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# Altered Neural Processing to Social Exclusion in Young Adult Marijuana Users

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## ABSTRACT

**BACKGROUND:** Previous studies have reported that peer groups are one of the most important predictors of adolescent and young adult marijuana use, and yet the neural correlates of social processing in marijuana users have not been studied.

**METHODS:** In the current study, marijuana-using young adults ($n = 20$) and nonusing control subjects ($n = 22$) participated in a neuroimaging social exclusion task called Cyberball, a computerized ball-tossing game in which the participant is excluded from the game after a predetermined number of ball tosses.

**RESULTS:** Control subjects, but not marijuana users, demonstrated significant activation in the insula, a region associated with negative emotion, when being excluded from the game. Both groups demonstrated activation of the ventral anterior cingulate cortex, a region associated with affective monitoring, during peer exclusion. Only the marijuana group showed a correlation between ventral anterior cingulate cortex activation and scores on a self-report measure of peer conformity.

**CONCLUSIONS:** This study indicates that marijuana users show atypical neural processing of social exclusion. This differential activation may have preexisted and may have contributed to the onset of marijuana use, and/or it may have developed as a result of marijuana exposure.

*Keywords:* ACC, Anterior cingulate cortex, Cannabis, Exclusion, Insula, Marijuana, Peer groups, Social Influence

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Marijuana use is steadily increasing among young adults (1). As evidence accumulates that adolescent and young adult marijuana use is associated with greater negative cognitive effects (2) and increased addiction rates (3) compared with adult use, it has become increasingly important to understand behavioral and neural processes underlying motivation for use among this population. Motivation for use among young adults (e.g., age 18–25) is particularly important to understand, as this age group has the highest rate of dependence on marijuana (as well as on alcohol) (4). Young adults are at a critical developmental stage in the initiation of marijuana use; whereas first use of alcohol and tobacco occurs between 10 and 16 years, onset of illegal drug use occurs later (5). Furthermore, during young adulthood, particularly among college students, there is a pronounced shift in influence from parents to peers (6), as young adults are often away from home and therefore independent of parental oversight or control (7) and are seeking to establish a peer network for support (8).

One of the strongest determinants of both initiation and maintenance of use of marijuana is peer networks (9–11). Particularly for adolescents and young adults, peer groups are one of the most important predictors of marijuana initiation, progression to regular use, and failure to discontinue use (11). It is therefore possible that the desire to fit in with a peer group and to avoid social exclusion is one of the factors that contribute to marijuana use. Young adults tend to use marijuana in social settings among friends (12), and indeed, in a survey of 227 marijuana users (average age = 25.4), over half of participants cited pleasant time with others as a primary reason for using marijuana (13). However, the relationship between response to social rejection and drug use is complex. Some studies have reported that youth who are isolated from their peers are more likely to use tobacco than those who belong to peer groups (14–16). A study using social network analysis found that even among adolescents who were socially isolated, those peripheral to substance-using peer groups had an increased likelihood of substance use (17).

Group cohesiveness and belonging to a group are fundamental evolutionary strategies for survival, security, reproductive success, and mental health (18). Social exclusion causes significant distress, sadness, and anger and even sends neural signals of pain (19,20). It is possible that people who use drugs are more sensitive to social exclusion than nonusers and that their desire to avoid social rejection underlies their desire to use drugs in social settings. It is also possible that social exclusion is a contributing factor that leads individuals to use drugs. Though the directionality is unknown, sensitivity to ostracism may be a fundamental component of drug use.

In the current study, we examined the neural mechanisms underlying social exclusion in young adult light-to-moderate marijuana users (e.g., weekly use or more) (MJ) and in nonusing control subjects (CON). We chose to study lighter



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users because evidence suggests that peer influence may have more of an impact in recreational users than it would in substance-dependent patients, in whom drug taking may become less social and more habitual (21). To elicit feelings of social exclusion, we used Cyberball, an interactive computerized ball-toss game (22), which has been used extensively in functional magnetic resonance imaging (fMRI) studies to examine brain responses to ostracism [e.g., (23–26)]. A quantitative meta-analysis of the Cyberball paradigm identified three main brain regions that were reliably recruited when a participant was rejected by peers—the anterior insula, the left ventral anterior cingulate cortex (vACC), and the left inferior orbitofrontal cortex (OFC) (27)—all of which have been linked to the emotional response to exclusion. In this study, we investigated whether these regions activated differentially in MJ compared with CON. We hypothesized that MJ would show greater activation relative to CON in brain regions associated with peer rejection. As an exploratory analysis, we also investigated whether self-reported peer conformity scores were associated with activation in these regions.

## METHODS AND MATERIALS

Study procedures were approved by the Partners Human Research Committee. Participants completed a written, documented informed consent form before initiation of study procedures.

### Participants

Participants in this study were 42 young adults, ages 18 to 25 years; 20 participants regularly used marijuana and 22 were nonusing control subjects. Participants were primarily recruited from Boston-area colleges (though current enrollment in college was not a requirement for inclusion). All participants were given a Structured Clinical Interview for the DSM-IV (28). Both groups were medically healthy with no history of head trauma and did not meet DSM-IV criteria for any current or lifetime Axis I or Axis II psychiatric disorders, with the exception of cannabis use disorders in the MJ group. No participant reported a past history of a psychological disorder, and no participant was taking any medication other than oral contraceptives at the time of the study procedures.

MJ reported using marijuana recreationally at least once a week and were asked to refrain from using substances on the day of the study. Those who presented with clinical signs of intoxication on the day of the study were rescheduled. CON had used marijuana on less than five lifetime occasions and had not used marijuana in the past 3 months. Participants were excluded if they met abuse or dependence criteria for any drug other than marijuana, including alcohol and nicotine, although they may have tried other drugs in the past. No participants were regular cigarette smokers. Before study procedures were initiated, we performed a qualitative urine drug screen (Medimpex United Inc., Bensalem, Pennyslvania) that tested for illicit substances to ensure that no MJ participant tested positive for any drug other than marijuana and that no control participants tested positive for marijuana or any other drug.

### Cyberball Task Design

As in previous Cyberball studies, participants were told before scanning that we were interested in mental visualization ability, so that participants were not aware that we were studying social exclusion. They were told that they would play a game of catch over the Internet with two other players and were asked to try to imagine the experience as vividly as possible. In reality, the actions of these other players were actually preprogrammed to include or exclude the participant in different phases of the task. There were four successive blocks: 1) spectating block, in which participants were told that they would just be observing the other players; 2) inclusion, in which participants played with the other players; 3) exclusion, in which participants were then excluded from the game; and 4) reinclusion, in which participants were reincluded in the game for the remainder of the experiment. In the inclusion conditions, the other players threw the ball to the participant approximately 75% of the time to involve the participant enough to distinguish them from the spectating and exclusion phases. Each block lasted approximately 1.5 to 2 minutes (about 30 throws). Exact block length varied slightly with each block due to a number of factors designed to increase ecological validity (e.g., the participant could choose when to throw the ball). The game was self-paced. After the study, participants were debriefed to ensure they knew that they were not playing with real people.

### Acquisition and Analysis of Neuroimaging Data

Participants were scanned using a 3 Tesla Siemens (Erlangen, Germany) Skya scanner with a 32-channel head coil at the Martinos Center for Biomedical Imaging. Whole-brain T1-weighted 1-mm isotropic structural scans were collected using a three-dimensional multiecho magnetization prepared rapid acquisition gradient-echo sequence (176 sagittal slices, 256-mm field of view, repetition time 2530 ms, inversion time 1200 ms, 2× generalized autocalibrating partially parallel acquisitions acceleration, echo time 1.64/3.5/5.36/7.22 ms, bandwidth 651 Hz/px, $T_{acq}$ 6:03 min) (29). Functional scans were collected using a two-dimensional gradient-echo echo-planar imaging sequence (31 slices, 3-mm thick, .6-mm gap, 216-mm field of view, 3-mm$^2$ in-plane resolution, repetition time 2 seconds, echo time 30 ms, bandwidth 2240 Hz/px). All acquisitions were automatically positioned using AutoAlign (Martinos Center for Biomedical Imaging, Charlestown, Massachusetts) (30).

Functional magnetic resonance imaging data processing was carried out using FMRI Expert Analysis Tool Version 5.98, part of the FMRIB's Software Library (FSL) fMRI processing stream (www.fmrib.ox.ac.uk/fsl). Each subject's functional and structural scans were registered using FSL's linear registration tool, and these scans were registered to high-resolution structural and standard space images using both FSL's linear registration tool and FSL's nonlinear registration tool (31,32), so that each subject's brain was registered to the International Consortium for Brain Mapping-152 T1 template (33). In addition, the following preprocessing was applied; nonbrain removal using FSL's brain extraction tool (34); spatial smoothing using a Gaussian kernel of full width at half maximum 5 mm; grand-mean intensity normalization of the entire four-dimensional dataset; and high-pass temporal filtering