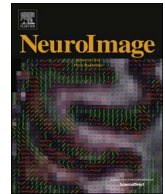




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Orbitofrontal cortex connectivity as a mechanism of adolescent behavior change

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ABSTRACT

An increasing number of studies have implicated the role of network functional connectivity in addiction. Yet, none have examined functional connectivity as a potential mechanism of adolescent behavior change. We examined the underlying neural mechanism of a promising treatment for adolescents, motivational interviewing (MI). We began by employing psychophysiological interaction (PPI) to evaluate network response in a sample of adolescent cannabis users (N=30). Next, we examined correlations between network connectivity and clinical metrics of treatment outcome. PPI analyses seeded on the orbitofrontal cortex (OFC) showed significant increases in functional connectivity across the inferior frontal gyrus (IFG), precentral gyrus, anterior and posterior cingulate gyrus, supplementary motor area (SMA), superior frontal gyrus, pallidus, caudate, and parahippocampal gyrus. Further, greater functional connectivity between the OFC and anterior cingulate/medial frontal gyrus was associated with less behavior change (e.g., greater post-treatment cannabis problems). These data support the role of the OFC network as a mechanism of adolescent treatment response.

1. Introduction

Cannabis and alcohol are two of the most widely abused substances among adolescents. Though it remains to be seen whether newly instantiated changes in United States (U.S.) cannabis legislation will cause rates of adolescent misuse to escalate (CDC, 2014), rates of daily cannabis use have steadily been on the rise for youth (CDC, 2016). By the start of high school, 26% of U.S. youth have used cannabis, a proportion that increases to 50% by graduation (CDC, 2016). Similarly, most adolescents experiment with alcohol during the high school years, with 51% drinking alcohol at least once by the time they start high school, a percent that rises to 73% by senior year (CDC, 2016). These levels of use are consequential, as cannabis and alcohol use are key contributors to accidents and injuries, the number one source of morbidity and mortality for this age group (Heron, 2013). Notably, most adolescents see little connection between their substance use and substance-related problems (Khan et al., 2014; Thompson et al., 2014; Roditis and Halpern-Felsher, 2015).

Motivational interviewing is an addiction treatment focused on catalyzing and enhancing an individual's intrinsic motivation and

movement toward behavior change (Miller and Rollnick, 2013); this is one reason why it represents a particularly good fit with non-treatment seeking youth (Peterson et al., 2006; McCambridge et al., 2008; D'Amico et al., 2008). MI is one of the strongest evidence-based treatments for adolescent cannabis and alcohol use (SAMHSA; <http://www.nrepp.samhsa.gov/>), and clinically, it is well received by adolescents (Stern et al., 2007; D'Amico et al., 2010). A single session of MI generates observable behavior change, with weighted effect sizes approaching $d=0.8$ ($M d=0.17$), and the strongest effect sizes observed within 6 months post-treatment ($d=0.32$) (Jensen et al., 2011).

Contrasting with other types of adolescent addiction treatment (Black and Chung, 2014), ambivalence is one of the central tenets of the clinical framework of MI (Feldstein Ewing et al., 2016). Ambivalence represents a client's experience of simultaneously wanting to make a change while also being reticent to do so. Concretely, within MI, ambivalence is operationalized as client expressions in favor of changing (change talk; CT), which most often co-occur with client expressions in favor of maintaining a target behavior (sustain talk; ST) (Miller and Rollnick, 2013) [e.g., "I know I shouldn't drink (CT), but it

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Table 1
Demographic characteristics of participating samples.

| Variable | Cannabis sample (n=30) Mean | Alcohol sample (n=15) Mean |
|------------------------------------|-----------------------------------|----------------------------------|
| Gender | | |
| Male (n) | 25 | 7 |
| Female (n) | 5 | 8 |
| Race/ethnicity | | |
| Hispanic American | 16 | 7 |
| Bi/Multi-racial | 4 | 4 |
| Asian American | 0 | 2 |
| Native American | 0 | 1 |
| African American | 1 | 0 |
| Caucasian | 9 | 1 |
| Age (years) | 16.09 | 16.62 |
| Age at first drink (years) | – | 13.86 |
| Age at first cannabis use (years) | 12.30 | – |
| Baseline past-month drinking days | 1.74 | 4.07 |
| Follow-up past month drinking days | 1.76 | 0.86 |
| Baseline past-month cannabis days | 18.33 | 6.36 |
| Follow-up past month cannabis days | 11.05 | 5.29 |

is so fun!” (ST). In practice, therapists must navigate the key challenge of MI: helping clients “resolve” their ambivalence in the direction of behavior change (Miller and Rose, 2009). Therapists can measure their degree of success in this effort by observing clients’ increased expressions of “change talk” and decreased expressions of “sustain talk” during a treatment session (Miller and Rollnick, 2013).

Yet, much of the knowledge base on MI was generated from samples of treatment-seeking adults who were actively trying to quit drinking (e.g., COMBINE; MATCH; UKATT) (Anton et al., 2006; Project Match Research Group, 1997; UKATT Research Team, 2005). In contrast, most youth in addiction treatment are non-treatment-seeking “opportunistic” clients (Spirito et al., 2011; D’Amico et al., 2015), who arrive at the clinician’s office because treatment is either an integrated component of their other medical (Stern et al., 2007; Spirito et al., 2011) or service system care (Stein et al., 2011; Walker et al., 2011), or because an adult brought them (Feldstein Ewing et al., 2013). Nevertheless, meta-analytic data on MI with adolescents [(Cohen’s $d=0.17$, 95% CI [.09, .25], $n=21$) (Jensen et al., 2011); (Hedge’s $g=.16$; 95% CI [.05, .27], $n=8$) (Cushing et al., 2014); (Hedge’s $g=0.28$; 95% CI [0.242, 0.323], $n=37$)] (Gayes and Steele, 2014) support that youth *still* show positive behavior change after receiving MI, despite their limited interest in receiving addiction treatment services.

One avenue to understand how this intervention operates is to examine the mechanisms of treatment response (Black and Chung, 2014). Defined by Morgenstern (Morgenstern et al., 2012), treatment mechanisms represent processes occurring within the client that facilitate or interfere with an individual’s movement toward successful behavior change. Unfortunately, at this time, numerous studies have tried to isolate behavioral drivers of individual change, but have failed to identify reliable factors upon which to “match” individuals to effective treatment (ProjectMatchResearchGroup, 1998).

To strengthen examination of potential treatment mechanisms, investigators are increasingly integrating basic biological approaches into this field of inquiry (Naqvi and Morgenstern, 2015; Berkman and Falk, 2013), including MRI (Gabrieli et al., 2015). Compellingly, work within our lab has generated support for this translational approach (Feldstein Ewing et al., 2011). For example, among our adolescent samples, we have found greater BOLD response for client speech in favor of reducing substance use (change talk) relative to client speech in favor of continuing to use (sustain talk) (Feldstein Ewing et al., 2013). Our lab and others’ have also found support for several neural regions in successful behavior change, including the precuneus, middle and superior frontal gyrus, inferior frontal gyrus (IFG), insula, and posterior cingulate/cingulate gyrus (Feldstein Ewing et al., 2013;

Feldstein Ewing et al., 2015; Falk et al., 2011). While recent reviews have highlighted the extensive network of neural systems that respond to drug cues (Jasinska et al., 2014), it is not known how functional networks, or communication between these neural regions, may drive successful treatment response (Feldstein Ewing et al., 2011).

These are important clinical questions, which are highly informative in the often less-than-intuitive translation of “bench-to-bedside”, or the use of neuroscience data to guide real-world clinical practice (Feldstein Ewing et al., 2016). Learning how networks within the adolescent brain process clinical elements, and evaluating the predictive validity of those neural network processes is integral in guiding clinicians’ selection of which approaches to use during clinical sessions.

Given that prior investigations of adolescent addiction treatment response have primarily focused on areas of regional activation, we sought to expand our evaluation to examine functional organization of these systems. Specifically, by generating an empirically-derived seed region, we identified the locus and nature of network cohesion as a relevant mechanism of adolescent behavior change. We sought to query the functional connectivity, or temporal correlation, of BOLD response with other relevant regions within the brain during the in-session proxy for adolescent movement on the key clinical construct of ambivalence: client change talk. To determine the association between network connectivity and adolescent treatment response, we evaluated the correlation between network connectivity and adolescent post-treatment behavior change. Finally, to determine the degree of generalizability of these networks across other types of adolescent substance abuse, we employed conjunction analysis with a *de novo* sample of adolescent alcohol abusers. Our aims were thus three-fold: (1) Employ psychophysiological interaction (PPI) to evaluate network response in a large sample of adolescent cannabis users, (2) utilize correlations to evaluate the link between network connectivity and treatment response within this sample, and (3) conduct an exploratory conjunction analysis to assess congruence of these networks across different substances of abuse.

2. Materials and methods

2.1 Participants

For this evaluation, 45 unique adolescent substance users (ages 14–19; $n=30$ in the cannabis sample, and $n=15$ in the alcohol sample) were recruited through community and/or high-risk (justice) centers in the Southwestern United States (Feldstein Ewing et al., 2013; Feldstein Ewing et al., 2016). For sample demographics, see Table 1. All adolescents agreed to participate in a translational study aimed at reducing adolescent health risk behavior. Written consent was obtained from participants ages ≥ 18 . For youth < 18 , adolescents provided written assent and parent/guardian informed consent was obtained via telephone following youth assent. All consent conversations were audio-recorded and logged. Study procedures were conducted with institutional review board approval and with a federal Certificate of Confidentiality.

Inclusion criteria required that youth be current users of cannabis and/or alcohol (defined as ≥ 7 past-month cannabis use episodes for the cannabis sample; ≥ 3 past-month binge-drinking episodes for the alcohol sample), and meet requisite MRI safety criteria (Filbey et al., 2008). Youth were excluded if they reported serious medical conditions (e.g., loss of consciousness > 5 min in the last 6 months, history of brain disease or brain illness), current psychosis, and/or serious psychopathology (as measured by current prescription medications for these disorders).

2.2. Procedure

Adolescents completed a psychosocial assessment, two MI sessions focused on reducing the target substance of abuse (cannabis or alcohol,

respectively), an MRI scan that included an fMRI paradigm to assess the neural correlates of client language, and a behavioral follow-up at one month post-treatment. Youth completed the baseline behavioral assessment and the first MI session during their first appointment. One week later, youth completed an MRI scan, immediately followed by their second MI session. One month after the scan session, youth completed their final behavioral follow-up.

Youth completed measures of demographics, substance use, and an MRI scan. In terms of accuracy, adolescent studies support the reliability and validity of adolescent self-report in assessing substance use behavior (Clark and Winters, 2002; Marlatt et al., 1998). Adolescents also completed the Timeline Followback (TLFB; (Sobell and Sobell, 1992)), an interviewer-administered measure that utilizes a calendar format to assess adolescents' past month quantity and frequency of substance use. From this measure, we derived past month totals for overall number of cannabis and alcohol use days at each assessment point. For the first sample (cannabis using youth), we also included a clinical metric of treatment response, a 58-item measure evaluating past-month cannabis-related problems (e.g., "Have you had a persistent chest infection or cough?", "Have you driven while stoned?"; CPQ-A; (Martin et al., 2006)).

The MI treatment followed a manualized approach (Feldstein Ewing et al., 2008). Master's level therapists administered all treatment sessions. The first author monitored treatment integrity and fidelity. Across sessions, therapists relied on MI-consistent approaches, including use of complex reflections, open-ended questions, affirmations, accurate empathy, support of youths' self-efficacy, and efforts to reduce youth resistance. All sessions were audio-recorded to gather requisite statements for the neuroimaging paradigm and to maintain treatment integrity and fidelity.

2.3. fMRI data acquisition

Participants were instructed to abstain from all substance use for a minimum of 24 hours prior to the MRI scan, which was verified by self-report prior to the scan session. Youth were screened for indicators of acute intoxication; no individuals were non-compliant, and thus no youth needed to be rescheduled. Once comfortable with the MRI procedures, youth were placed into the scanner for a high-resolution structural scan. This scan provided image registration and normalization. We utilized the standard audio volume setting for all participants, which was monitored by our MR technicians. As verified in our post-scan questionnaire, no youth reported difficulties hearing the audio statements within the fMRI paradigm.

MRI images were collected using a 3T Siemens Trio whole body scanner equipped with Sonata gradient subsystem (40 mT/m amplitude, 200 μ s rise time, 100% duty cycle) with a 12-channel coil combined with body coil transmission to achieve greater sensitivity in cortical areas. A high resolution whole brain anatomical MRI scan was also collected with a T1-weighted multi-echo Magnetization Prepared Rapid Gradient Echo or MPRAGE (MEMPR) sequence with the following parameters: TR/TE/TI=2300/2.74/900 ms, flip angle=8°, 192 sagittal slices, FOV=256×256 mm, slab thickness=176 mm, matrix=256×256×176, voxel size=1×1×1 mm, number of echos=4, pixel bandwidth=650 Hz. Whole brain fMRI scans were collected using a gradient echo, echoplanar (EPI) sequence with ramp sampling correction using the inter-commissural line (AC-PC) as a reference (TR: 2.0 s, TE: 27ms, α : 70°, matrix size: 64×64, 32 slices, voxel size: 3×3×4 mm for the cannabis study; TR: 2.0 s, TE: 27 ms, flip angle=75°, matrix size: 64×64, 33 slices, voxel size: 3.75×3.27×4.55 mm for the alcohol study) ventral to the surface of the OFC. A tilting acquisition previously described in Filbey et al. (Filbey et al., 2008) was applied to increase the signal-to-noise ratio in the OFC.

Our task (Fig. 1) was designed to assess the impact of in-session client statements on brain response. Throughout the past decade, this

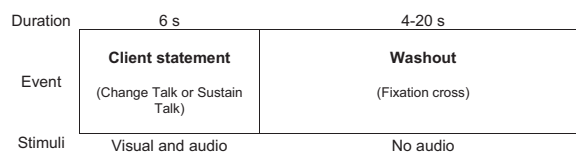


Fig. 1. Task schematic.

task has demonstrated the ability to extract relevant regional brain activation during client language across three different age groups (adolescents, young adults, and adults) and across two different substances of abuse (alcohol and cannabis) (Feldstein Ewing et al., 2013; Feldstein Ewing et al., 2016; Feldstein Ewing et al., 2014; Feldstein Ewing et al., 2011). For this task, we extracted 5 client "change talk" statements (CT; "I need to cut back my use") and 5 client "sustain talk" statements (ST; "I like using – it's fun!") from participants' therapy sessions.

Each type of client statement (change talk; sustain talk) was presented in 4 counterbalanced runs consisting of 10×65 s trials (TR 2s/volume; 1 run=10 trials×65 s/30 TRs per trial=325 TRs/10 minutes). Across the 4 runs, subjects were presented with each of the 10 CT and 10 ST trials twice for a total of 40 trials (20 CT and 20 ST). During the presentation of the CT and ST statements, participants were instructed to silently read their visually presented words and listen to their audio-recorded voice. For a single run, each trial started with their 6 second audio clip (recorded from the participant's therapy session) with a simultaneous visual presentation (seeing the written words) of their CT or ST statement. Statement presentations were then followed by a 4-20 second washout period with a fixation cross on the screen during which no audio was presented. The task was presented using front projection to a mirror system mounted on the head coil. Stimulus presentations were delivered using E-Prime (cannabis study) and Presentation (alcohol study). The timing of the stimulus presentation was synchronized with trigger pulses from the scanner to ensure precise temporal integration of stimulus presentation and fMRI data acquisition.

Given our interest in the expression of client language as a proxy or marker of behavior change, all analyses focused on the comparison of the client language condition relative to baseline. This facilitated a way for us to elucidate how the *brain* responds to this widely accepted mechanism of change in the behavioral treatment literature (Miller and Moyers, 2014). The baseline included the washout/fixation period.

2.4. fMRI data preprocessing and first-level analyses

All analyses were performed offline using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Before starting statistical analysis, the first six volumes of each EPI run were discarded to allow the MR signal to reach steady state. Pre-processing of these volumes started with motion correction using SPM's realignment module (Friston et al., 1995). This was followed by slice timing correction, which corrected for temporal differences in acquisition time of the BOLD signal across slices within each volume. The functional data were then normalized (Ashburner and Friston, 1999) into the Montreal Neurological Institute (MNI) standard space using the template provided in SPM. The resultant time series was then smoothed using a 6 mm (FWHM) Gaussian kernel. Also, for each dataset, the anatomical MPRAGE scan was co-registered to the BOLD first dynamic, normalized to MNI space, skull stripped and segmented to yield WM and CSF segments. The average BOLD time series within these segments were extracted using in-house Matlab scripts.

To determine neural mechanisms of client in-session language, we modeled BOLD activation during client language (change talk and sustain talk) in the GLM analysis. All regressors were convolved with a canonical HRF included in SPM8. Ancillary non-target conditions of interest to this study (e.g., cue types and urge rating in the cannabis

study, therapist language in the alcohol study) were modeled as nuisance regressors. The mean WM and CSF signal were also included as regressors of no interest in the model. Notably, these conditions did not contribute to baseline activation, and the resultant model fit was optimal.

2.5. fMRI data functional connectivity analysis

To determine functional connectivity, we performed whole brain psychophysiological interaction (PPI) analyses using the gPPI toolbox (McLaren et al., 2012) for SPM8. This approach shows how functional connectivity between brain regions is altered as a result of experimental or psychological context, such as following the receipt of psychotherapy or elements of psychotherapy (e.g., client language) (Friston et al., 1997). In order to maximize potential generalizability to both types of in-session client language, we wanted to ensure that we selected a seed region that would be relevant not just for change talk, but also for sustain talk. Thus, to identify a seed region that was (a) significantly activated for both groups and both conditions of interest, and (b) within the same anatomic region across all subjects, we performed a conjunction analysis over the effects of interest (both client language conditions: change talk vs. baseline; sustain talk vs. baseline; FDR corrected $p < 0.05$) (Nichols et al., 2005) and in the pooled sample of user groups (cannabis users and alcohol users). This approach generated a common region of activation within the orbitofrontal cortex (OFC) for all subjects across conditions; the functional mask for the OFC was then used as the seed region for all subsequent PPI analyses (see Supplementary Figures 4, 5, and 6).

For each subject, the first eigenvariate of fMRI signal was extracted from the OFC seed, temporally filtered, and corrected for non-neuronal components of the design (such as session-specific mean). This time series was deconvolved by the canonical HRF to estimate the time series for the neural activity (the physiological vector). The psychological vector was obtained by encoding the onset and duration of the client language blocks. The physiological and psychological vectors were multiplied to obtain the corresponding PPI vector. Similar psychological and PPI vectors were also obtained for other conditions in the study to improve model fit. The averaged WM and CSF signals were included in the model. The single subject PPI GLM thus comprised the PPI vectors, the corresponding psychological vectors, and physiological vector, each of which was convolved by the canonical HRF prior to GLM analysis.

2.6. Group-level analyses: correlation between network connectivity strength and treatment response

To assess whether functional connectivity during change talk events differed as a function of post-treatment behavior change, we examined the associations between PPI estimates and treatment response in our adolescent cannabis-using sample ($n=30$). Specifically, we correlated the change talk vs. baseline contrast map against the post-treatment measure of cannabis problems. Analysis was restricted within a mask consisting of cortical and subcortical grey matter. In line with other neurodevelopmental and addiction connectivity studies (Agcaoglu et al., 2015; Thayer et al., 2016), we corrected for multiple comparisons via SPM's voxel-wise False Discovery Rate (FDR) correction for multiple comparisons at $p < 0.05$ (Genovese et al., 2002) and utilized an extent threshold (k) of at least 50 voxels for all analyses. The anatomical localization for all regions of activation was found using the `xjview` software (<http://www.alivelearn.net/xjview>). For visualization and display of significant activation, the z -maps were overlaid on the MNI template provided within SPM.

All results were examined with the addition of framewise displacement (FD) as a covariate. Mean FD values were very low for both samples ($M=0.21$ for each sample), as subjects with substantive head movement had already been omitted from analyses prior to the

calculation of FD for each subject. In all cases, results with FD as a covariate did not differ from results without the inclusion this covariate. Thus, we retained original results and tables/figures without the inclusion of FD.

2.7. Exploratory conjunction analysis

To test the potentially cross-substance congruence of this network response across different adolescent substances of abuse (Feldstein Ewing et al., 2015), we performed a conjunction analysis to see whether a *de novo* sample of youth with alcohol abuse showed the same activation in the PPI network as the sample of cannabis users. We utilized the same OFC seed region for both groups, and compared PPI maps from this cluster for both groups (see Supplement Figure 6). The conjunction analysis included a total of 45 subjects (30 adolescent cannabis users, 15 adolescent alcohol users).

Due to original study questions, both the cannabis study and the alcohol study included several variables that were not the focus of the current study, which were subsequently modeled as nuisance regressors (e.g., cannabis study=cannabis cues, rating period; alcohol study=therapist statements). PPI analyses in the alcohol study paralleled the cannabis study in explicitly modeling change talk (vs. baseline) and sustain talk (vs. baseline) seeded on the functional mask within OFC and regressing out all other vectors.

The single subject PPI GLM comprised the PPI vectors, the corresponding psychological vectors and physiological vector, each of which was convolved by the canonical HRF prior to GLM analysis. Here as well, all results were similar with the inclusion of FD values as covariates. We also included time derivatives of the HRF in the model to account for any variations in response across subjects. Motion parameters along with averaged WM and CSF signals were included in the model as regressors of no interest to improve model fit. This approach is in line with recommendations by Power et al. (2015) that caution against decoupling covariates that may be related to the anticipated variables of interest. This is an especially important consideration in young, clinical populations where motion tends to be high.

The connectivity maps from both cannabis and alcohol users were entered into a random effects ANOVA model to look at the degree of conjunction (Nichols et al., 2005), or overlapping regions of increasing or decreasing connectivity with the OFC, for both substance abuse populations. Analyses were restricted within a mask consisting of cortical and subcortical grey matter. Significant activations were identified within the mask using SPM's voxel-based FDR corrected $p < 0.05$, $k \geq 50$ voxels.

3. Results

3.1. Treatment response

As observed in Table 1, both groups of adolescents reported heavy baseline substance use at baseline. Both studies had excellent retention at the 1-month follow-up (97.67% for cannabis sample; 82% for alcohol sample). Consistent with similar studies that have highlighted challenges in retaining substance using youth (Montanaro et al., 2014), missing youth were unreachable despite repeated staff efforts. Importantly, adolescents in both samples evidenced clinically-significant behavior change for their target substance of abuse from baseline to follow-up, as measured by statistically significant reductions in frequency of use (substance use days for only the target substance of abuse) and a halving of substance-related problems (p 's $< .001$; see Table 1). Notably, no behavior change was observed for the non-target substance of abuse (e.g., alcohol use did not decrease in the cannabis study; cannabis use did not decrease in the alcohol study), indicating the specificity of the treatment effects to the target substance.

Table 2

Functional connectivity and treatment mechanisms: PPI results for change talk. Maximum loci of regions that showed change in connectivity with the OFC during change talk for the adolescent cannabis using sample. Activations have been thresholded at FDR $p < 0.05$, $k \geq 50$ voxels. R=right; L=left.

| # voxels | Localization | t value | x (mm) | y (mm) | z (mm) |
|--|--|---------|--------|--------|--------|
| (a) Regions of increased connectivity | | | | | |
| 1466 | L. Inferior frontal gyrus (Pars orbitalis) | 11.58 | -44 | 26 | -8 |
| | L. Precentral gyrus | 8.41 | -42 | 6 | 50 |
| 2467 | L. Middle Temporal Gyrus | 10.2 | -60 | -32 | -6 |
| | L. Middle Temporal Gyrus | 9.22 | -52 | -36 | -2 |
| 1379 | L. Supplementary motor area | 9.38 | -4 | 16 | 62 |
| | L. Medial superior frontal gyrus | 7.27 | -8 | 34 | 56 |
| 1148 | R. Middle Temporal Gyrus | 7.66 | 52 | -34 | 2 |
| | R. Superior temporal gyrus | 5.96 | 62 | -24 | -2 |
| 137 | R. Inferior Occipital Gyrus | 7.06 | 26 | -98 | -4 |
| | R. Calcarine gyrus | 5.43 | 18 | -96 | -4 |
| 798 | L. Posterior cingulate gyrus | 6.5 | -6 | -50 | 28 |
| | R. Posterior cingulate gyrus | 4.39 | 2 | -48 | 26 |
| 96 | L. Inferior occipital gyrus | 6.32 | -26 | -94 | -6 |
| 350 | R. Medial superior frontal gyrus | 6.29 | 8 | 62 | 24 |
| 193 | L. Pallidum | 5.36 | -18 | 4 | -4 |
| | L. Caudate | 3.75 | -8 | 4 | 4 |
| 418 | L. Middle temporal pole | 5.1 | -46 | 14 | -30 |
| | L. Inferior temporal gyrus | 4.78 | -44 | 2 | -40 |
| 140 | L. Middle cingulate gyrus | 5.04 | -2 | -16 | 40 |
| | L. Anterior cingulate gyrus | 2.57 | -2 | -4 | 30 |
| 134 | L. Parahippocampal Gyrus | 3.96 | -16 | -14 | -14 |
| 202 | R. Inferior Frontal Gyrus (Pars triangularis) | 3.87 | 52 | 24 | 2 |
| | R. Inferior Frontal Gyrus (Pars triangularis) | 3.72 | 58 | 28 | 14 |
| 68 | R. Caudate | 3.83 | 14 | 10 | 8 |
| | R. Pallidum | 3.79 | 18 | 4 | -6 |
| 112 | L. Rectus | 3.55 | -6 | 46 | -16 |
| | L. Rectus | 3.24 | -2 | 38 | -20 |
| (b) Regions of decreased connectivity | | | | | |
| 1201 | R. Middle frontal gyrus | 7.12 | 34 | 34 | 40 |
| | R. Superior frontal gyrus | 6.01 | 24 | 4 | 68 |
| 2604 | R. Middle temporal gyrus | 6.98 | 52 | -62 | 2 |
| | R. Precuneus | 6.63 | 10 | -58 | 62 |
| 1429 | L. Precuneus | 6.89 | -8 | -60 | 60 |
| | L. Middle temporal gyrus | 6.61 | -50 | -68 | 6 |
| 1230 | L. Lingual gyrus | 6.39 | -16 | -78 | -8 |
| | L. Parahippocampal gyrus | 5.66 | -32 | -26 | -24 |
| 551 | R. Supramarginal gyrus | 5.91 | 60 | -32 | 30 |
| | R. Postcentral gyrus | 4.39 | 54 | -24 | 52 |
| 939 | R. Inferior temporal gyrus | 5.77 | 50 | -46 | -18 |
| | R. Fusiform gyrus | 4.44 | 38 | -30 | -18 |
| 62 | R. Superior occipital gyrus | 5.47 | 16 | -100 | 16 |
| 61 | L. Superior occipital gyrus | 5.39 | -18 | -100 | 14 |
| 83 | R. Thalamus | 5.27 | 14 | -26 | 10 |
| 52 | L. Thalamus | 4.91 | -14 | -30 | 12 |
| 261 | L. Supramarginal gyrus | 4.9 | -62 | -30 | 40 |
| | L. Inferior parietal lobule | 3.39 | -52 | -36 | 52 |
| 55 | L. Middle frontal gyrus | 4.69 | -22 | 2 | 68 |
| | L. Superior frontal gyrus | 3.88 | -22 | 4 | 58 |
| 158 | R. Olfactory gyrus | 4.65 | 4 | 14 | -10 |
| 89 | L. Middle cingulate gyrus | 4.02 | -10 | 4 | 40 |
| 212 | L. Middle frontal gyrus | 4 | -32 | 36 | 40 |
| | L. Middle frontal gyrus | 3.79 | -30 | 30 | 32 |
| 101 | R. Superior temporal pole | 3.81 | 46 | 6 | -12 |
| (c) Correlations between OFC network connectivity strength and treatment response | | | | | |
| 87 | L. Anterior cingulate gyrus/Medial frontal gyrus | 6.26 | -2 | 40 | 26 |
| | L. Medial frontal gyrus | 5.46 | -2 | 48 | 30 |
| 50 | R. Anterior cingulate gyrus | 5.88 | 4 | 36 | 24 |

3.2. Functional connectivity and treatment mechanisms: PPI results

In line with recent neurodevelopmental and addiction studies (Lopez-Larson et al., 2015; Dwyer et al., 2014; Gee et al., 2013), all adolescents in this sample had movement within standard neurodevelopmental limits (< 2 mm translation and $< 2^\circ$ rotation). Additionally, motion parameters were included as nuisance regressors in the GLM for both activation and PPI analysis. The averaged WM and CSF signal were included as nuisance regressors in the GLM.

For this analysis, we examined OFC network connectivity as a mechanism of behavior change. When examining functional connec-

tivity during change talk vs. baseline, we observed significant increases in functional connectivity between the OFC seed and areas including the IFG, precentral gyrus, anterior and posterior cingulate gyrus, SMA, superior frontal gyrus, pallidus, caudate, and parahippocampal gyrus. We also observed significant decreases in functional connectivity between the OFC seed and several areas including the precuneus, superior/middle frontal gyrus, parahippocampal gyrus, thalamus, inferior parietal lobule, cingulate gyrus. All analyses were FDR corrected $p < 0.05$, $k \geq 50$. (Tables 2a and b; Fig. 2).

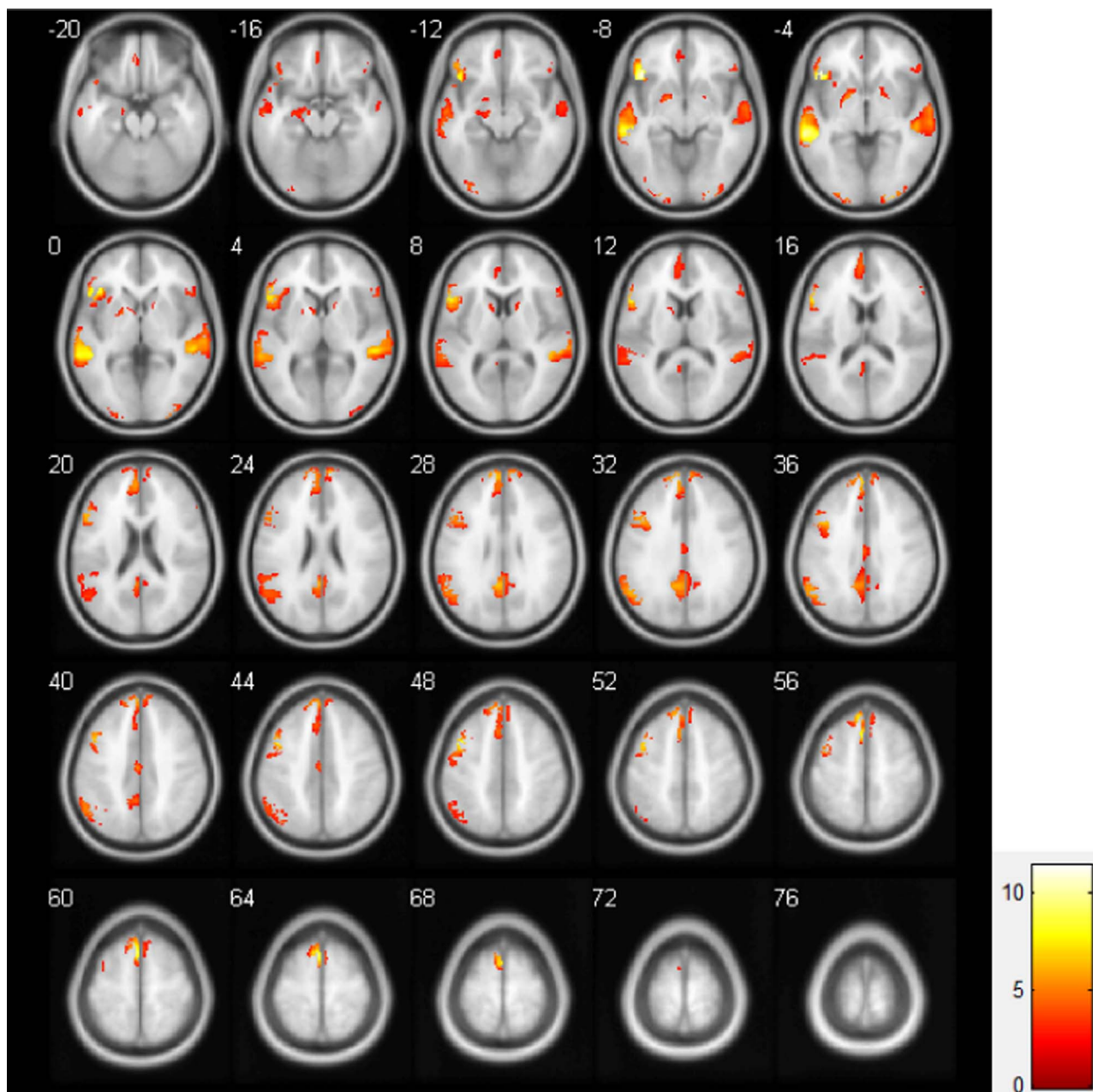


Fig. 2. Main Effects. Regions of increased connectivity with OFC seed during change talk (cannabis users, $n=30$). Activations (FDR corrected $p < 0.05$, $k \geq 50$) are displayed on contiguous slices of the EPI template. The color bar indicates t range. Orientation: Right=Right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Functional connectivity and treatment response

To examine how functional connectivity may serve as a mechanism of adolescent behavior change, we examined the correlation between OFC connectivity and post-treatment cannabis problems. We found a significant positive correlation, such that greater connectivity between the OFC and anterior cingulate/medial frontal gyrus was associated with more post-treatment cannabis problems (FDR corrected $p < 0.05$, $k \geq 50$). There were no negative correlations, or correlations with regions of decreased connectivity (Table 2c; Fig. 3).

3.4. Exploratory conjunction analysis between adolescent cannabis and alcohol users

We also explored how congruent these networks were across youth receiving treatment targeting two different substances of abuse:

cannabis vs. alcohol. Networks of functional connectivity were specific to the target substance of abuse discussed during the treatment sessions (cannabis for the cannabis sample; alcohol for the alcohol sample). For substance-specific conversations about changing the target substance of abuse (e.g., change talk), we observed no areas of overlapping connectivity increases or decreases at the chosen threshold (FDR corrected $p < 0.05$; $k \geq 50$).

3.5. Post hoc examination of the sustain talk condition

Post hoc analyses of the sustain talk condition are detailed in the Supplementary section. We examined the contrast between change talk and sustain talk for the PPI analysis; no significant regions emerged at our pre-determined level of statistical correction. However, within the conjunction analysis, we did observe a significant overlap in functional connectivity between the adolescent cannabis and alcohol using

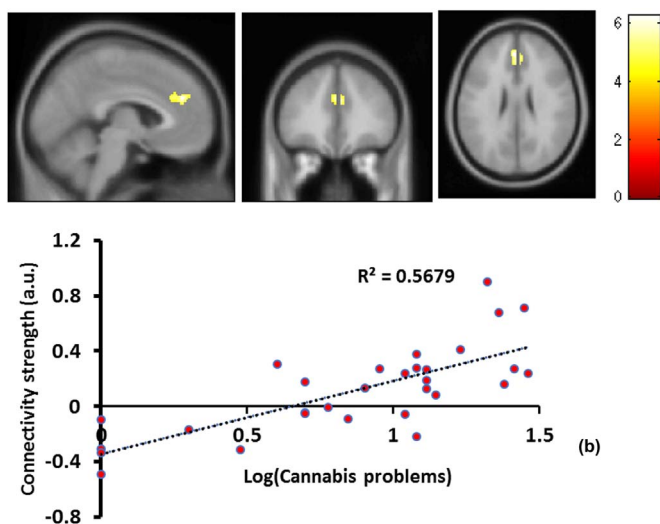


Fig. 3. Positive correlation between OFC network connectivity strength and treatment response. Maximum loci of activation between connectivity during change talk and post-treatment behavior change for the adolescent cannabis using sample (FDR corrected $p < 0.05$). (a) Activations have been overlaid onto the single subject template. The color bar indicates t values. Orientation: Right=Right. (b) Scatter plot of parameter estimates for connectivity strength between this ROI and the OFC seed region. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

samples during the sustain talk condition (OFC seed with IFG, SMA, superior frontal gyrus, middle temporal gyrus; see [Supplement, Table 4](#)).

4. Discussion

While studies are increasingly using PPI to evaluate functional connectivity in the brain and its role in addiction ([Claus et al., 2013](#); [Weiland et al., 2013](#); [Filbey and Dunlop, 2014](#)), this evaluation represents the first published study, to our knowledge, to examine functional connectivity as a mechanism of change in adolescent addiction treatment. Based on foundational behavioral and neuroimaging work, which has identified the importance of client language in adolescents' MI treatment response ([Feldstein Ewing et al., 2013](#); [Gaume et al., 2016](#)), we took a three-step approach to identify the extent and location of network connectivity during a key aspect of treatment (client language in favor of change; change talk), the link between that connectivity and post-treatment behavior change, and an exploratory look at the generalizability of those networks across two different substances of abuse (cannabis and alcohol).

The OFC is a highly relevant region, both within addiction, and across the broader field of psychopathology. For example, recent studies reflect that the OFC may underlie neural sensitivity to cannabis cues ([Filbey et al., 2016](#)), and place individuals at greater risk for a more protracted trajectory of use, particularly when use begins at an earlier age ([Filbey et al., 2014](#)). In addition to its role in cannabis addiction, OFC dysregulation appears to be a signature feature across anxiety, OCD, and anorexia nervosa ([Cha et al., 2016](#); [Park et al., 2016](#); [Yang et al., 2015](#)), subsequently indicating its relevance as a marker of neural health, and potentially, a region that may be disrupted during the transition into more long-standing psychiatric conditions.

In this study, during client statements in favor of change (change talk), we found increased neural cohesion between the OFC seed and a number of regions including the IFG, precentral gyrus, anterior and posterior cingulate gyrus, SMA, superior frontal gyrus, pallidus, caudate, parahippocampal gyrus. We also observed decreased functional connectivity between the OFC seed and a number of areas, including the precuneus, superior/middle frontal gyrus, parahippocampal gyrus, thalamus, inferior parietal lobule, and cingulate gyrus.

We believe that these findings are of high clinical relevance, as they represent an advance beyond regional activation studies, to reflect the existence of a cohesive network of neural communication during client language in favor of change. Compellingly, this study also offers the first empirical support for networks that our team had previously hypothesized might be relevant in treatment response in 2011 ([Feldstein Ewing et al., 2011](#)). More specifically, we proposed that the OFC might co-activate with the IFG, in what we had titled the “executive control network”, to clinically facilitate an individual’s movement toward behavior change. In this capacity, we believed that this OFC-based network might underlie an individual’s capacity to actually *implement* ideas generated during the treatment session to *real-world* reductions in substance use.

Interestingly, while sustain talk was not the original focus of this investigation, we also examined areas of regional connectivity for this comparison condition (see [Supplementary section](#)). Here we found that sustain talk was associated with increased connectivity between the OFC and regions including the IFG, SMA, superior frontal gyrus, posterior cingulate, pallidus, and caudate. As with change talk, connectivity during sustain talk additionally showed decreased connectivity between the OFC and regions including the precuneus, caudate, middle/superior frontal gyrus, thalamus, insula, and SMA. Most simply, these data reflect the substantive OFC network communication during adolescents’ processing of both types of clinical, in-session language. Interestingly, when contrasted directly, we found a parallel level of response across both types of client language response; in other words, network connectivity was not greater for one type of client statement relative to the other (CT vs. ST). We posit that, for adolescents, comparable, and similarly powered, neural network systems are activated during client language in favor of changing, along with client language in favor of staying the same. Notably, these two types of client language that have been associated with very different behavioral response within the adult treatment literature; more specifically, client change talk has been associated with positive treatment response (lower substance use post-treatment), whereas client sustain talk has been associated with much poorer treatment outcomes (greater substance use post-treatment) ([Magill et al., 2014](#); [Moyers et al., 2009](#)). We believe that future work must disentangle the nature of neural response during both types of client language in order to understand the strength and pattern of brain response in adolescent addiction treatment, with a particular eye to how network response and post-treatment behavior change may be unique within this developmental period, as compared with other age groups who are more often examined in treatment contexts (e.g., treatment-seeking adults) ([Feldstein Ewing et al., 2016](#)).

In terms of treatment response, OFC connectivity with the anterior cingulate/medial frontal gyrus - during change talk (only) - was significantly correlated with adolescents’ behavior change in this study. These results reflect that greater OFC connectivity may be a flag, or indicator, of *more* post-treatment cannabis problems. This is interesting, as it maps onto larger scale studies of cannabis use, wherein greater OFC connectivity has been a distinguishing marker of a much greater risk profile, in terms of protracted use and associated problems ([Filbey et al., 2014](#)). Further, these data are also in line with a recent meta-analysis in the field of depression, which supported the impact of psychotherapy on similar neural circuits ([Boccia et al., 2016](#)). Moreover, OFC network systems may not only be responsive to therapy, but potentially modifiable through therapy directly, and/or potentially through an adjunctive venue to enhance brain response to psychotherapy (e.g., neurostimulation) ([Ouellet et al., 2015](#)). For instance, others have found that not only is ACC response particularly responsive to social reward, with neurofeedback, it can be refined and enhanced ([Mathiak et al., 2015](#)).

While we observed a relationship between network connectivity and treatment response for change talk, our supplementary analyses did **not** reflect the same neural relationship for client language in favor of

staying the same (sustain talk). In other words, while the functional connectivity maps for change talk and sustain talk appeared comparable in terms of strength, direction, and location, *only one* type of client language was significantly associated with post-treatment behavior change: change talk. Clinically – this is a salient finding, and one that is highly informative in terms of guiding in-session clinician efforts. In other words, even though these types of language (sustain talk and change talk) may be processed in the adolescent brain similarly, they are highly different in terms of clinical predictive validity; only change talk was associated with reductions in substance use (Feldstein Ewing et al., 2016). This is a real-world tangible difference that is relevant for clinicians, as it continues to indicate the importance of eliciting and bolstering client statements in favor of change during in-session clinical exchanges (Feldstein Ewing et al., 2013); these exchanges may be predictive of true, real-world, behavior change.

One additional compelling element to consider in this equation is the dyadic and social role of the therapeutic exchange. Emerging studies have suggested that functional coupling between ACC and frontal cortex corresponds with less efficient inhibitory processing (Spielberg et al., 2015). This is relevant because the anterior cingulate has been implicated in social processing, including for cannabis users (Gilman et al., 2016). Further, the connection between frontal and cingulate cortical regions has also been implicated in children's neural processing of feedback from their parents (Lee et al., 2015); similar substrates are likely to be involved in clinical, dyadic exchanges with a therapist.

Our final exploratory examination was the degree of neural overlap with a small, *de novo* sample of adolescent alcohol users. While this comparison was limited by a small sample size, we did not observe any regions of overlapping connectivity for client language about change (change talk). In contrast, in our supplementary exploration, we did observe areas of conjunction during client language about continuing substance use (sustain talk) across the IFG, SMA, and superior frontal gyrus. While interpretation of these findings must be made with caution due to the very small sample size, these data serve as preliminary indication that within the adolescent brain, processes underlying or driving addiction (such as reasons for using) may be more common across substances of abuse, than potential reasons for changing; in contrast, cognition around behavior change may be substance-specific. We will continue to examine these relationships in larger, more fully powered samples to get more definitive data in the future.

In terms of clinical relevance, the next question is how these data may translate to the treatment context. Based on advances in the field of translational “bench-to-bedside” science (Naqvi and Morgenstern, 2015; Gabrieli et al., 2015; Allen and Dahl, 2015), there are two different avenues through which these data could inform direct care. One is by evaluating the strength of the role of the OFC network as a predictor of treatment response. Emerging studies with adults and adolescents suggest that brain markers may indeed represent more sensitive and powerful metrics of clinical symptoms and behavior change than conventional metrics (Gabrieli et al., 2015; Magnan et al., 2013). A second role for the use of neural measurement is to continue to examine different facets and mechanisms of behavior change (Naqvi and Morgenstern, 2015). This is still very much at the cutting edge, with an increasing number of studies examining how to integrate neural parameters into clinical trials. However, it is our position that this approach is scientifically savvy; if we can continue to identify which neural mechanisms underlie positive behavior change, we can then take steps to strengthen those treatment elements in our clinical approaches (Feldstein Ewing and Tapert, Molina).

5. Limitations and conclusions

While there are several strengths to the current study, including the novel use of in-session client language to better understand brain

networks during psychotherapeutic exchange and their relation to behavior change, the following limitations also warrant consideration. First, and most importantly, while advances are being made in this direction, it is still not possible to conduct behavioral interventions in the MRI environment; an *in vivo*, temporal evaluation of these relationships represents an important next step to advance these data. Second, the binge drinking sample was a pilot study with a small sample size; we are currently conducting a larger study which will allow us to better parse auditory and narrative components of the task for added specificity of findings. Replication of the conjunction analysis with this larger sample will help strengthen study findings, and allow for additional exploration into potential age and gender differences in neural networks and treatment response. Third, in line with standard protocols in adolescent addiction treatment studies (Dennis et al., 2004), there was no healthy control group in this study; this is because the sample needed to have sufficient levels of substance abuse in order to be able to detect behavior change in post-treatment substance use. In other words, it would not be possible for participants to show behavior change (e.g., reduction in substance use) if they began as a non-user. Fourth, while client change talk was the focus of this investigation, we included the results for the sustain talk condition in the supplemental analyses; compellingly, these data support that the link between OFC network response and treatment outcomes was specific to change talk only. No relationship was observed between OFC connectivity during sustain talk and client treatment outcomes. However, future work will examine the relationship between change talk vs. sustain talk, in order to disentangle the relationship between treatment elements, neural network response, and treatment outcomes for adolescents. Fifth, we acknowledge that head movement in the scanner during fMRI data acquisition can cause artifacts. Although task-based fMRI data is less systematically affected by very low amplitude head movements, we utilized several strategies to minimize head movement during data collection (e.g., mock scanner motion training, foam padding) as well as approaches to assess data quality and account for motion during processing and analysis (regressing motion estimates and other nuisance regressors). Further, tests of motion correlates did not indicate greater motion during change talk relative to sustain talk; together, our observed effects in the presence of sub-millimeter motion suggests that these significant findings are robust. Finally, we suggest that the examination of neural network response is useful in that it offers a creative and innovative approach to accelerate discovery of critical neural mechanisms. In other words, it is important to consider that one of the critical contributions of this manuscript is that it sets the foundation for those who want to pursue this type of translational research. This is a multi-step approach, which we hope will culminate in generating practical, clinical data to inform improvements in behavioral strategies to facilitate positive behavior change for adolescents.

Conflict of interest

This research was supported by 1R01AA023658-01 (PI: Feldstein Ewing). The funder had no involvement in any aspect of the study. The authors have no competing financial or other conflicts of interest relating to the data included in the manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.neuroimage.2016.12.076](https://doi.org/10.1016/j.neuroimage.2016.12.076).

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