mean response time: 864 (SD 314) ms] than the mean response time for the No Conflict condition [mean response time: 572 (SD 90) ms; Wilcoxon signed rank test, $Z = -3.11; P < 0.01$]. These data (i.e., slower reaction time) provide evidence that the Conflict condition was more cognitively demanding and required more effort than the No Conflict condition.

PET scan acquisition

Scans were acquired with a Siemens ECAT EXACT HR +, in 63 planes with a 15.5-cm field of view in 3D mode. Images were reconstructed using a Hann filter with 0.5 cutoff frequency. The average transverse resolutions [full width half maximum (FWHM)] of the scanner at 1 and 10 cm from the center of the field of view, measured in 3D mode and determined using a Fluorine-18 line source and a ramp filter (with a 0.5 cutoff frequency), were 4.66 and 5.45 mm, respectively. Axial resolutions of the scanner (FWHM), measured using a point source of F 18 and the same reconstruction algorithm, were 4.21 and 5.0 mm at 0 and 10 cm from the center, respectively. In case of application of a Hann filter with a 0.5 cutoff frequency, used for reconstruction of brain images, the average transverse resolutions were 6.52 and 7.16 mm, respectively. For the same reconstruction algorithm, the average axial resolution at 0 cm from the center was 3.72 mm and at 10 cm, 5.64 mm.

Image processing and statistical analyses

PET images were realigned, spatially normalized into the Montreal Neurological Institute (MNI) coordinate system, and smoothed with a 12-mm$^3$ Gaussian kernel by using Statistical Parametric Mapping Software (SPM 99; Welcome Department of Cognitive Neurology). A two-stage procedure was implemented for statistical analyses for between-group effects ($n = 22$). In the first stage, PET images from each participant were used to create an individual adjusted mean image, representing the relative change in brain activity (normalized rCBF) between the conflict condition and the no conflict condition (all scans from the conflict condition minus the no conflict condition). This change in brain activity was taken to reflect the “conflict effect” by subtracting the motor, auditory, and visual components involved in the task (no
conflict condition) from the higher cognitive functions of response inhibition (conflict condition). Proportional scaling was used to correct for within-session variations in global signal for each adjusted mean image. Importantly, no significant differences were found in the correlation between global signal and the conditions of interest (Andersson, 1997; Dejardins et al., 2001; Matochik et al., 2003; Worsley et al., 1996). Stage 2 of the procedure to examine between-group differences involved entering the adjusted mean image for each participant into a random effects two-sample t test \((n = 22)\) with 20 degrees of freedom. All coordinates were converted into Talairach space.

To examine our specific regions of interest (ACC, LPFC, hippocampus, and cerebellum) and correct for multiple comparisons, we employed the “small volume correction” method featured in SPM99 using our own voxel volume of interest (VVOI) image templates (Matochik et al., 2003). This method did not restrict the search volume for statistical analyses to a single stereotaxic \(xyz\) coordinate point taken from previous findings in the literature, but rather used the actual spatially normalized volume of the region of interest to limit the search. For example, the entire dorsal midcingulate region volume is searched rather than an area within a sphere or box centered around single coordinate that may be on or near the region of interest. This procedure ensured that our experiment-wise false-positive rate (type I error) for a particular or near the region of interest. This procedure ensured that our experiment-wise false-positive rate (type I error) for a particular region of interest was maintained at the \(z < 0.05\) level. Bilateral small volume templates were constructed for the following brain regions: cingulate gyrus [infragenual (Brodmann area [BA] 25, 32), perigenual (BA24, 32, 33), and dorsal midcingulate (BA24) regions] and the lateral prefrontal cortex (BA9, 10, 44, 45, 46) [middle and inferior frontal gyrus]. Small volume templates were also created for the hippocampus and cerebellum to examine regions previously shown to be affected by MJ use.

**Results**

**Demographics and drug use**

The comparison group \((N = 11)\) and the MJ group \((N = 11)\) were matched on Shipley IQ. Participants were men and did not differ on age, years of education, maternal education, Hollingshead Index of Socioeconomic Status, alcohol (drinks per week), or cigarette use (8 of 11 MJ users and 6 of 11 in comparison group). Estimates of average amount and frequency of MJ use (joints per week) were derived from participants’ self-reports of the amount of money spent each week on MJ (US$2.00/joint that the Drug Enforcement Agency reports for the Baltimore area). Individuals in the MJ group reported marijuana as their drug of choice. They reported no current or past use of other drugs including cocaine, heroin, opiates, amphetamines including MDMA, and barbiturates (Table 1).

**Modified Stroop task performance analyses**

Using a Mann–Whitney \(U\), no group differences were found in RT for the No Conflict condition \((Z = –0.295, P < 0.77)\) or the Conflict condition \((Z = –0.492, P < 0.62)\). The MJ users had a mean No Conflict RT of 633 (SD 99.454) ms, and the comparison group had an RT of 608 (SD 122) ms. For the mean Conflict RT, MJ users had an RT of 783 (SD 171) ms, and the comparison group had an RT of 868 (SD 313) ms.

**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Marijuana group ((n = 11))</th>
<th>Comparison group ((n = 11))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>25 (21–35)</td>
<td>29 (22–34)</td>
</tr>
<tr>
<td>Education, years</td>
<td>13 (10–16)</td>
<td>14 (11–19)</td>
</tr>
<tr>
<td>Mother’s years of education</td>
<td>10 (9–20)</td>
<td>13 (9–18)</td>
</tr>
<tr>
<td>Shipley IQ</td>
<td>102 (92–115)</td>
<td>102 (91–118)</td>
</tr>
<tr>
<td>Hollingshead SES</td>
<td>4 (1–5)</td>
<td>4 (1–5)</td>
</tr>
<tr>
<td>Race, AA/C</td>
<td>7/2 (1 Other, 6 Hispanic)</td>
<td>7/3 (1 Asian, 1 Hispanic)</td>
</tr>
<tr>
<td>Marijuana use per week (joints)</td>
<td>34.7 (8–63)</td>
<td>–</td>
</tr>
<tr>
<td>Marijuana use duration (years)</td>
<td>7.5 (2–22)</td>
<td>–</td>
</tr>
<tr>
<td>Marijuana start age (years)</td>
<td>15.7 (12–21)</td>
<td>–</td>
</tr>
<tr>
<td>Alcohol use drinks per week</td>
<td>3 (0–12)</td>
<td>1 (0–6)</td>
</tr>
<tr>
<td>Cigarette smokers</td>
<td>6/11</td>
<td>4/11</td>
</tr>
</tbody>
</table>

Numbers in parentheses are ranges.

**Group differences in brain activation during the task**

Several a priori regions survived corrections for multiple comparisons. MJ users had greater activation compared to the comparison group in the left and right hippocampus. Conversely, MJ users failed to activate to the same extent as the comparison group in the left DLPFC and the left perigenual ACC. Post hoc analysis of the entire brain revealed several other regions with greater activation in MJ users compared to the comparison group; these include the right paracentral lobule [BA6] and the left occipital lobe [BA18,19]. Within BA 10, MJ users activated less in the right anterior ventromedial PFC and right anterior DLPFC compared to the comparison group (Table 2, Fig. 1).

**Discussion**

As expected, the MJ users showed less activation than the comparison group in the left perigenual ACC and left DLPFC and more activation in the hippocampus bilaterally when performing a modified Stroop task. These results suggest that MJ users have specific decreases in brain activation in the perigenual ACC, a subdivision of the ACC which is involved primarily in cognitive functions (Bush et al., 2000). Although we searched the infragenual ACC, we did not observe rCBF alterations in this subregion which has been shown to be responsible for emotional processing (Bush et al., 2000). The increased activation observed in the hippocampus suggests that THC might have affected the hippocampus selectively since it is an area dense with cannabinoid receptors (Mailieux et al., 1992; Ong and Mackie, 1999). Although the hippocampus is not generally recruited during the Stroop task, one possibility is that these MJ users are utilizing this region to compensate for the decreased activation in the left perigenual ACC and left LPFC, two regions reported to be specific to this task (MacDonald et al., 2000). Another possibility is that the manual response modification to the task may have added an additional working memory component by requiring subjects to maintain in memory the button that corresponds to each color. This additional working memory component may involve the recruitment of the hippocampus, a region involved in working memory (Davachi and Wagner, 2002; Ranganath and D’Esposito, 2001), to a greater
extent in MJ users than the comparison group to perform the task effectively. Although we hypothesized that group differences would be observed in the cerebellum, unlike past studies, we did not find abnormal activation in the MJ users during this task. In the study of 26-h abstinent MJ users, there was an increase in the posterior cerebellum during performance on a verbal memory task (RAVLT) (Block et al., 2002). This discrepancy may indicate that the hyperactivity in the cerebellum in MJ users may be task-
dependent, as we have also observed cerebellar hyperactivity in MJ abusers during performance of the Iowa Gambling Task (Bolla et al., unpublished observations).

Prefrontal cortical dysfunction may be secondary to the vasoconstrictive actions of MJ and to possible subtle ischemic changes in their brains (Heming et al., 2001). Thus, we addressed this concern by examining changes in brain activity in the motor cortex (−26, −44, 65) where normal levels of activity were expected for both groups (Kiehl and Liddle, 2001) and no group differences were observed. This implies that the observed group differences in brain activity in the left perigenual ACC and left LPFC are not due to global group differences in vascular reactivity or dysfunction. Our current research suggests that MJ users have lower gray matter density in a region of the parahippocampal gyrus and greater density bilaterally near the precentral gyrus and the right thalamus compared to nondrug using controls (Matochik et al., in press). MJ users also showed less white matter density in the left parietal lobe and right precentral gyrus and higher density in the left parahippocampal and fusiform gyri. The alterations in rCBF seen in this group of MJ users may be related to these differences in tissue composition. Finally, chronic MJ use is known to disrupt dopaminergic pathways (Loeber and Yurgelun-Todd, 1999). Specifically, chronic MJ use causes decreased firing of the ventral tegmental area neurons projecting to the nucleus accumbens, which lowers dopamine metabolism in the medial PFC (Loeber and Yurgelun-Todd, 1999). Therefore, this disruption may, in part, explain the decreased rCBF in the prefrontal regions where the VTA has its strongest connections (Loeber and Yurgelun-Todd, 1999).

Although we reported performance deficits in heavy MJ users with lower Shipley IQ scores using the clinical version of the Stroop task (Bolla et al., 2002), our current group of MJ users performed as well as the comparison group on our modified Stroop task. The inconsistency may be due to the modification of the Stroop task used in this study. Unlike our previous study, this task was computerized and the participants responded manually rather than orally (Bolla et al., 2002). Another possibility is that the sample size may have been too small to detect performance differences. Because the group of MJ users in this study showed functional abnormalities when compared with the comparison group, it is possible that these MJ users were able to compensate during this task by recruiting alternative neural pathways than those used by the comparison group. Neuroimaging methods are more sensitive for detecting abnormalities in brain functioning than neuropsychological tests (Kiehl and Liddle, 2001). Therefore, changes may be detected by imaging techniques before any neuropsychological testing deficits.

Although the abnormalities in the PFC regions responsible for ECF are not reflected in the behavioral data, it is possible that the roles of the dysfunctional left perigenual ACC and left DLPFC in the MJ users might have been subsumed by other regions such as the hippocampus, right paracentral lobule [BA6], and the left occipital lobe. The right paracentral lobule [BA6], which was more activated in the MJ users, has been shown to be involved in generic working memory operations, whereas the comparison group utilized the DLPFC [BA8, 9], which has been shown to contribute to monitoring operations (Cabeza et al., 2002). The hippocampus, which was activated more in the MJ users, has been shown to be involved in indexing operations (Cabeza et al., 2002). Regions where MJ users showed increased rCBF compared to controls may indicate a compensatory mechanism.

Corticocortical connections and distributed connections in the various cortical brain regions (Mesulam, 2000) may make such a compensatory mechanism viable. These compensatory mechanisms in the MJ users may fail under periods of stress, when it is important to inhibit certain behaviors (e.g., drug self-administration). While this study investigates the persistent effects of MJ use over a 25-day abstinence period, future studies will be needed to address the issue of functional recovery by acquiring baseline measures of brain activation and performance before the abstinence period. Due to the regulations on exposure to radioactive tracers in PET studies, it was impossible for us to collect scans at two separate times over the 25 days. We are currently conducting an fMRI study that will address these questions. Lastly, these findings are beginning to provide windows through which to peer to better explain the functional and fundamental bases of substance dependence/abuse and other neuropsychiatric disorders.

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