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Distinct patterns of prefrontal cortical disengagement during inhibitory control in addiction: A meta-analysis based on population characteristics

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Abstract

Prefrontal cortical dysfunctions underlying inhibitory control deficits in addiction are complex and likely dependent on population characteristics. Here, we conducted a meta-analysis to examine alterations in brain activations during response inhibition in addicted individuals. We characterized imaging findings based on substance use status, diagnosis, substance classes, and task performance. Results revealed in those with active drug addiction hypoactivation of the left dorsal anterior cingulate cortex (dACC) and right middle frontal gyrus (MFG), compared with healthy controls. Weakening of the dACC and MFG activations was particularly pronounced in nicotine users and stimulant users with impaired task performance, respectively. In contrast, abstinent users did not exhibit any significant differences. Those with behavioral addictions were characterized by higher midcingulate cortical activation. Thus, the neural disengagement during response inhibition in active drug addiction was limited to a small number of prefrontal cortical regions and dependent on population characteristics. Finally, the evidence for potential

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List of studies in meta-analysis:
(Ahmadi et al., 2013), (Czapla et al., 2017), (Li et al., 2009), (Molnar et al., 2018), (Schulte et al., 2012), (Sjoerds et al., 2014), (Taylor et al., 2016), (Hester et al., 2009), (Kober et al., 2014), (Barrós-Loscertales et al., 2011), (Bell et al., 2014a), (Bell et al., 2014b), (Hester and Garavan, 2004), (Hester et al., 2013), (Kaufman et al., 2003), (Li et al., 2008), (Li et al., 2010b), (Ma et al., 2015), (Moeller et al., 2012), (Moeller et al., 2014), (Wang et al., 2018), (Jan et al., 2014), (L. J. Nestor et al., 2011), (Morein-Zamir et al., 2013), (Smith et al., 2013), (Taylor et al., 2016), (Chaarani et al., 2018), (De Ruiter et al., 2012), (Lesage et al., 2020), (Luijten et al., 2013a), (Luijten et al., 2013b), (L. Nestor et al., 2011), (Xu et al., 2007), (Fu et al., 2008), (Lee et al., 2005), (Yücel et al., 2007), (De Ruiter et al., 2012), (Luijten et al., 2015), (Potenza et al., 2003), (van Holst et al., 2012), (Chen et al., 2015), (Dong et al., 2012), (Dong et al., 2017), (Liu et al., 2014).

normalization of hypofrontality following substance use cessation highlights the benefits of abstinence in restoring cerebral functions.

Keywords

meta-analysis; Substance addiction; behavioral addiction; response inhibition; inhibitory control deficits; prefrontal cortex; fMRI

1. Introduction

Inhibitory control deficits have long been regarded as the hallmark feature of cognitive dysfunctions in addiction. Characterized by compulsive drug taking and pathological behaviors, the deficits have been associated with disruptions in the neural circuits subserving executive functions (Feil et al., 2010; Goldstein and Volkow, 2011). Decades of cellular and neural systems-level research have documented profound anatomical and neurochemical abnormalities in individuals with chronic exposure to substances of abuse (Jentsch and Taylor, 1999; Koob and Volkow, 2010). Notably, drug-induced alterations in the prefrontal cortex (PFC) including dopamine depletion and neuroadaptation are thought to weaken top-down modulation on various brain circuits implicated in reward processing, stress reactivity, and decision making (George and Koob, 2010; Li and Sinha, 2008). Such disruptions have been proposed to underlie the preferential response to the rewarding effects of drugs, diminished control, and eventual transition to compulsive drug use (Ferrario et al., 2005; Kalivas, 2008). Prefrontal cortical disengagement is further linked with heightened trait and behavioral measures of impulsivity, thus potentially serving as a risk factor for addiction (Crews and Boettiger, 2009). As such, characterizing the regional substrates implicated in impaired response inhibition may help explain the pharmacological effects of drug addiction and uncover the neural markers of addiction susceptibility.

Recent human imaging research has made significant progress in identifying the brain dysfunctions associated with deficient inhibitory control in addicted individuals. These studies typically employed response inhibition tasks including the Stroop, Flanker, Go/No-go (GNG), and Stop signal task (SST) which measure the control over unwanted, prepotent, or reflexive actions. Evidence appears to show widespread and diverse disruptions of the brain circuitries supporting behavioral regulation in addicted individuals. For instance, compared to healthy controls, subjects with cocaine dependence exhibited lower activation in the right lateralized frontoparietal network including the dorsal anterior cingulate cortex (dACC) (Hester and Garavan, 2004; Li et al., 2008), middle frontal gyrus (MFG), precentral gyrus (Ma et al., 2015), inferior frontal gyrus, and inferior parietal lobule (Barrós-Loscertales et al., 2011). Increased recruitment in dependent cocaine users has also been reported in the lingual gyrus and cerebellum (Moeller et al., 2012). Similarly, those with alcohol use disorders showed both decreased activations in the left dorsolateral PFC (dlPFC) (Li et al., 2009) and left postcentral gyrus (Czapla et al., 2017) as well as increased activations in the right superior parietal lobule, left cingulate gyrus, and thalamus (Ahmadi et al., 2013). Alterations during response inhibition in other cohorts have also been demonstrated, including hypoactivation in dependent smokers (L. Nestor et al., 2011) and

cannabis users (Kober et al., 2014) as well as hyperactivation in dependent opiate users (Yücel et al., 2007) and methamphetamine users (L. J. Nestor et al., 2011). Such findings both highlight the complex changes in the neural networks subserving inhibitory control and provide insights into the impaired ability to regulate responses to drug cues, drug urges, and impulsive behaviors in individuals with addiction.

As patterns of findings varied considerably across studies, different interpretations have been put forth as to which neural processes are affected during response inhibition in addiction. For instance, in a systematic review of the brain substrates underlying behavioral dysregulation in substance dependence, structural and functional alterations were proposed to primarily involve the frontostriatal pathways (Feil et al., 2010). Induced by chronic drug exposure, these alterations impair decision making, as manifested by the inability to evaluate risky choices, detect errors, and resist craving. In another review, Luijten and colleagues suggested that the core neural basis underlying loss of control in addicted individuals is likely to be limited to the dACC due to evidence of its reduced recruitment during response inhibition and error processing (Luijten et al., 2014). In contrast, Zilverstand and colleagues recently postulated that inhibitory control deficits in addiction may be associated with large-scale changes in not only the executive network (i.e., dorso/ventrolateral PFC) but also in those implicated in the salience and memory domains (Zilverstand et al., 2018).

Discrepancies in past reviews reflect the lack of a unifying view of the brain mechanisms of inhibitory control deficits in addiction. Such discrepancies are likely related to the heterogeneity of the population's clinical characteristics which may influence the location, extent, and direction of imaging findings (Kwako et al., 2016). Notably, substance use status (i.e., active vs. abstinent) can potentially alter brain responses due to the presence/absence of the acute pharmacological effects of substances of abuse. For instance, abstinence for as short as 15 days of cocaine (Connolly et al., 2012), nicotine (Chaarani et al., 2018), and alcohol (Czapla et al., 2017) use has been associated with enhanced PFC activations to response inhibition, indicating partial normalization of hypofrontality in abstinent individuals. Furthermore, while different substances can have distinct impacts on the neurochemical processes critical for motivation (Wise, 1996; Licata and Renshaw, 2010), it remains unclear whether the neural substrates underlying response inhibition undergo substance-specific alterations. Another important factor is individual differences in task performance. Previous reviews of neuropsychological assessments in addiction found varying degrees of impairment across investigations (Smith et al., 2014; Verdejo-García et al., 2008). Further, impairment levels are predictive of brain responses to inhibition (Li et al., 2008), suggesting a relationship between individual differences in performance deficits and their neural underpinnings. Thus, to understand how the brain processes for inhibitory control are affected in addiction, more nuanced quantitative evaluations which account for these population characteristics are needed.

In recent years, the scope of addiction research has extended to include disorders of behavioral nature, namely gambling and internet gaming. This extension is partly motivated by the mounting evidence that inhibitory control deficits may not be unique to substance use disorders, but rather indicative of fundamental neurobiological vulnerabilities across the range of addictive behaviors (Grant et al., 2006). Individuals with behavioral addictions

indeed exhibit impaired performance in the SST, GNG, and Stroop tasks (Choi et al., 2014; Kertzman et al., 2008; Lipszyc and Schachar, 2010; Yao et al., 2015). In parallel, several imaging studies have reported evidence of reduced inferior parietal lobule activity in gambling addiction (Luijten et al., 2015) as well as hypoactivation in the right dlPFC (Liu et al., 2014) and hyperactivation in the midcingulate cortex (Dong et al., 2012) in internet gaming disorder during response inhibition. Nevertheless, the absence of a direct effect on dopaminergic activity and the motivation associated with a primary reinforcer (i.e., drugs) in behavioral addictions may result in differentiable functional changes during response inhibition. As no previous work has quantitatively differentiated neural deficits in substance vs. behavioral addictions, the matter remains to be clarified.

Here, we conducted a voxel-based meta-analysis to investigate for the first time changes in regional activations to response inhibition in addicted individuals. First, we determined the specific brain substrates underlying inhibitory control deficits in each of the cohorts with active substance use, abstinent substance use, and behavioral addictions. As subject characteristics concerning substance classes and task performance level (impaired vs. non-impaired) likely contributed to inconsistencies in past systematic reviews, the studies of active substance use were subsequently divided into subgroups for additional analyses. We hypothesized that distinct clinical characteristics would be associated with differentiable patterns of dysfunction. Our results may help disentangle the discrepancies in the literature and shed light on the neural bases of inhibitory control deficits in addiction.

2. Methods

2.1 Literature selection

Following the guidelines detailed in the PRISMA Statement (Moher et al., 2009), we conducted a systematic and comprehensive search of the literature up to September 2020 using PubMed, Web of Science, and Google Scholar databases. The search terms (including all variants and abbreviations) were specified to select peer-reviewed articles of (1) imaging method (i.e., “functional magnetic resonance imaging”), AND (2) response inhibition experimental paradigms (i.e., “cognitive control” OR “response inhibition” OR “inhibitory control” OR “stop signal” OR “go/no-go”, OR “Stroop”, or “Flanker”), AND (3) substance or behavioral addiction (i.e., “alcohol” OR “cannabis” OR “cocaine” OR “methamphetamine” OR “stimulant” OR “heroin” OR “opiate” OR “opioid” OR “nicotine” OR “polysubstance” OR “Internet” OR “Gaming” OR “gambling”), OR (4) populations of addiction (i.e., “addiction” OR “dependence” OR “disorder” OR “misuse”).

2.2 Inclusion criteria

The following were the inclusion criteria:

1. Studies employing response inhibition contrasts (see below) in imaging data analysis measuring brain activity during the performance of response inhibition tasks.
2. Studies including healthy adults as a control group with no upper limit on age. Studies using children or adolescents were excluded.

3. Studies reporting whole-brain findings or using functional ROIs defined from the control group's whole-brain analysis. Studies with a priori ROIs (e.g., anatomical masks, masks defined from previous work, etc.) were excluded.

4. Studies applying appropriate imaging thresholds (e.g., false discovery rate, family-wise error, etc.) and providing information on peak coordinates and stereotactic space.

2.3 Response inhibition tasks

As with previous meta-analyses of response inhibition (Argyriou et al., 2017; Manza et al., 2017; Smith et al., 2014), we included the SST, GNG, and Stroop tasks as they all require cognitive control over a predominant response tendency and/or context-dependent initiation of a behavioral alternative. Briefly, in a typical SST, subjects are instructed to make a button press following the presentation of a "go" stimulus (e.g., a circle) and withhold the response if the "go" stimulus is followed by a stop signal (e.g., an "x"). The stop signal is presented randomly, at a variable delay, and often on a low percentage of trials. Thus, imaging findings from the contrasts [Stop success > Stop error] or [Stop success > Go success] were selected, in accordance with the literature. In a GNG task, subjects are instructed to make a button press at the presentation of the "go" stimulus (e.g., green circle) and withhold the response at the presentation of the "no-go" stimulus (e.g., red circle). Imaging findings from the contrasts [No-go success > Go success] or [No-go success > No-go error] were selected. In a Stroop task, subjects typically view color names presented in various ink colors and are instructed to name the presented ink color. In the congruent/incongruent condition, color names are presented in matching/nonmatching ink colors. Imaging findings from the contrasts [Incongruence > Congruence] were selected. All contrasts were created from general linear models which were constructed to measure brain activity associated with event onsets of relevant go, stop, no-go, and congruent/incongruent cues.

2.4 Study classification

We considered the following population characteristics for subgroup analyses. First, studies were categorized based on whether they included subjects with drug or behavioral addictions. Second, within the drug addiction category, we determined whether the subjects were abstinent or active users. In accordance with previous work (Schulte et al., 2014), abstinence for alcohol, nicotine, cocaine, methamphetamine, and opiates was defined as a minimum 15-day period of substance use cessation immediately prior to study participation. Due to the longer lasting sub-acute effects of cannabis on neural and cognitive functions (Pope et al., 2001; Schweinsburg et al., 2010), 30-day abstinence minimum is required for cannabis users. Thus, those who engaged in substance use within 15 days (30 days for cannabis) of study participation were considered active users. As there was a sufficient number of studies for each of active stimulant and nicotine use, analyses were performed for these subgroups. Finally, we differentiated active drug addiction studies that reported impaired task performance from those that found performance levels comparable to healthy controls.

2.5 Seed-based d mapping

Voxel-wise meta-analysis was performed using the Seed-based d Mapping with Permutation of Subject Images (SDM-PSI version 6.21) (Albajes-Eizagirre et al., 2019b; Radua et al., 2012a). Briefly, the SDM-PSI is a voxel-based meta-analysis software which converts peak coordinates and their t-values as reported from the original studies to Hedges' effect sizes and their associated variance. A standard random-effects model was run with each study weighted by its variance and between-study heterogeneity. Multiple imputations were pooled using Rubin's rules (Albajes-Eizagirre et al., 2019b). The statistical significance of the resulting SDM-Z maps, as thresholded with correction for family-wise error (FWE) of multiple comparisons, was estimated through a subject-based permutation test (Smith and Nichols, 2009). SDM-PSI uses MetaNSUE (Albajes-Eizagirre et al., 2019a) to estimate the maximum likely effect size within the lower and upper bounds for each study separately and then adds realistic noise (Albajes-Eizagirre et al., 2019b). To address the issues of spatial uncertainty and biases associated with single imputation, each study image generated during preprocessing underwent multiple imputations (Rubin, 2004). Then, to allow voxel-wise FWE correction for multiple comparisons, SDM generated multiple imputations of subject images and performed subject-based permutation testing. Preprocessing was performed according to SDM guidelines, using a 20-mm FWHM anisotropic Gaussian kernel and 2-mm voxel size. For all meta-analyses, the numbers of imputations and permutations were set to 50 and 1,000, respectively.

2.6 Meta-analysis

We performed separate meta-analyses to investigate neural alterations associated with inhibitory control in (1) active drug addiction, (2) abstinent drug addiction, (3) behavioral addictions, (4) active stimulant use vs. nicotine use, and (5) active drug addiction with vs. without impaired task performance. Meta-analysis for each subgroup was performed using a combined threshold of voxel $p = 0.005$, peak height $Z = 1$, cluster extent = 10 voxels in accordance with previous research of optimal balance of sensitivity and specificity (Lieberman and Cunningham, 2009; Radua et al., 2012b). To minimize spurious findings, we increased the cluster extent threshold to 100 voxels. We also reported significance at the voxel-level threshold of $p < .05$ FWE where applicable.

For the comparison between the active vs. abstinent drug addiction subgroups, we performed a whole-brain group comparison. In addition, we assessed differences in activation between behavioral addictions vs. active drug addiction, active stimulant vs. nicotine use, and active drug addiction with vs. without impaired task performance. Due to the low number of studies involved in these latter comparisons, we conducted ROI analyses in which Cochran's Q was employed to determine whether each region exhibited significantly different activation between two subgroups. Cochran's Q measures between-group heterogeneity in effect sizes which were weighted by the sample size of each study. For instance, to determine whether individuals with drug and behavioral addictions differed significantly in brain activations, we first identified ROIs from each subgroup's contrast with healthy controls. The ROIs' effect sizes were then extracted for each study and entered in a group comparison of drug vs. behavioral addictions, using Cochran's Q.

To examine the potential effects of age, sex, smoothing level, scanner strength, and repetition time (TR) across studies, we conducted meta-regressions with these variables as the predictors. Finally, publication bias was assessed by Egger's test (Egger et al., 1997) for asymmetry of the funnel plots.

All literature search (TL, SZ), study selection (TL, SZ), data extraction (TL, SZ), and data analysis (TL, SP) were independently verified by the other authors.

3. Results

3.1 Study characteristics

Forty-three studies met the inclusion criteria, including 35 studies of drug addiction and 8 of behavioral addictions (Fig. 1, Table 1). Of the 35 drug addiction studies, subjects from 26 studies were diagnosed with substance dependence whereas subjects from 9 studies met criteria for substance abuse/dependence. Twenty-four studies involved active drug addiction whereas the remaining 11 studies assessed abstinent users.

Across studies, there was a total of 918 individuals with either drug or behavioral addiction (M ± SD age = 33.3 ± 8.3 years, 19.1% females) and 985 healthy controls (age = 31.8 ± 7.4 years, 22.3% females). The drug addiction subgroup included alcohol, cannabis, stimulants (i.e., cocaine and methamphetamine), nicotine, and opiates. The behavioral addiction subgroup included problematic gambling and internet gaming. Sixteen studies reported impaired response inhibition task performance whereas 27 studies found no differences in comparison to healthy subjects.

3.2 Active vs. abstinent drug addiction

Relative to healthy controls, those with active drug addiction (N = 24 studies) exhibited significant hypoactivation in the left dACC and right MFG (Fig. 2A, Table 2). No significant hyperactivation was found. In contrast, abstinent drug users (N =11 studies) showed no significant differences in activation compared with healthy controls. A whole-brain group comparison revealed significantly weaker activation in the right MFG in individuals with active vs. abstinent substance use (Fig. 2B, Table 2).

In the analysis of publication bias, the Egger test of funnel plot asymmetry was not statistically significant for either dACC or MFG (p's > .59, Fig. S1), indicating these results were unlikely to be primarily driven by any specific study. The meta-regressions of sex, age, smoothing, scanner strength, and TR did not show any significant results for any of the variables.

3.3 Behavioral addictions vs. active drug addiction

Relative to healthy controls, those with behavioral addictions demonstrated significantly greater activation in the midcingulate cortex (MCC) (Fig. 2C, Table 2). A whole-brain comparison between individuals with behavioral addictions and those with active substance use did not reveal any significant activation, likely due to the small sample size of the former group. To address this limitation, we conducted an ROI analysis in which we extracted for each study the effect sizes of the dACC and MFG defined from the active drug addiction

subgroup as well the MCC defined from the behavioral addiction subgroup. Cochran's Q revealed significant between-group heterogeneity for the MFG ($Q = 7.0$, $p = .008$), dACC ($Q = 7.8$, $p = .005$), and MCC ($Q = 24.6$, $p < .001$). Thus, those with active drug addiction exhibited significantly lower activations in the right MFG, dACC, and MCC relative to those with behavioral addictions (Fig. S2).

In the analysis of publication bias, the Egger test of funnel plot asymmetry was not statistically significant for the MCC ($p = .35$, Fig. S3). The meta-regressions of sex, age, smoothing, scanner strength, and TR did not show any significant results for any of the variables.

3.4 Active stimulant vs. Active nicotine use

Within the active substance use cohort, we examined the subgroups of stimulant and nicotine users. Compared with healthy controls, stimulant users ($N = 11$ studies) showed reduced activation in the right MFG but increased activation in the right cuneus (Fig. 3A, Table 2). At a slightly lower cluster size threshold ($k = 93$), nicotine users ($N = 8$ studies) exhibited weaker activation in the dACC relative to healthy controls (Fig. 3B, Table 2).

For group comparisons, we extracted for each study the effect sizes for each of the regions defined from the two subgroup meta-analyses. Cochran's Q revealed significant between-group heterogeneity for the MFG ($Q = 15.4$, $p < .001$), cuneus ($Q = 13.3$, $p < .001$), and dACC ($Q = 10.1$, $p = .002$). Thus, those with active stimulant use exhibited significantly lower activations in the right MFG but greater activation in the cuneus and dACC relative to those with active nicotine use.

3.5 Impaired vs. non-impaired task performance in active drug addiction

Finally, we determined whether addicted individuals with active substance use exhibited differential changes in neural responses to inhibitory control based on their task performance. Relative to healthy controls, individuals with impairment ($N = 10$ studies) showed hypoactivation in the right MFG (Fig. 4A, Table 2). Those without impairment ($N = 14$ studies) demonstrated diminished activation in the bilateral dACC (Fig. 4B, Table 2).

For group comparisons, we extracted for each study the effect sizes for each of the regions defined from the two subgroup meta-analyses. Cochran's Q revealed significant between-group heterogeneity for the MFG ($Q = 20.3$, $p < .001$) and dACC ($Q = 15.6$, $p < .001$). Thus, individuals with impaired task performance demonstrated significantly lower activations in the MFG but higher dACC relative to those without impairment (Fig. 4C)

4. Discussion

In the present work, we conducted a meta-analysis to quantitatively characterize for the first time the functional changes associated with inhibitory control deficits in individuals with addiction, taking into account distinct clinical characteristics. First, those with active substance use exhibited decreased activations in the right MFG and left dACC. Further analyses of this cohort revealed that dACC deactivation was particularly pronounced in nicotine users whereas MFG hypoactivity was most evident in stimulant users and those

with impaired task performance. In contrast, no significant activation differences were observed in abstinent substance users relative to healthy controls, suggesting functional normalization. Those with behavioral addictions also exhibited distinct neural alterations, characterized by increased activation of the MCC. Taken together, the current work demonstrates that diminished recruitment of the prefrontal cortical network during response inhibition in active drug addiction was limited to the dACC and MFG. These findings clarify the inconsistencies in past studies and systematic reviews examining the neural substrates underlying loss of control over prepotent responses in addicted individuals. Finally, there is evidence for the potential recovery of brain functions following cessation of substance use, thus highlighting neural plasticity and the benefits of abstinence and clinical interventions.

4.1 Prefrontal cortical disengagement during response inhibition in active drug addiction

In line with various neurobiological models for the development and maintenance of drug addiction (Goldstein and Volkow, 2011; Kalivas and O'Brien, 2008; Verdejo-García and Bechara, 2009), we found robust evidence for the underperforming prefrontal system during response inhibition in addicted substance users. Our findings are corroborated by past animal research showing loss of inhibitory control after lesioning in the medial PFC (including the dACC) and dlPFC (including the MFG) (Jacobsen, 1936; Matsuzaka et al., 1992; Pribram et al., 1952). The relationship between impaired control and substance use was subsequently demonstrated as medial PFC lesions were found to accelerate cocaine self-administration (Weissenborn et al., 1997) and lead to drug seeking even in the absence of continued reinforcement (McGregor et al., 1996; Schenk et al., 1991). These findings suggest the integrity of these brain structures may be integral to the regulation of motivated behaviors. Similarly in humans, lesions in the dACC (Picton et al., 2007) and MFG (Pierrot-Deseilligny et al., 2003) have both been associated with deficient inhibitory control. In those with drug addiction, various measures of PFC functions including cerebral blood flow (Adinoff et al., 2003; Volkow et al., 1988), glutamate levels (Yücel et al., 2007), and dopaminergic activity (Volkow et al., 2009) have also been found to be significantly reduced. Taken together, both the neurobiological frameworks of addiction as well as clinical and preclinical evidence demonstrate support for hypofrontality as a core neural feature of addiction.

Findings of PFC hypofrontality raise the question how it affects the region's functional involvement in response inhibition and how it ultimately contributes to compulsive substance use. The involvement of the dACC and right MFG in response inhibition is widely acknowledged, evidenced by multiple meta-analyses reporting in healthy controls their enhanced activation during the SST (Swick et al., 2011), GNG (Simmonds et al., 2008), and Stroop (Laird et al., 2005) tasks. The distinct functional role of the dACC in inhibitory control likely involves conflict monitoring including response competition (Carter and van Veen, 2007) and error processing (Menon et al., 2001). The region, anatomically connected with both motor and limbic circuits (Paus, 2001), is thought to play a crucial role in shifting the focus of attention, strengthening top-down control, and selecting appropriate actions (Botvinick et al., 2004). Deficits in conflict monitoring have been associated with dACC hypoactivity, as measured by event related potentials, in those with cocaine (Sokhadze et al., 2008), heroin (Yang et al., 2009), and cannabis (Battisti et al., 2010) addiction. Failures to

detect conflicts and errors as well as to effectively assess response alternatives may hinder addicted individuals' ability to initiate corrective actions over harmful habitual tendencies.

In contrast, the MFG is broadly implicated in cognitive control, including working memory updating (Brunoni and Vanderhasselt, 2014), attentional control (Langner and Eickhoff, 2013), and motivation/emotion regulation (Kohn et al., 2014; Kouneiher et al., 2009). Diminished recruitment of the MFG likely weakens its top-down modulation on these processes, leading to deleterious consequences for goal-directed behaviors, including the escalation to and maintenance of addiction. In support, various investigation have showed decreased dlPFC resting-state functional connectivity (rsFC) with reward-related regions including the ventral striatum and orbitofrontal cortex in those with heroin (Ma et al., 2010), cocaine (Hu et al., 2015), and alcohol (Liu et al., 2019) addiction. Similarly, blunted dlPFC-insula rsFC was reported in dependent smokers (Bi et al., 2017) and opioid users (Upadhyay et al., 2010), indicating weakened PFC modulation on salience processing. Additionally, reduced dopamine receptor density in the MFG due to chronic drug exposure has been associated with attenuated regulation of dopamine release in the nucleus accumbens (Kalivas et al., 2005). As dopamine plays a contributory role in response inhibition, such attenuation likely has a negative impact on the inhibitory control processes in addicted individuals (Pattij et al., 2007). Thus, due to the diverse roles of the MFG in supporting response inhibition, its disengagement may reflect aberration in multiple aspects of inhibitory control, influencing the motivation and regulation of addictive behaviors.

While the mechanisms underlying PFC disengagement in addiction remain unclear, there is evidence for drug-induced neurotoxicity. Animal studies revealed long-lasting increases in oxidative stress, apoptosis, and decreases in energy consumption in the PFC after chronic drug exposure (Cunha-Oliveira et al., 2008). Human morphometric studies have reported decreased gray matter volume in the MFG and dACC in those with alcohol (Pfefferbaum et al., 1998; Rando et al., 2011), cocaine (Franklin et al., 2002; Matochik et al., 2003), nicotine (Fritz et al., 2014; Liao et al., 2012), and polysubstance (Kaag et al., 2018; Liu et al., 1998) dependence. Postmortem studies further confirmed neuronal degeneration in the PFC of individuals with alcohol (Harper and Kril, 1989; Kril et al., 1997), methamphetamine (Khoshsirat et al., 2020), cocaine (Hitri et al., 1994), and heroin (Büttner et al., 2000) dependence. These cellular and structural abnormalities may contribute to the diminished PFC engagement and poor self-control in drug addiction.

Another potential mechanism which may relate inhibition impairment to addiction is the effects of neuroadaptation. While substances of abuse produce their reinforcing effects primarily through actions in the basal ganglia (Pierce and Kumaresan, 2006), synaptic plasticity following chronic substance use is evident in the medial PFC. As the region receives rich dopaminergic and glutamatergic innervation (Jones and Bonci, 2005), acute administration of drugs such as cocaine increases extracellular dopamine levels (McFarland et al., 2003; Park et al., 2002) and glutamate release (Xi et al., 2002). However, repeated exposure reduces glutamatergic transmission, indicating neuroadaptations which likely play a role in heightened responses to drug cues and inhibitory control disruptions (Van den Oever et al., 2010). In support, a recent rodent study found evidence for both glutamate neuroadaptations to nicotine in mice and impaired behavioral flexibility in the set-shifting

task (Cole et al., 2020). The interpretation that neuronal plasticity may be associated with the prefrontal cortical disengagement during inhibitory control is also in alignment with our finding of recovery of PFC responses following abstinence.

It is striking that past systematic reviews of the neural alterations during response inhibition in addiction implicated a large number of brain structures including those involved in not only executive control but also saliency (e.g., insula, amygdala), motivation (e.g., striatum, orbitofrontal cortex), memory (e.g., hippocampus, parahippocampus), sensory (e.g., occipital cortex, temporal cortex), and motor processing (e.g., primary motor cortex, cerebellum) (Feil et al., 2010; Luijten et al., 2014; Zilverstand et al., 2018). As a result, dysfunctions in various pathways have been proposed to explain the neural basis of inhibitory control deficits in addiction. In clarifying these differing proposals, the current meta-analysis identified changes in substantially fewer regions, with most subgroup results pertaining to the MFG and dACC. The lack of evidence for consistent hypoactivation in other brain systems does not infer their negligible involvement. Rather, our findings offer the argument that the neuropathology underlying deficient response inhibition in drug addiction is characterized by both consistent hypofrontality in a few core regions as well as diverse abnormalities that are likely subject sample- and/or study design-specific.

4.2 Distinct neural alterations in behavioral addictions

Various theoretical models of emphasizing the process (Jacobs, 1986), appetitive (Orford, 2001), syndrome (Shaffer et al., 2004), components (Mark Griffiths, 2005), and treatment (Kim and Hodgins, 2018) aspects of addictive disorders consider inhibitory control deficits as a common feature across both behavioral and drug addictions. Despite behavioral evidence supporting this position (Argyriou et al., 2017; Grant and Chamberlain, 2014), recent imaging studies have not found consistent shared patterns of neural alterations during response inhibition between the two addiction types (Luijten et al., 2014). Factors including tolerance, withdrawal, and pharmacological effects, all of which can impact both the cognitive and brain processes underlying inhibitory control, are typical in drug addiction but either absent or inconsistently observed in behavioral addictions (King and Delfabbro, 2014; Morris and Voon, 2016). Results from the current work also do not align well with the notion of common brain dysfunctions. Distinct neural changes characterized by MCC hyperactivation in the behavioral addiction group and dACC/MFG hypoactivation in the drug addiction group suggest at least partially distinguishable neuropathological processes. Nevertheless, due to the low number of studies in the current analysis, this finding will need to be replicated.

Increased activation in the MCC during response inhibition in those with behavioral addictions indicates potential alterations in the brain substrates underlying motivated avoidance. The MCC is associated with complex motor functions including preparation, selection, and monitoring (Vogt, 2016). Due to the high density of dopaminergic afferents and dopamine-1 receptors in the region, it is thought that the MCC effects motor control via reward prediction (Shima and Tanji, 1998) and response to errors (Fiehler et al., 2004). Its connections with multiple regions important in motor (e.g., supplementary motor area), reward (e.g., basal ganglia), attention (e.g., supramarginal gyrus), and cognitive control (e.g.,

dlPFC) processing likely enable the integration of inputs to guide goal-directed behaviors (Touroutoglou et al., 2019). In both gambling and internet gaming addiction, motivational outcomes (e.g., wins or losses) are closely associated with motor processing. As such, the role of MCC in mediating the relationship between movement and reward/punishment may be especially heightened in behavioral addictions, resulting in its enhanced activation during response inhibition.

It is also plausible that MCC is more responsive to behavioral regulation associated with secondary rewards. Pathological gamblers are primarily motivated by monetary gains and the excitement derived from such gains (Goudriaan et al., 2004). Those who engage in excessive internet gaming typically do so to satisfy psychological needs for social acceptance, self-esteem, and autonomy (King and Delfabbro, 2014). Both monetary and social rewards are categorized as secondary whereas substances of abuse are typically considered primary reinforcers (Wheeler and Carelli, 2009). In an imaging meta-analysis of responses to rewards, MCC activation was found for monetary but not food or erotic rewards (Sescousse et al., 2013). Positive social reinforcement (Mathiak et al., 2010) and the monitoring of social outcomes (Apps et al., 2013) have also been reported to elicit MCC activation. Thus, hyperactivation of the MCC may be reflective of the bias for the motor system tuned to support actions in pursuit of secondary rewards.

4.3 Differential PFC deactivations across performance levels and substance classes

We found deactivation of the MFG both in those with impaired task performance and in stimulant use group. Given the MFG's significant role in inhibitory control (Banich and Depue, 2015; Chikazoe, 2010), our findings of its deactivation in those with impaired performance reveals a potential mechanism through which substance use disrupts cognitive functions. The MFG receives rich dopamine projections from the nucleus accumbens and ventral tegmental area, forming an important pathway regulating dopamine release (Del Arco and Mora, 2008). Dopamine signaling is critical for learning, motivation, and inhibitory control (Wise, 2004). Accordingly, dopamine receptor availability in the right human MFG has been shown to negatively correlate with stop-signal reaction time of the SST (Albrecht et al., 2014) whereas dopamine depletion in the non-human primate PFC impaired inhibition (Collins et al., 1998). Furthermore, dopaminergic manipulation via haloperidol, a dopamine D2/D3 receptor antagonist, elicited both right MFG deactivation and reduced no-go accuracy in smokers and non-smokers performing the GNG task (Luijten et al., 2013b). Chronic use of methamphetamine (Sekine et al., 2003), cocaine (Hitri et al., 1994), and alcohol (Narendran et al., 2014) has been associated with dopamine transporter loss and decreased dopamine transmission in the MFG. Thus, diminished MFG dopaminergic activity induced by drug addiction may contribute to response inhibition failure in addicted individuals.

It is worth noting that although there were several substance types in the 10 studies that reported impaired task performance, most ($N = 7$) involved stimulant use. Thus, MFG dysfunctions may be primarily driven by neural alterations in those with stimulant dependence. Indeed, our subgroup analysis confirmed this possibility. Such result is in agreement with past evidence of diminished frontal activations, specifically in the MFG,

in stimulant-dependent individuals performing various cognitive tasks including response inhibition (Aron and Paulus, 2007). Importantly, chronic stimulant use is associated with significant dopamine depletion, including reduction in both dopamine D2 receptors and in dopamine release, in the MFG (Volkow et al., 2009). This dopamine depletion likely disrupts the region's involvement in inhibitory control, resulting in poor task performance. Chronic stimulant use has also been linked with the MFG's lower gray matter volume (Ersche et al., 2013) which further predicted increased trait impulsivity (Moreno-López et al., 2012). It is plausible that MFG changes, coupled with heightened impulsivity, lead to the prevalence of control deficits observed in stimulant-dependent individuals. A past behavioral meta-analysis indeed reported the strongest effect of response inhibition impairment in this cohort in comparison with users of other substances (Smith et al., 2014). Thus, response inhibition impairments and PFC disengagement may specifically characterize the cognitive and neural vulnerability profile in stimulant dependence.

In contrast, those with active nicotine use exhibited lowered dACC activity during response inhibition. Several lines of evidence point to a significant role of the dACC in the development and maintenance of nicotine addiction. First, the dACC is particularly rich in nicotinic acetyl choline receptors (Picard et al., 2013) which are important in mediating the reward effects of nicotine and likely part of the neuronal mechanisms involved in nicotine addiction (Changeux, 2010). Furthermore, the α5 subunit gene of the receptors expressed in the dACC is associated with both risk for nicotine addiction and reduced dACC rsFC with the ventral striatum in smokers relative to non-smokers (Hong et al., 2010). As weakened dACC-ventral striatum rsFC is predictive of greater nicotine addiction severity (Hong et al., 2009), enhanced nicotine binding to the receptors likely contributes to the attenuated dACC top-down modulation on the reward-related ventral striatum, leading to difficulty in resisting smoking craving and urges. In support, dACC-ventral striatum rsFC has been found to increase in non-relapsing smokers whereas the opposite pattern was observed in relapsers (Sweitzer et al., 2016). Other studies have corroborated the regulatory role of the dACC in smoking addiction, showing that its activation to smoking cues increases with abstinence (McClernon et al., 2005) and positively predicts abstinence duration (Allenby et al., 2020). Thus, our finding of reduced dACC in dependent nicotine users during inhibitory control aligns well with past literature which implicates the region in the diminished control over addictive behaviors in smokers.

4.4 Possible normalization of brain functions in abstinence

In contrast with active substance users, abstinent individuals did not exhibit consistent prefrontal cortical disengagement, indicating potential recovery of the neural processes involved in inhibitory control. Previous studies have reported partial normalization of both structural and functional cerebral measures in addicted individuals following short-term abstinence. For instance, the PFC gray matter volume of alcoholics showed gains after two (van Eijk et al., 2013), three (Gazdzinski et al., 2005; Trabert et al., 1995), six (Bartsch et al., 2007), and eight (Cardenas et al., 2007) weeks of abstinence. Similar increases were observed in heroin (Hanlon et al., 2011) and cocaine (Wang et al., 2012) users following three and four weeks of abstinence, respectively. While the neuronal processes underlying such changes remain unknown, it is possible that dendritic spine density increases and

afferent axons arborize in the absence of drug use, leading to denser local connections (Hanlon et al., 2013). Increases in prefrontal cerebral blood flow and activity were also reported in abstinent dependent drinkers (Berglund et al., 1987; Dresler et al., 2012), cocaine users (Gottschalk et al., 2001), and chronic cannabis users (Sneider et al., 2008). Other mechanisms have been proposed to account for the recovery including reperfusion, remyelination, and reactive astrocytosis (Bartsch et al., 2007; Gazdzinski et al., 2005) though they remain to be validated. Moreover, both the right MFG and dACC have been found to be common neural targets for pharmacological and cognitive-based treatment in drug addiction (Konova et al., 2013), reinforcing the notion of their plasticity and recovery.

The rehabilitation of hypofrontality in abstinent individuals is of translational importance as PFC activation may serve as a neural index to monitor treatment effects (Spechler et al., 2016). In a longitudinal study examining a large sample of treatment-seeking cocaine-dependent users, reduced dACC response to errors during the SST was found to predict time to relapse (Luo et al., 2013). Hypoactivation of the right MFG in abstinent methamphetamine users performing a 2-choice prediction task was also associated with shorter time to relapse (Paulus et al., 2005). The relationship between enhanced activity of the executive control circuit and sustained abstinence demonstrates that normalized prefrontal cortical activity may underlie broad improvement in cognitive functioning. Indeed, behavioral studies have reported restoration of inhibitory control along with other functions including memory, attention, and cognitive processing speed in abstinent substance users (Hanson et al., 2010; Schulte et al., 2014; Tang et al., 2019). It is worth noting that among the 11 studies of abstinent individuals included in the current meta-analysis, five reported no significant group differences in brain activations and eight found comparable task performance levels between addicted and healthy subjects. Thus, the current findings suggest both neural and neuropsychological recovery following a minimum of 15-day cessation of drug use. As distinct substances likely exert different pharmacological effects on the brain, it remains to be seen whether or how the path to recovery differs between drugs of abuse. Further, the changes in neural responses to cognitive challenges may not follow a linear path (Li et al., 2010a), an additional issue to consider in future work.

5. Limitations and Conclusions

Several limitations of the current work should be noted. First, many studies did not include information on health status, particularly comorbidity of the participants. Comorbidity with other psychiatric conditions such as depression and anxiety may impact brain response to inhibitory control. Second, complete behavioral data were not available in some studies (despite our requests). Thus, analyses aimed at assessing behavioral impairments in addicted individuals were not possible. Nevertheless, previous meta-analyses of behavioral studies did indeed report poorer response inhibition in those with addiction relative to healthy controls (Argyriou et al., 2017; Smith et al., 2014). Finally, from the active substance use studies with complete behavioral results, we extracted the effect sizes from the group difference analyses. We next correlated the effect sizes with the dACC and MFG activation strength (data not shown) but did not find a significant relationship, likely due to the small sample size in our sub-group analyses. Thus, the current findings would need to be revisited when additional studies are available in the future.

In sum, our meta-analyses showed strong evidence for diminished recruitment of the dACC and MFG in addicted individuals with active substance use during response inhibition. Deactivations of the dACC and MFG were primarily driven by neural dysfunctions in nicotine users and stimulant users with impaired performance, respectively. In contrast, abstinent substance users did not exhibit significant activation differences whereas individuals with behavioral addictions showed increased MCC activation, both relative to healthy controls. These distinct patterns of findings across different cohorts of addicted individuals illustrate the importance of considering clinical characteristics involving diagnosis, substance use status, substance classes, and performance levels. The current work also clarifies suggestions from recent systematic reviews by showing that cerebral disengagement associated with inhibitory control deficits may be limited to a small number of core prefrontal cortical regions implicated in cognitive control. Finally, our finding of the amelioration of hypofrontality following abstinence not only highlights the plasticity of brain functions but also offers hope and potential guidance for the treatment of addiction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Individuals with active drug addiction showed lower dACC & MFG activation
- No differences were found for those in abstinence, suggesting functional recovery
- Those with behavioral addictions exhibited higher activation in midcingulate cortex
- Current results clarify discrepancies in recent systematic reviews

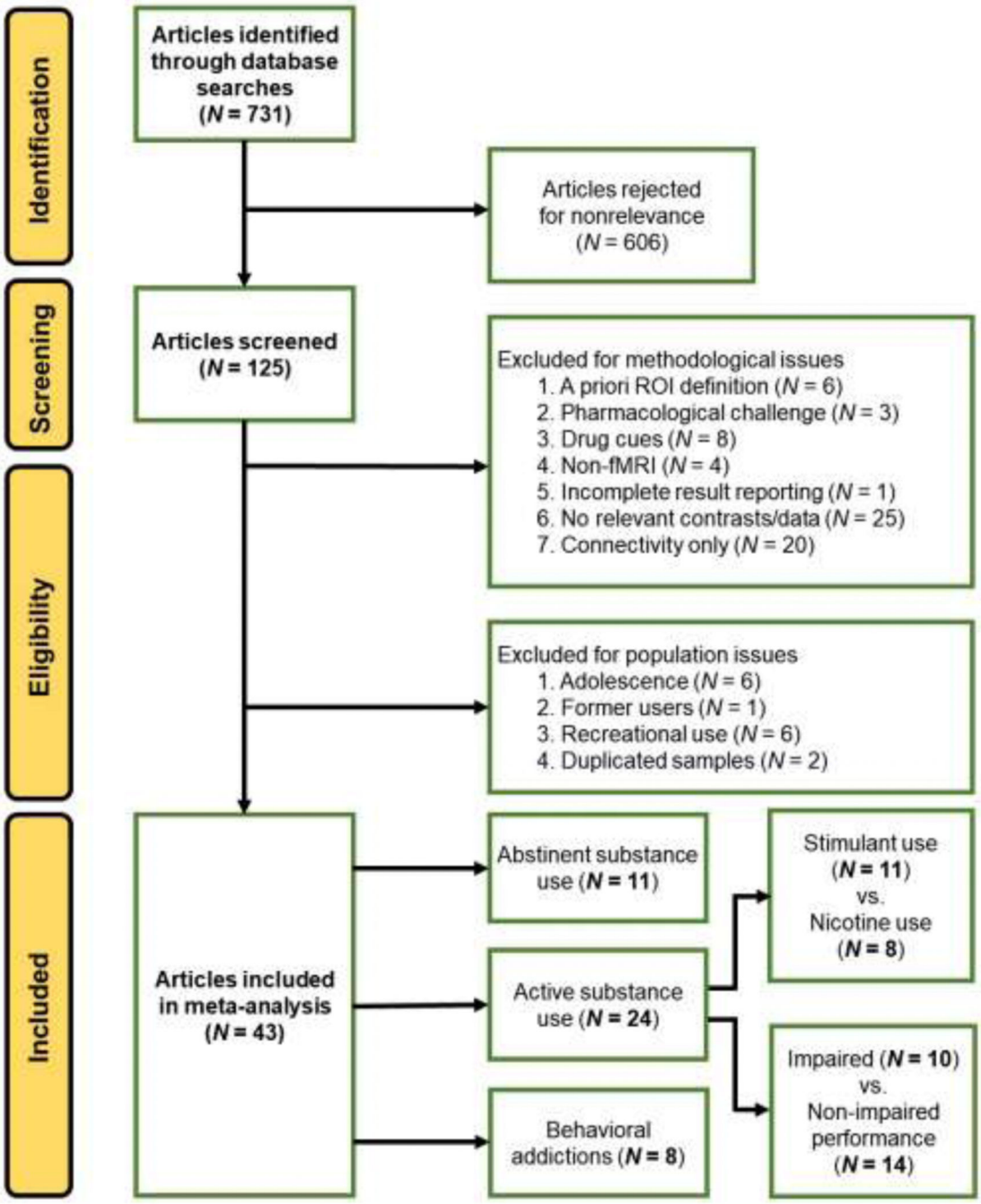

Figure 1:

PRISMA flow diagram. The search using Medline/PubMed, Web of Science, and Google Scholar databases identified 731 articles, 43 of which met inclusion criteria of the current meta-analysis.

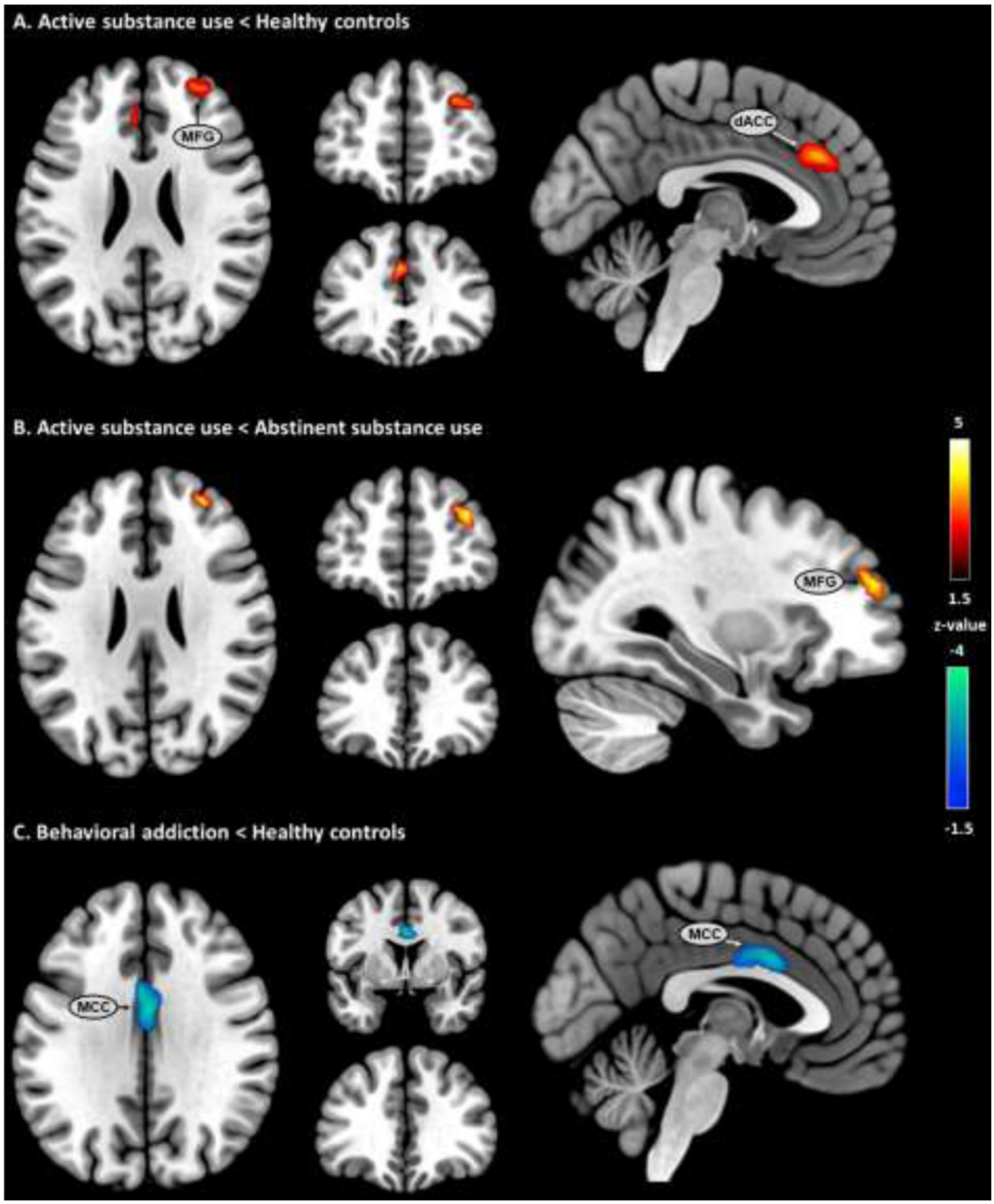

Figure 2:

Alterations of neural processes underlying response inhibition in addicted individuals with active substance use, abstinent substance use, and behavioral addictions. (**A**) Relative to healthy controls, those with active substance use demonstrated significantly lower activation in the left dorsal anterior cingulate cortex (dACC) and right middle frontal gyrus (MFG). (**B**) Relative to abstinent individuals, those with active substance use exhibited significantly lower activation in the right MFG. (**C**) Relative to healthy controls, individuals with

behavioral addictions showed greater activation in the midcingulate cortex (MCC)†. †Also significant at the more stringent voxel-level threshold of $p < .05$ FWE.

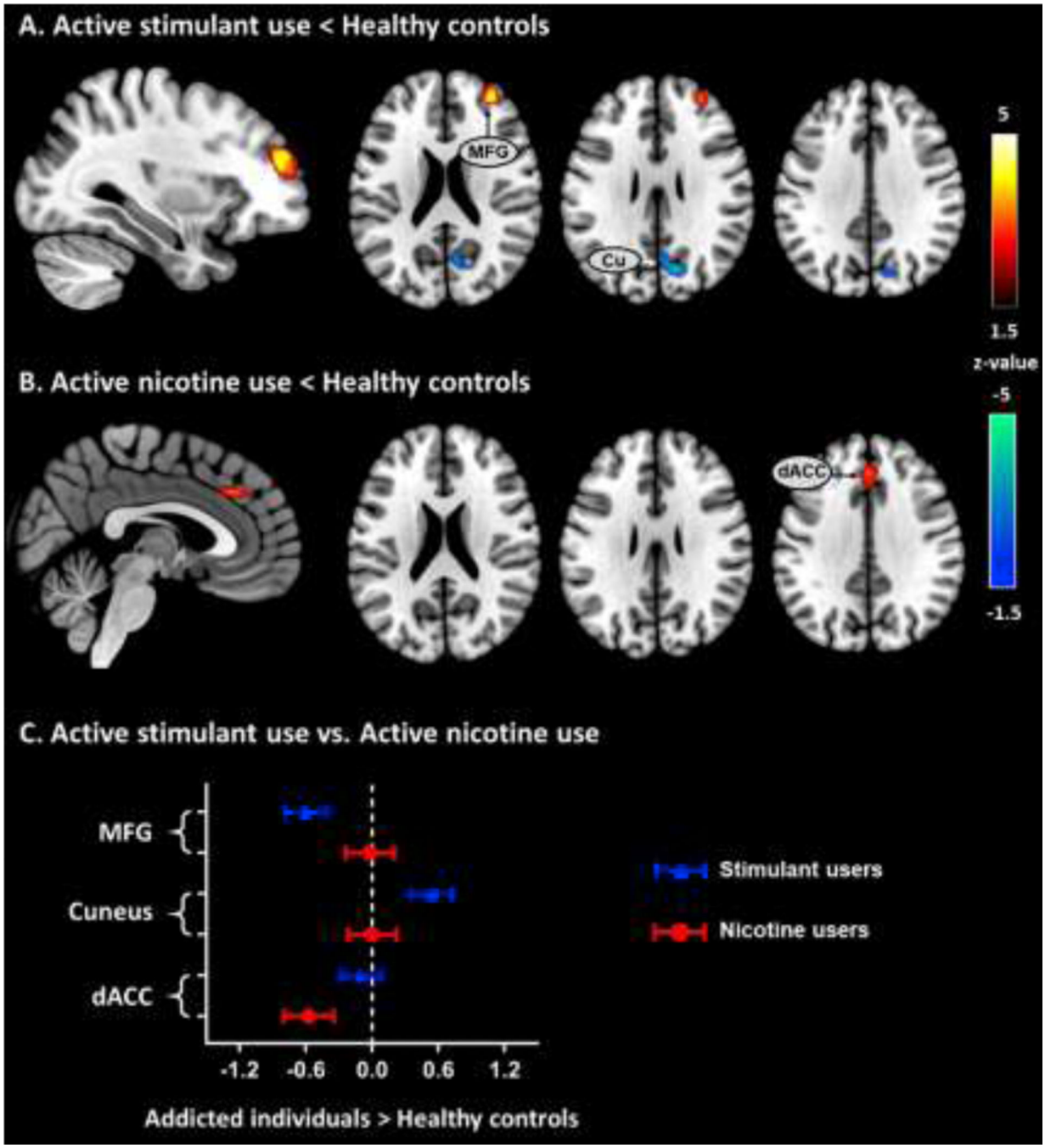

Figure 3:

Alterations of neural processes underlying response inhibition in individuals with active stimulant and nicotine use. (**A**) Relative to healthy controls, those with active stimulant use showed diminished activation in the right middle frontal gyrus (MFG) but elevated activation in the cuneus (Cu). (**B**) Relative to healthy controls, those with active nicotine use exhibited lower activation in the dorsal anterior cingulate cortex (dACC). (**C**) Group comparisons showed significantly lower right MFG but greater cuneus and dACC activation in individuals with active stimulant use relative to those with active nicotine use.

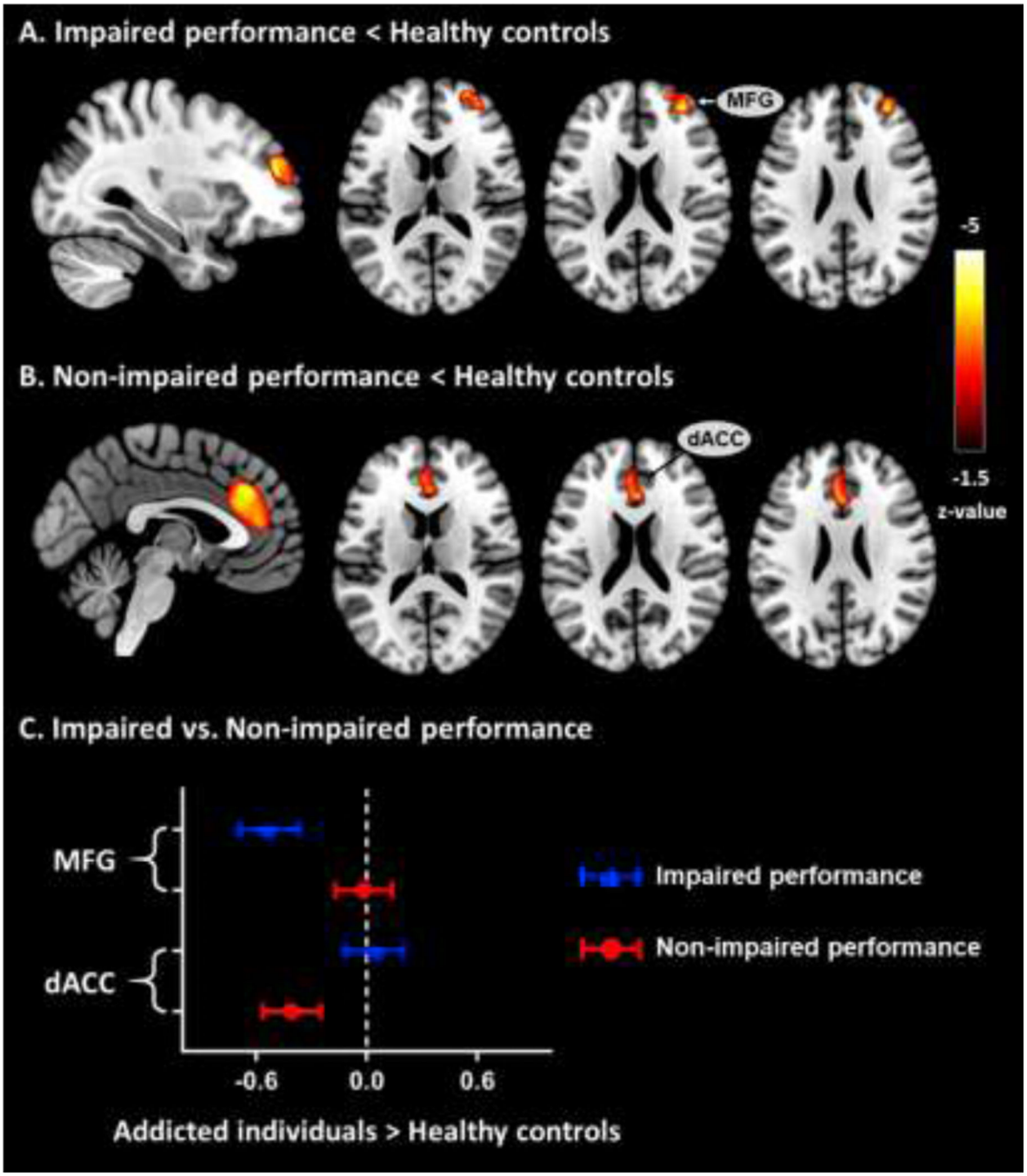

Figure 4:

Differential alterations in neural responses to inhibitory control in active substance use addicted individuals with vs. without task performance impairment. (**A**) Individuals with impairment demonstrated diminished activations in the right middle frontal gyrus (MFG). (**B**) Individuals without impairment showed reduced activation in the bilateral dorsal anterior cingulate cortex (dACC)†. (**C**) Group comparisons showed significantly lower right MFG but greater dACC activation in those with impaired relative to those with non-impaired

performance. †Also significant at the more stringent voxel-level threshold of $p < .05$ FWE.
** $p < .001$.

Table 1:

Study characteristics

Study	Task	Patients (N)	HC (N)	Mean age (years)	Male (%)	Status	Abstinence	Diagnosis	Task performance
Alcohol									
Ahmadi (2013)	GNG	36	56	18.9	59.7	Active	N/A	AB	Impaired
Czapla (2017)	GNG	19	21	46.6	85.0	Abstinent	3 weeks	DP	Non-impaired
Li (2009)	SST	24	24	37.1	75.0	Abstinent	> 2 weeks	DP	Non-impaired
Molnar (2018)	Stroop	14	17	24.7	41.9	Active	N/A	AB	Impaired
Schulte (2012)	Stroop	18	17	50.5	100.0	Abstinent	36.4 weeks	DP	Non-impaired
Sjoerds (2014)	SST	31	16	46.8	79.4	Abstinent	15 days	DP	Non-impaired
Taylor (2016)	GNG	27	57	44.1	77.8	Abstinent	20.8 weeks	DP	Non-impaired
Cannabis									
Hester (2009)	GNG	16	16	24.9	93.8	Active	38 hours	AB	Non-impaired
Kober (2014)	Stroop	20	20	28.0	100.0	Active	N/A	DP	Non-impaired
Stimulants									
Barros Loscertales (2011)	Stroop	16	16	34.3	100.0	Abstinent	> 2 days	DP	Non-impaired
Bell (2014a)	GNG	20	19	38.0	81.9	Abstinent	45 weeks	DP	Non-impaired
Bell (2014b)	GNG	27	45	38.0	81.9	Abstinent	32 weeks	DP	Non-impaired
Hester (2004)	GNG	15	15	35.5	53.3	Active	41 hours	AB	Impaired
Hester (2013)	GNG	15	15	40.5	86.7	Abstinent	48 weeks	DP	Impaired
Kaufman (2003)	GNG	13	14	33.5	33.3	Active	18–72 hours	AB	Impaired
Li (2008)	SST	15	15	37.2	100.0	Active	< 2 weeks	DP	Non-impaired
Li (2010)	SST	10	36	38.0	82.6	Active	1 week	DP	Non-impaired
Ma (2015)	GNG	13	10	36.3	82.6	Active	N/A	DP	Non-impaired
Moeller (2012)	Stroop	33	20	42.0	84.9	Active	N/A	DP/AB	Impaired
Moeller (2014)	Stroop	21	17	37.9	100.0	Active	N/A	AB	Impaired
Wang (2018)	SST	55	55	39.7	70.0	Active	< 2 weeks	DP	Impaired
Jan (2014)	Stroop	7	10	33.2	69.7	Active	N/A	DP	Impaired
Nestor (2011a)	Stroop	10	18	35.0	57.1	Active	< 1 week	DP	Impaired
Morein-Zamir (2013)	SST	32	41	33.8	76.7	Active	N/A	DP	Impaired
Smith (2013)	Stroop	42	47	33.3	76.1	Abstinent	N/A	DP	Impaired
Taylor (2016)	GNG	59	57	44.1	83.1	Abstinent	15.6 weeks	DP	Non-impaired
Nicotine									
Chaarani (2018)	SST	17	16	23.7	69.7	Active	24 hours	AB	Non-impaired
de Ruiter (2012)	SST	36	17	34.3	100.0	Active	N/A	AB	Non-impaired
Lesage (2020)	GNG	24	20	33.1	50.0	Active	12 hours	DP	Non-impaired
Luijten (2013a)	GNG	25	23	22.2	64.0	Active	> 4 hours	DP	Impaired
Luijten (2013b)	GNG	19	17	25.7	36.1	Active	> 1 hour	DP	Non-impaired
Nestor (2011b)	GNG	13	13	24.0	52.2	Active	N/A	DP	Non-impaired
Xu (2007)	Stroop	9	13	36.2	54.5	Active	N/A	DP	Non-impaired

Study	Task	Patients (N)	HC (N)	Mean age (years)	Male (%)	Status	Abstinence	Diagnosis	Task performance
Opiates									
Fu (2008)	GNG	30	18	31.5	100.0	Abstinent	8 weeks	DP	Impaired
Lee (2005)	GNG	11	10	29.3	100.0	Active	3–7 hours	DP	Impaired
Yucel (2007)	MSIT	24	24	29.7	54.2	Active	N/A	DP	Non-impaired
Gambling									
de Ruiter (2012)	SST	36	17	34.3	100.0	Active	N/A	DP	Non-impaired
Luijten (2015)	Stroop	18	16	21.1	100.0	Active	N/A	AB	Impaired
Potenza (2003)	Stroop	13	11	32.1	100.0	Active	N/A	DP	Non-impaired
van Holst (2012)	GNG	16	15	35.3	100.0	Abstinent	N/A	DP	Non-impaired
Internet gaming									
Chen (2015)	GNG	15	15	24.6	100.0	Active	N/A	AB	Non-impaired
Dong (2012)	Stroop	12	12	23.9	100.0	Active	N/A	AB	Non-impaired
Dong (2017)	Stroop	18	19	21.5	97.3	Active	N/A	AB	Impaired
Liu (2014)	GNG	11	11	23.0	100.0	Active	N/A	AB	Non-impaired

Abbreviations: AB – abuse, DP – dependence, GNG – go/no-go, MSIT – Multi-Source Interference Task, SST – stop signal task

Table2:

Meta-analysis results

		MNI coordinates (mm)			Voxel	Cluster
	Region	**x**	**y**	**z**	**z-stats**	**k**
Active substance use < HC	dACC	−2	32	32	−3.99	194
	Middle frontal gyrus	30	28	48	−4.16	102
Behavioral addictions < HC	Midcingulate cortex *	−2	6	32	4.03	283
Active < Abstinent substance use	Middle frontal gyrus	32	52	22	−3.69	114
Active stimulant use < HC	Cuneus	12	−74	28	4.39	238
	Middle frontal gyrus	32	50	18	−4.67	226
Active nicotine use < HC	dACC	2	30	36	−3.61	93
Active with impairment < HC	Middle frontal gyrus *	32	50	18	−4.49	325
Active without impairment < HC	dACC *	−2	30	32	−4.24	797

Abbreviations: dACC – dorsal anterior cingulate cortex, HC – healthy controls.

*significant at voxel-level p < .05, corrected for familywise error (FWE).