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Altered neural activities during response inhibition in adults with addiction: a voxel-wise meta-analysis

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Review Article

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Abstract

Background. Previous literature has extensively investigated the brain activity during response inhibition in adults with addiction. Inconsistent results including both hyper- and hypo-activities in the fronto-parietal network (FPN) and the ventral attention network (VAN) have been found in adults with addictions, compared with healthy controls (HCs).

Methods. Voxel-wise meta-analyses of abnormal task-evoked regional activity were conducted for adults with substance dependence (SD) and behavioral addiction during response inhibition tasks to solve previous inconsistencies. Twenty-three functional magnetic resonance imaging studies including 479 substance users, 38 individuals with behavioral addiction and 494 HCs were identified.

Results. Compared with HCs, all addictions showed hypo-activities in regions within FPN (inferior frontal gyrus and supramarginal gyrus) and VAN (inferior frontal gyrus, middle temporal gyrus, temporal pole and insula), and hyper-activities in the cerebellum during response inhibition. SD subgroup showed almost the same activity patterns, with an additional hypoactivation of the precentral gyrus, compared with HCs. Stronger activation of the cerebellum was associated with longer addiction duration for adults with SD. We could not conduct meta-analytic investigations into the behavioral addiction subgroup due to the small number of datasets.

Conclusion. This meta-analysis revealed altered activation of FPN, VAN and the cerebellum in adults with addiction during response inhibition tasks using non-addiction-related stimuli. Although FPN and VAN showed lower activity, the cerebellum exhibited stronger activity. These results may help to understand the neural pathology of response inhibition in addiction.

Introduction

Addiction is characterized by the obsession with addictive substances or behaviors despite harmful consequences, and the exclusion of other activities (Campbell, 2003). It can be broadly divided into two categories: substance dependence (SD) and behavioral addiction (American Psychiatric Association, 2013). SD is characterized by problematic substance use (e.g. alcohol, cannabis and cocaine), which results from repeated drug administrations and leads to physical disturbances when the substance is withdrawn (NIDA, 2019). Gaming disorder is one behavioral addiction classified as a medical illness in International Classification of Diseases (World Health Organization, 2019). It refers to the persistent involvement with video games and the inability to reduce or quit gaming. Addiction exerts serious negative impacts on people's physical health (Degenhardt et al., 2018; Evren, Evren, Dalbudak, Topcu, & Kutlu, 2020) and mental well-being (Evren et al., 2020; Kaptsis, King, Delfabbro, & Gradisar, 2016). A sound understanding of the corresponding pathophysiology is vital to develop effective interventions and treatments for addiction.

A significant body of research has revealed disturbances in response inhibition in SD (Brewer & Potenza, 2008; Zilverstand, Huang, Alia-Klein, & Goldstein, 2018) and behavioral addiction (Argyriou, Davison, & Lee, 2017; Moccia et al., 2017). Response inhibition is a core sub-process of cognitive control and is one of the more extensively studied components of cognitive control in healthy populations (Zhang, Geng, & Lee, 2017) and individuals with addiction (Smith, Mattick, Jamadar, & Iredale, 2014). Response inhibition refers to the ability to withhold a prepotent motor response (Chambers, Garavan, & Bellgrove, 2009; Nigg, 2000), and is often assessed using paradigms including the Go/No-go task, the stop-signal task and the Stroop task (Meule, 2017; Stahl et al., 2014; Verbruggen & Logan, 2008). A common process underlying these tasks is that participants are required to selectively respond to target stimuli while ignoring distracting stimuli. For example, in a Stroop task (Stroop, 1935), participants need to report the color a word is presented in while avoiding reading the color the word describes. In a Go/No-go task or a stop-signal task (Donders, 1969; Logan, 1994), participants are required to respond to certain stimuli (e.g. 'K') and suppress a response when other stimuli are presented (e.g. 'X'). For SD, it is hypothesized that chronic intake of

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drugs, stimulants in particular, may damage the dopaminergic prefrontal-subcortical pathways, which are crucial for successful behavioral inhibition (Smith et al., 2014). Meanwhile, deficits in response inhibition may predate or exacerbate substance use by making it difficult for people to abstain from drug administrations (Moeller, Bederson, Alia-Klein, & Goldstein, 2016). For behavioral addiction, impairments in response inhibition are often associated with poor self-regulation and high impulsivity (Argyriou et al., 2017), which may lead to problematic gaming. Considering the validated deficits in response inhibition in addiction, it is necessary to reveal the neural pathophysiology underlying impaired response inhibition.

In the past two decades, neuroimaging techniques, especially functional magnetic resonance imaging (fMRI), have been widely used to reveal the altered neural activity during response inhibition in individuals with addiction. The neural basis underlying intact response inhibition involves a wide range of brain regions. For example, the fronto-parietal network (FPN) and the ventral attention network (VAN) are two core neural systems in response inhibition (Zhang et al., 2017), which are crucial for attention, working memory and goal-directed response selections (Nee, Wager, & Jonides, 2007; Simmonds, Pekar, & Mostofsky, 2008). Meanwhile, communications among cortical and subcortical areas as well as the cerebellum were shown essential for successful inhibition (Rae, Hughes, Anderson, & Rowe, 2015). Luijten and colleagues (2014) reviewed and summarized results from various studies on the neural pathophysiology of impaired response inhibition in SD and they found an overall pattern of hypoactivities in the FPN and VAN in individuals with SD (see also Moeller *et al.* 2016; Morein-Zamir & Robbins, 2015; Zilverstand *et al.* 2018), especially in response to non-addiction-related stimuli (Zilverstand et al., 2018). For example, most studies found hypoactivities in the inferior frontal gyrus (IFG), anterior cingulate cortex and dorsolateral prefrontal cortex in individuals with SD during inhibitory control (Luijten et al., 2014). Others found hypoactivities in the occipital lobe (Li et al., 2008) and the insula (Fu et al., 2008). However, several researchers reported hyperactivations of regions within the FPN (Hester, Nestor, & Garavan, 2009) and VAN (Luijten et al., 2013). For behavioral addiction, there has not yet been a review summarizing the results on the neural abnormalities during response inhibition, but previous studies have reported mixed results. Some researchers observed greater activation in the FPN (e.g. Ding *et al.* 2014; Dong, DeVito, Du, & Cui, 2012) and the fronto-striatal pathway (Ko et al., 2014) in individuals with behavioral addiction during response inhibition while others reported lower activity of these regions (e.g. De Ruiter, Oosterlaan, Veltman, Van Den Brink, & Goudriaan, 2012; Wang *et al.* 2017). The inconsistencies between hypo- and hyper-activities in previous literature may be due to several factors. Abstinence or treatment status (e.g. Moeller et al., 2012), addiction duration (e.g. Claus, Feldstein Ewing, Filbey, and Hutchison, 2013) and the substance of abuse of individuals with SD may modulate response inhibition. The experimental tasks and stimuli (e.g. addiction-related *v.* addiction-unrelated stimuli) may also influence task performance and/or the corresponding neural activity in individuals with addiction (Luijten et al., 2014; Moeller et al., 2016).

Considering the inconsistencies in the altered neural activity during response inhibition in addiction, a quantitative meta-analysis is needed to unravel the conflicting results. This study aimed to use meta-analysis to reveal consistent neural alterations in response inhibition in adults with addiction. Because individuals with addiction are characterized with excessive use of addictive substances or engagement in behavioral addiction, which are behavioral manifestations of impaired response inhibition (Argyriou et al., 2017; Smith et al., 2014), we hypothesized that individuals with all addictions would show reduced activity in regions in the FPN and VAN, core neural systems for successful response inhibition. Additionally, because SD and behavioral addiction are likely distinct in nature, it is reasonable to expect different patterns of neural abnormalities between these two addiction subtypes.

Method

Study selection

We searched Scopus, PubMed and Web of Science for articles published in English before 15 November 2020, using the following terms and their derivatives: 'functional magnetic resonance imaging' OR 'fMRI'; AND 'addiction' OR 'drug use' OR 'drug addiction' OR 'substance addiction' OR 'substance dependence' OR 'cocaine' OR 'marijuana' OR 'cannabis' OR 'thc' OR 'methamphetamine' OR 'amphetamine' OR 'ecstasy' OR 'mdma' OR 'heroin' OR 'opiate' OR 'polysubstance' OR 'nicotine dependence' OR 'alcohol abuse' OR 'alcohol dependence' OR 'alcohol addiction' OR 'nicotine addiction' OR 'gambling' OR 'gamblers' OR 'gaming addiction' OR 'gaming disorder'; AND 'response inhibition' OR 'inhibitory control' OR 'interference resolution' OR 'action withholding' OR 'action cancellation' OR 'stop signal' OR 'go nogo' OR 'countermanding'. The reference lists of relevant review articles were also examined to include additional papers.

We included a study if it: (1) was published in English, in a peer-reviewed journal; (2) used fMRI; (3) compared neural activation between adult human healthy controls (HCs) and adult human participants with SD, gambling disorder or gaming disorder; (4) used tasks that required participants to inhibit prepotent responses and (5) conducted whole-brain analyses in the form of three-dimensional coordinates in standard stereotactic coordinate space (i.e. Talairach or Montreal Neurological Institute).

We excluded a study if it: (1) was conducted in non-human or non-adult participants; (2) included comorbid participants; (3) did not include a HCs group; (4) included occasional users (e.g. occasional smokers) for the addiction group and/or the control group; (5) used the same patient data as other included studies; (6) was a connectivity study or a diffusion tensor imaging study; (7) did not investigate task-based neural activation (e.g. resting-state fMRI study); (8) did not conduct comparisons between the addiction group and HCs and (9) only included ROI findings. Reviews and meta-analytic studies were also excluded.

Quality assessment of each study included was conducted with a 9-point checklist (online Supplementary Table S1). The current study was performed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000). See Fig. 1 for the PRISMA flow diagram on the study selection for this meta-analysis.

Data analysis

Voxel-wise meta-analysis

We used the signed differential mapping (SDM) software package (version 5.15 for Windows; http://www.sdmproject.com/software) to perform meta-analyses on the different neural activation patterns for people with addiction and HCs. The SDM method

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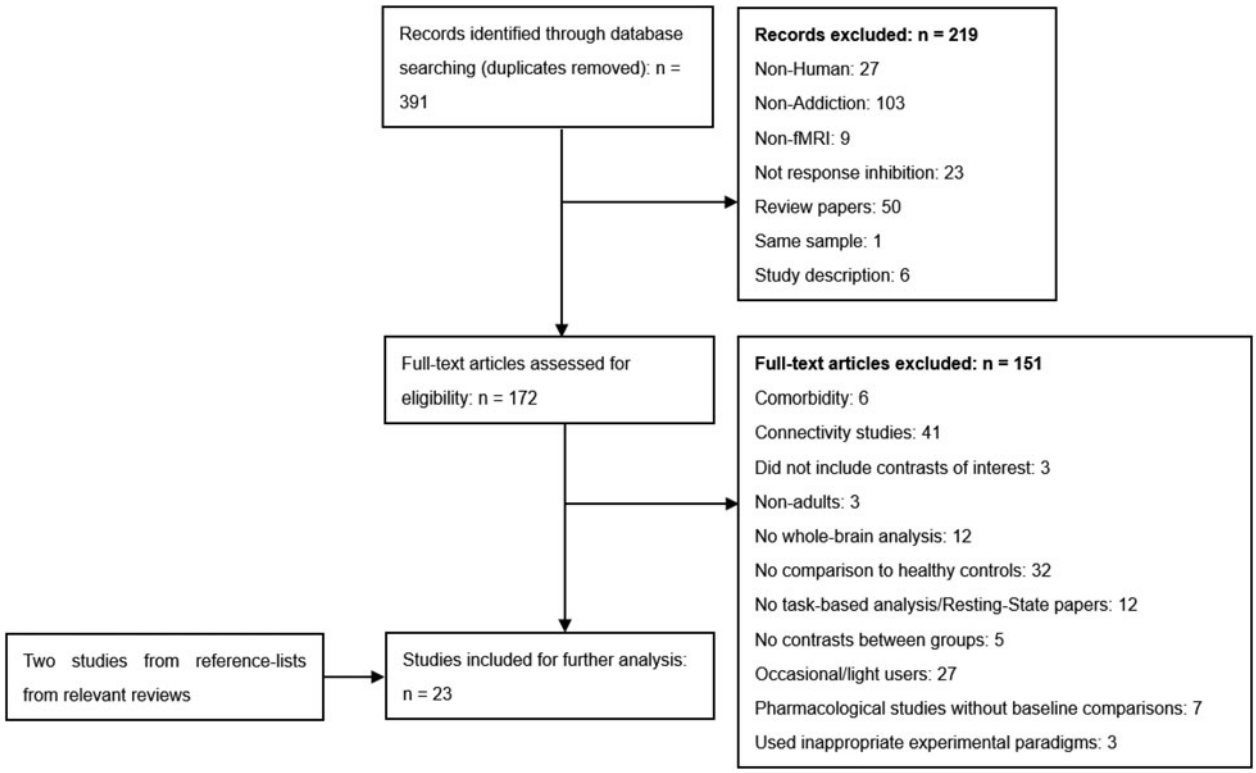

Fig. 1. PRISMA flow diagram of study selection.

allows the combination of statistical parametric maps and peak coordinates originally reported in individual studies (for reviews see Radua *et al.*, 2014b; Radua & Mataix-Cols, 2009). Briefly, we first extracted peak coordinates and effect sizes (i.e. *t* values) of different patterns of brain activity between addiction groups and HCs from each individual study. Note that *z* scores reported as effect sizes were converted to *t* values using an online converter (http://www.sdmproject.com/utilities/?show=Statistics). Second, a standard MNI map of the activation differences was re-created by applying an anisotropic Gaussian kernel for each included study. We used the anisotropic kernel in order to improve the plausibility of the maps by allocating different values to distinct voxels of a peak contingent on relevant spatial correlations and used an isotropic full-width at half-maximum = 20 mm for smoothing to control false-positive results (Radua et al., 2012, 2014b). Third, we applied a random-effects general linear model to create the mean map after accommodating the effect size maps. Consequently, the included studies were weighted differentially based on their sample sizes, and between-study heterogeneities and intra-study variances, amplifying the contributions of the studies with larger sample size or smaller variance (Radua & Mataix-Cols, 2012).

We conducted meta-analytic comparisons between all addictions and HCs, contrasting conditions where response inhibition was entailed or successful, to conditions where response inhibition was not needed or unsuccessful, from tasks including Stroop tasks, Go/No-go tasks and stop-signal tasks. Only contrasts using neutral or non-addiction-related stimuli were used (for more information, see online Supplementary materials). We calculated the differences between the two groups for each voxel and extracted the statistical significance results from a standard randomization test (Radua, van den Heuvel, Surguladze, & Mataix-Cols, 2010; Tang et al., 2018). The SDM kernel size and thresholds used in this meta-analysis were $p < 0.005$ with peak height $Z > 1$ and a cluster size of larger than 10 voxels, which have been validated to optimize sensitivity while correctly controlling false-positive rate in the empirical validation of SDM (Radua et al., 2012).

Jackknife sensitivity analysis

We assessed the replicability of the results by conducting a systematic whole-brain voxel-based jackknife sensitivity analysis. This was accomplished through the repetition of main statistical analysis while removing one study each time (Radua & Mataix-Cols, 2009).

Analyses of heterogeneity and publication bias

We performed a heterogeneity analysis with *Q* statistic maps to investigate between-study variability left unexplained (Radua & Mataix-Cols, 2012). Additionally, we performed the Egger's test to look for potential publication bias in these findings (Radua et al., 2014a).

Meta-regression analysis

Two meta-regressions were conducted, regressing the abnormal neural activity on addiction duration and abstinence days, respectively. To reduce spurious results, we used a more conservative threshold ($p < 0.0005$) and only considered clusters showing a significant slope in addition to a significant difference with HCs at one of the extremes (Radua & Mataix-Cols, 2009).

Additionally, we repeated all analyses above for the SD subgroup, but not for behavioral addiction subgroup due to limited number of studies.

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Table 1. Demographic and clinical characteristics of the dataset included in this meta-analysis

	Sample, *N*		Mean age ± standard deviation, years		Age range, years		Female, *N*						
Dataset	SDs	HCs	SDs	HCs	SDs	HCs	SDs	HCs	Addiction type	Mean use duration ± standard deviation, years	Onset use age ± standard deviation, years	Medication	Abstinence, days
Sample from SD subgroup													
Barrós-Loscertales et al. (2011)	16	16	34.4 ± 7.2	34.2 ± 8.9	NA	NA	0	0	Cocaine	13.9 ± 5.9	19.9 ± 6.3	No	3
Bell, Foxe, Ross, and Garavan (2014a)	27	45	37.8 ± 7.8	38.1 ± 10.6	NA	NA	3	10	Cocaine	8.2	NA	NA	226.10
Bell, Garavan, and Foxe (2014b)	19	18	47.8 ± 8.5	42.2 ± 12.1	NA	NA	0	0	Cocaine	NA	NA	NA	314.30
Czapla et al. (2017)	19	21	51.2 ± 7.4	42.0 ± 10.0	NA	NA	2	4	Alcohol	11.5 ± 8.5	NA	NA	19.16
Fu et al. (2008)	30	18	33.4 ± 6	29.6 ± 6.9	24–44	23–44	0	0	Heroin	6.3 ± 3.5	NA	No	53.48
Jan et al. (2014)	15	18	35.3 ± 7.0	31.1 ± 8.1	18–46	18–46	4	6	Methamphetamine	10.8	23.8	No	0
Kaufman et al. (2003)	13	14	37 ± 4.5	30 ± 8.7	27–44	19–45	5	10	Cocaine	11.2	NA	NA	0
Kober, DeVito, DeLeone, Carroll, and Potenza (2014)	20	20	26.7 ± 9.8	29.2 ± 10.1	NA	NA	0	0	Cannabis	12.4 ± 10.3	NA	No	0
Leland, Arce, Miller, and Paulus (2008)	19	19	40.4 ± 9.9	40.3 ± 8.1	24–54	26–56	2	3	Methamphetamine	17.4 ± 10.0	NA	NA	33.90
Li et al. (2008)	15	15	37.7 ± 6.8	36.6 ± 6.0	NA	NA	0	0	Cocaine	10.2 ± 7.3	NA	No	14
Li et al. (2009)	24	24	38.7 ± 8.3	35.5 ± 5.9	NA	NA	6	6	Alcohol	10.2 ± 7.3	NA	No	14
Livny et al. (2018)	15	15	27.0 ± 6.2	23.4 ± 5.7	18–43	18–41	0	0	Synthetic cannabinoids	5.3 ± 3.2	21.7 ± 6.0	No	31.50
Moeller et al. (2014a)	21	17	43.2 ± 6.5	32.6 ± 6.4	NA	NA	0	0	Cocaine	17.8 ± 7.3	NA	No	0
Moeller et al. (2014b)	33	20	43.5	39.6	NA	NA	5	2	Cocaine	14.3	26.7	NA	23
Morein-Zamir, Jones, Bullmore, Robbins, and Ersche (2013)	32	41	34.5 ± 7.8	31.7 ± 8.5	NA	NA	2	15	Stimulant	15.9 ± 6.7	16.6 ± 3	NA	0
Nestor et al. (2011a)	10	13	23.0 ± 1.0	23.6 ± 1.3	NA	NA	5	5	Cigarette	6.7 ± 1.2	NA	NA	0
Nestor, Ghahremani, Monterosso, and London (2011b)	10	18	33.5 ± 9.3	36.4 ± 10.4	20–46	20–55	5	7	Methamphetamine	8.3 ± 3.7	NA	No	5.50

Schulte, Müller-Oehring, Sullivan, and Pfefferbaum (2011)	18	17	51.0 ± 6.6	50.0 ± 14.9	NA	NA	0	0	Alcohol	NA	NA	No	257.70
Smith, Jones, Bullmore, Robbins, and Ersche (2013)	42	49	34.2 ± 7.4	32.6 ± 8.4	NA	NA	2	25	Stimulant	15.7 ± 6.4	16.5 ± 2.9	NA	0
Weywadt, Kiehl, and Claus (2017)	81	38	59	61	NA	NA	48	27	Cigarette	30.7	NA	NA	0.04
Sample from gaming subgroup													
Dong et al. (2012)	12	12	23.6 ± 3.5	24.2 ± 3.1	NA	NA	0	0	Gaming	NA	NA	No	0
Dong, Shen, Huang, and Du (2013)	15	15	23.8 ± 3.7	24.1 ± 3.3	NA	NA	0	0	Gaming	NA	NA	No	0
Liu et al. (2014)	11	11	23.5 ± 2.3	22.5 ± 1.7	NA	NA	0	0	Gaming	NA	NA	No	0

SD, substance dependence; HCs, healthy controls; NA, not available.

Results

The literature search yielded 391 publications in the databases. Based on our inclusion and exclusion criteria (see online Supplementary materials for a detailed description), 23 studies reporting 23 datasets were ultimately identified in the current meta-analysis, including 20 SD datasets (comprising 479 substance users and 456 matched HCs) and three gaming disorder datasets (comprising 38 gamers and 38 matched HCs). The demographic and clinical characteristics of the included studies are shown in Table 1. The quality score of each study and other information including experimental paradigms and image acquisition techniques are presented in the online Supplementary Tables S1–S3.

Consistent with our hypotheses, all addictions showed hypoactivity in regions within the FPN and VAN. Specifically, compared with HCs, all addictions showed hypoactivity in the right insula (BAs 38, 47, 48), right middle temporal gyrus (MTG; BAs 20, 21, 22), right temporal pole (BAs 20, 21, 38, 48), right IFG (orbital part, BAs 38, 47) and right supramarginal gyrus (BAs 2, 40, 48). Additionally, all addictions exhibited significant hyperactivities in the left cerebellum (hemispheric lobule VIIB). Detailed results are presented in Table 2 and Fig. 2*a*.

Similarly, the SD subgroup showed hypoactivity in the right insula (BAs 38, 47, 48), right middle temporal gyrus (BAs 20, 21, 22), right temporal pole (BAs 20, 21, 38), right IFG (orbital and opercular parts, BAs 38, 44, 47), right supramarginal gyrus (BAs 2, 40, 48) and right precentral gyrus (BAs 6, 44), compared with HCs. They also exhibited significant hyperactivities in the left cerebellum (hemispheric lobule VIIB). Detailed results are presented in Table 3 and Fig. 2*b*.

The findings on all addictions and SD group described above remained largely unchanged under the jackknife sensitivity analysis, indicating high robustness (Tables 2 and 3). For all addictions and the SD subgroup, the heterogeneity analysis showed non-significant results for all reported regions, indicating a non-significant unexplained between-study variability. The Egger's test showed no evidence of publication bias for most of the reported regions except for the left cerebellum ($p = 0.010$ for all addictions; $p = 0.012$ for the SD subgroup). Detailed results are summarized in Tables 2 and 3.

Finally, the meta-regression analysis revealed that individuals with longer SD duration (available in 18 SD datasets) showed enhanced abnormal activity in the left cerebellum ($x = -16$, $y = -78$, $z = -38$, $Z = 3.744$, $p < 0.0005$, 154 voxels). However, abstinence days were not associated with any change in the neural activity patterns.

Discussion

The current meta-analysis revealed several patterns of altered brain activations for adults with addiction during response inhibition. We found that all addictions showed reduced brain activity in the IFG, MTG, temporal pole, insula and supramarginal gyrus, and enhanced brain activity in the cerebellum, compared with HCs. The SD subgroup showed almost the same patterns, with additional hypoactivity observed in the precentral gyrus. A meta-regression analysis showed that longer addiction duration was related to stronger activity in the cerebellum for SD subgroup.

Consistent with our hypothesis, we observed lower activation of regions within the VAN (IFG, insula, MTG and temporal pole) during response inhibition for adults with addiction,

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Table 2. Meta-analysis results regarding regional differences of task-evoked activation between participants with all addictions and HCs during response inhibition

Local maximum				Cluster		Egger's test (p value)	Jackknife sensitivity	Heterogeneity
Region	Peak MNI coordinates (x, y, z)	SDM-Z value	p value	No. of voxels	Breakdown (no. of voxels)			
All addictions > HCs								
L cerebellum, hemispheric lobule VIIB	−14, −76, −42	1.097	2.23×10^{-3}	367	L cerebellum, crus II (169) L cerebellum, hemispheric lobule VIIB (111) L cerebellum, hemispheric lobule VIII (55)	0.010	22/23	No
All addictions < HCs								
R insula, BA 47	38, 18, −6	−1.938	∼0	1739	R insula, BA 47 (227) R temporal pole, superior temporal gyrus, BA 38 (207) R insula, BA 48 (183) R inferior network, inferior longitudinal fasciculus (129) R temporal pole, superior temporal gyrus (71) R insula, BA 38 (69) R inferior network, inferior fronto-occipital fasciculus (64) R middle temporal gyrus, BA 21 (56) R inferior frontal gyrus, orbital part, BA 38 (53) R inferior frontal gyrus, orbital part, BA 47 (45) R lenticular nucleus, putamen, BA 48 (39) R temporal pole, middle temporal gyrus, BA 21 (36) R inferior network, uncinate fasciculus (31) R temporal pole, superior temporal gyrus, BA 21 (28) R insula (28) R temporal pole, middle temporal gyrus, BA 20 (23) R inferior frontal gyrus, orbital part (20) R temporal pole, superior temporal gyrus, BA 20 (18) R amygdala, BA 36 (18) R frontal orbito-polar tract (13) R temporal pole, middle temporal gyrus, BA 38 (12) R temporal pole, superior temporal gyrus, BA 48 (11) R middle temporal gyrus, BA 20 (11)	0.781	22/23	No

R supramarginal gyrus, BA 40	52, −38, 34	−1.326	8.26×10^{-4}	251	R supramarginal gyrus, BA 40 (121) R supramarginal gyrus, BA 48 (55) R superior longitudinal fasciculus III (44) R supramarginal gyrus, BA 2 (23)	0.119	21/23	No
R middle temporal gyrus, BA 21	58, −48, 4	−1.271	1.18×10^{-3}	179	R middle temporal gyrus, BA 21 (87) R middle temporal gyrus, BA 22 (69) R arcuate network, posterior segment (20)	0.431	21/23	No
L middle frontal gyrus, BA 44	−50, 18, 38	−1.098	3.27×10^{-3}	14		0.745	20/23	No

HCs, healthy controls; BA, Brodmann area; R, right; L, left.

compared with HCs (Fig. 2*a* and Table 2). VAN is specialized for the detection of unexpected yet behaviorally relevant information and for response reorientation based on goals and conflicts (Nee et al., 2007; Vossel, Geng, & Fink, 2014). Specifically, in healthy populations, IFG and insula are activated in response to unexpected and infrequent stimuli (Shulman et al., 2009) and during suppression of pre-potent actions (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003). Additionally, the temporal pole and the insula were found to engage in action planning and selection (Kircher, Brammer, Levelt, Bartels, & McGuire, 2004; Paulus, Feinstein, Leland, & Simmons, 2005). Our results were consistent with previous literature that reported attenuated VAN activity in individuals with addiction (e.g. Fu et al. 2008; Hendrick, Luo, Zhang, & Li, 2012; Nestor, McCabe, Jones, Clancy, & Garavan, 2011). The attention of adults with addiction may be automatically oriented to some salient stimuli (e.g. drugs and internet games) even though they do not voluntarily intend so. The observed hypoactivities in this network may also indicate that adults with addiction were less efficient at putting a brake to their actions, even in the presence of a stop signal (i.e. action cancelation; Schachar et al., 2007). This might be one of the reasons why it is rather difficult for people with addiction to abstain from addictive behaviors. Additionally, VAN is often considered to be involved in stimulus-driven or involuntary attention (Asplund, Todd, Snyder, & Marois, 2010). For individuals with SD in particular, the bottom-up attentional processes were likely associated with continuing substance exposure (Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009; Smith et al., 2014). Importantly, according to the impaired response inhibition and salience attribution model (iRISA; Goldstein & Volkow, 2011; Zilverstand *et al.* 2018), individuals with addiction tend to show a blunted response to non-addiction-related stimuli during diverse cognitive processing including reward processing and inhibitory control. The recruitment of related networks is, however, strengthened during the processing of addiction-related stimuli. Because the stimuli in the included studies were all neutral or non-addiction stimuli (e.g. alphabetical letters), the reduced VAN activity may indicate an impaired bottom-up processing of non-addiction-related stimuli as VAN is perhaps frequently and excessively activated in response to addiction-related cues, for individuals with addiction.

In our study, we also observed hypoactivation of the FPN (i.e. orbital part of IFG and supramarginal gyrus) in adults with addiction, compared with HCs (Fig. 2*a* and Table 2). FPN is another important network involved in response inhibition in healthy populations (Zhang et al., 2017). FPN is associated with goal-directed behaviors as well as the integration of bottom-up inputs and top-down information (Dodds, Morein-Zamir, & Robbins, 2011; Marek & Dosenbach, 2018). IFG, specifically, seems to support context monitoring by modulating the activation of parietal cortices based on task demand (Hampshire & Sharp, 2015). The attenuated FPN activity observed in our study were consistent with previous research on response inhibition in individuals with addiction (e.g. Fu *et al.* 2008; Kaufman, Ross, Stein, & Garavan, 2003; Li, Luo, Yan, Bergquist, & Sinha, 2009). Lower activation of the FPN may reflect diminished top-down activity and weakened integration of information from different neural resources, which may lead to less effective control initiation (e.g. action withholding; Marek & Dosenbach, 2018) and task adaptation (e.g. action cancelation; Zhang et al., 2017). Specifically, compared with HCs, adults with addiction may be less well at withholding responses to an inhibited stimulus (i.e. 'no-go') while they were asked to quickly respond to another

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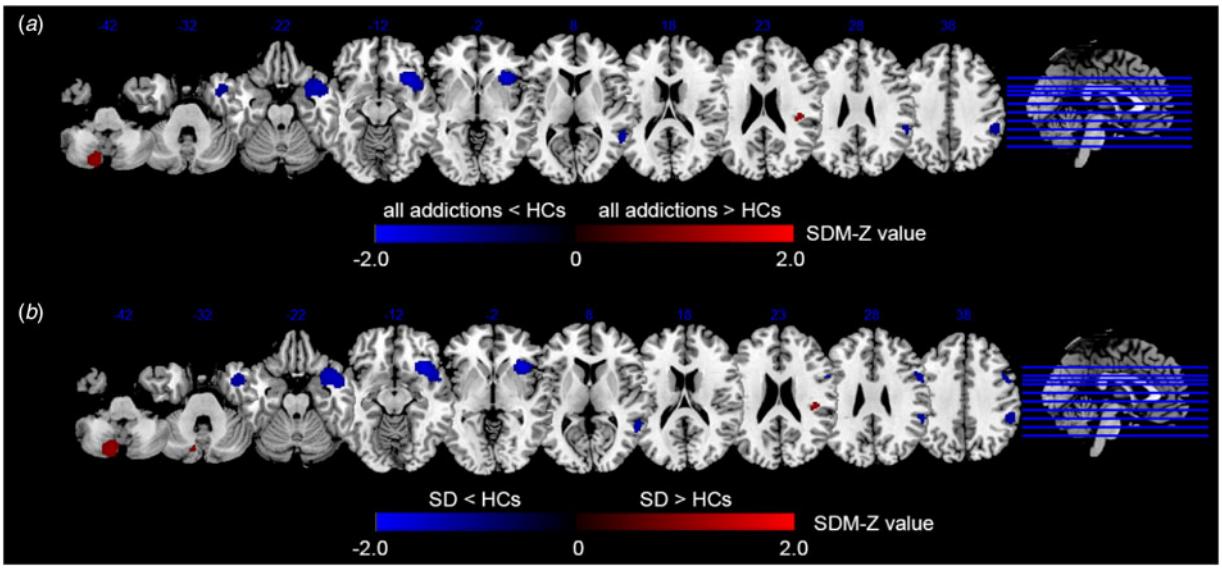

Fig. 2. Meta-analyses results regarding regional differences of task-evoked activation between (*a*) all addictions and HCs during response inhibition, (*b*) SD subgroup and HCs during response inhibition. Areas with hypo-activity are displayed in blue, and areas with hyper-activity are displayed in red. The color bar indicates the maximum and minimum SDM-*Z* values. HCs, healthy controls; SD, substance dependence; SDM, signed differential mapping.

stimulus (i.e. 'go'). Perhaps, individuals with addiction were less efficient at voluntarily regulating their actions. This may explain why individuals with addiction tend to increase engagement in addictive behaviors overtime (Jazaeri & Habil, 2012; Miller, Dackis, & Gold, 1987) and relapse after treatment (Azevedo & Mammis, 2018; Brecht & Herbeck, 2014). Supporting this, previous research reported more pronounced disruptions in response inhibition in abstinent individuals who experienced strong urge to take drugs, which may later lead to relapse (Verdejo-García et al., 2012).

It should be noted that we observed hypoactivation of VAN and FPN, two large-scale networks, rather than any specific module in the brain. Our results may be seen as new evidence for the network perspective on response inhibition (Hampshire & Sharp, 2015). According to this perspective, response inhibition is one component of the broader cognitive control processes and is therefore supported by common networks underlying a wide range of cognitive processes. For example, FPN was found to show altered activity in individuals with cocaine addiction during reward processing (Costumero et al., 2017) and implicit moral processing (Caldwell et al., 2015). The overall hypoactivation of the FPN and VAN can also be explained by the iRISA (Goldstein & Volkow, 2011; Zilverstand et al., 2018). As explained earlier, the attenuation of large-scale neural networks (i.e. FPN and VAN) during non-addiction-related processing in individuals with addiction may function as a compensation for the increased recruitment of these networks during addiction-related processing, maintaining the functional stability of these networks. Supporting this, Czapla et al. (2017) found that alcohol-dependent individuals showed enhanced activity of FPN during response inhibition to alcohol stimuli (i.e. pictures of alcoholic beverages), compared with HCs. However, they showed reduced FPN activity when the stimuli were non-addiction-related (i.e. geometrical shapes). The iRISA explanation nevertheless remains speculative because we did not investigate brain activity in individuals with addiction during addiction-related response inhibition. Future research can aim to examine brain activity during response inhibition using stimuli with different nature (i.e. non-addiction-related and addiction-related) in individuals with addiction.

We also observed hyperactivation of the cerebellum during response inhibition in adults with addiction, compared with HCs (Fig. 2*a* and Table 2). This is consistent with previous research where cerebellar activity was strengthened in individuals with cocaine addiction during response inhibition (Hester & Garavan, 2004) and in individuals with alcohol addiction during a working memory task (Desmond et al., 2003). The cerebellum has been validated to regulate voluntary actions over cortical pathways (Brunamonti et al., 2014). Our result of the hyperactivity of the cerebellum, as also suggested by previous research (Desmond et al., 2003; Hester & Garavan, 2004), may constitute a compensatory mechanism to the attenuated activation of other brain regions (i.e. FPN and VAN) in order to successfully perform a task of high demand (i.e. response inhibition) for individuals with addiction. Perhaps, in order to reach a similar level of task performance in healthy participants, individuals with addiction over-relied on the cerebellum when regions specialized for response inhibition could not be properly activated. Furthermore, the compensatory functions of cerebellum may not be restricted to motor aspects. Several researchers have suggested that cerebellum is a modulator in several neural networks that are altered in individuals with addiction (Miquel et al., 2016; Moulton, Elman, Becerra, Goldstein, & Borsook, 2014).

In addition, a meta-regression analysis revealed that, longer addiction duration was associated with stronger activity in the cerebellum in individuals with SD. This may be a result of overreliance on the cerebellum as a compensatory mechanism overtime in individuals with SD. Those with longer addiction duration may have more experience with activating the cerebellum to inhibit an action optimally. In other words, the brain of an individual with long-time addiction may have a more well-developed and strategic compensatory mechanism during response inhibition, compared with that of a person who has a shorter addiction duration. This is likely because, for an individual who only recently becomes addicted to substance, the activities in FPN and VAN may be

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Table 3. Meta-analysis results regarding regional differences of task-evoked activation between participants with SD subgroup and HCs during response inhibition

Local maximum				Cluster				
Region	Peak MNI coordinates (*x*, *y*, *z*)	SDM-*Z* value	*p* value	No. of voxels	Breakdown (no. of voxels)	Egger's test (*p* value)	Jackknife sensitivity	Heterogeneity
SD subgroup > HCs								
L cerebellum, hemispheric lobule VIIB	−14, −76, −42	1.143	1.49×10^{-3}	499	L cerebellum, crus II (215) L cerebellum, hemispheric lobule VIIB (130) L cerebellum, hemispheric lobule VIII (95)	0.012	19/20	No
SD subgroup < HCs								
R insula, BA 47	34, 20, −4	−1.940	∼0	1876	R insula, BA 47 (226) R temporal pole, superior temporal gyrus, BA 38 (210) R insula, BA 48 (181) R inferior network, inferior longitudinal fasciculus (162) R middle temporal gyrus, BA 21 (123) R temporal pole, superior temporal gyrus (72) R insula, BA 38 (68) R inferior network, inferior fronto-occipital fasciculus (64) R inferior frontal gyrus, orbital part, BA 38 (53) R inferior frontal gyrus, orbital part, BA 47 (45) R temporal pole, middle temporal gyrus, BA 21 (45) R lenticular nucleus, putamen, BA 48 (38) R inferior network, uncinate fasciculus (31) R temporal pole, superior temporal gyrus, BA 21 (29) R insula (28) R temporal pole, middle temporal gyrus, BA 20 (27) R inferior frontal gyrus, orbital part (20) R middle temporal gyrus, BA 20 (20) R temporal pole, superior temporal gyrus, BA 20 (18) R amygdala, BA 36 (16) R frontal orbito-polar tract (13) R temporal pole, superior temporal gyrus, BA 48 (12) R temporal pole, middle temporal gyrus, BA 38 (11) R superior temporal gyrus, BA 21 (11)	0.672	19/20	No

(*Continued*)

Table 3. (*Continued.*)

Local maximum			Cluster			Egger's test (p value)	Jackknife sensitivity	Heterogeneity
Region	Peak MNI coordinates (x, y, z)	SDM-Z value	p value	No. of voxels	Breakdown (no. of voxels)			
R supramarginal gyrus, BA 40	52, −38, 34	−1.376	8.93×10^{-4}	252	R supramarginal gyrus, BA 40 (121) R supramarginal gyrus, BA 48 (53) R superior longitudinal fasciculus III (45) R supramarginal gyrus, BA 2 (23)	0.075	18/20	No
R precentral gyrus, BA 44	50, 8, 34	−1.337	1.17×10^{-3}	212	R precentral gyrus, BA 6 (88) R precentral gyrus, BA 44 (42) R inferior frontal gyrus, opercular part, BA 44 (42)	0.479	17/20	No
R middle temporal gyrus, BA 21	58, −48, 4	−1.322	1.27×10^{-3}	181	R middle temporal gyrus, BA 21 (87) R middle temporal gyrus, BA 22 (71) R arcuate network, posterior segment (20)	0.303	18/20	No
L middle frontal gyrus, BA 44	−50, 18, 38	−1.144	3.26×10^{-3}	14		0.615	18/20	No

SD, substance dependence; HCs, healthy controls; BA, Brodmann area; R, right; L, left.

less impaired by substance intake than someone with longer addiction history and correspondingly more substance exposure. Consequently, those with shorter addiction duration may be able to, at least partially, activate response inhibition networks, easing the need of cerebellum activation as a compensation.

Furthermore, compared with HCs, the SD subgroup exhibited hypoactivity of the precentral gyrus, in addition to the above-reported activation patterns in all addictions (Fig. 2*b* and Table 3). This was consistent with previous research that found a negative association of substance use with the activation of the precentral gyrus (Ye et al., 2018). This region has been considered as an inhibitory motor region, controlling voluntary movements, and is activated in response inhibition tasks in healthy people (e.g. Criaud & Boulinguez, 2013). The weaker activation of the precentral gyrus may suggest that individuals with SD had deficits in planning and executing an appropriate action, compared with HCs. Interestingly, most of the studies reported decreased precentral signaling in individuals with SD in the absence of behavioral deficits at task, compared with HCs. Perhaps, impairments in response inhibition are not easily and consistently observed at the behavioral level with the experimental paradigms, especially considering the heterogeneity of tasks used across studies and the variability of behavioral indices reported for even a single paradigm (Meule, 2017). It is also worth mentioning that the hypoactivity of the precentral gyrus was not observed in all addictions. Perhaps, the activation of the precentral gyrus and correspondingly action planning and execution were somewhat preserved, if not enhanced, in individuals with behavioral addiction. Indeed, hyperactivity of this region and the cingulate cortex (e.g. Dong et al., 2012), another region often showing hypoactivity in SD, was reported in individuals with internet gaming disorder during response inhibition and was interpreted as a result of gaming skill acquisition (Ding et al., 2014).

There were some limitations in this study. First, due to the small number of studies on behavioral addiction (three), we could not investigate the impaired brain activity in response inhibition for this subgroup. Consequently, we were not able to compare and contrast the brain activity patterns between SD and behavioral addiction subgroup meta-analytically. Future research should gain more insights into response inhibition in behavioral addiction. Second, there are likely subtle differences in the neural abnormality associated with different substances of abuse (e.g. stimulants and depressants). For example, four out of six included studies on depressants (e.g. alcohol) showed hypoactivity of the response inhibition network whereas the results from studies on stimulants (14 studies) were mixed. Again, due to the limited number of included studies, we could not investigate the potential differences across various substance at a meta-analytic level. Further investigations are needed to detect the effects of different substance categories. Similarly, we did not conduct separate meta-analyses based on the types of experimental tasks due to the limited number of studies for each task type. The heterogeneity of tasks may modulate the activation patterns as some tasks may involve subtly different cognitive components, compared with others (Fineberg et al., 2014). It is also difficult to discern the extent to which task difficulty levels or cognitive demands modulate the results. Future research on response inhibition should aim to detect potential effects of task heterogeneity on neural activity. Fourth, because we could not obtain the unthresholded activation maps from the included studies, and that there was a substantial variability in the thresholding and correction methods across studies (see online Supplementary Table S3), we did not supplement

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our analyses with a meta-analysis on unthresholded activation maps, or using a common thresholding or correction technique. It would be desirable if future research can develop and/or follow a standard reporting guideline and make accessible most of their research data for potential reuse purposes. Furthermore, the current study sample limited the ability to investigate potential impacts of reward contingencies on neural abnormalities during response inhibition in addiction. It would be interesting for future research to investigate whether and how reward contingencies modulate neural activity during response inhibition tasks for individuals with addiction. Finally, we only included data from adults with addiction in this meta-analysis. This was because the neural networks for response inhibition in adolescents are rather immature, compared with adults (Vara, Pang, Vidal, Anagnostou, & Taylor, 2014). And adolescents undergo developmental changes in brain regions related to response inhibition both structurally and functionally (e.g. Van Leijenhorst et al., 2010). Whether and how these changes may affect adolescents' susceptibility to addictive behaviors is yet unclear. On these grounds, we only investigated adults with addiction in our meta-analysis.

Conclusion

This meta-analysis revealed reduced brain activity in the IFG, MTG, temporal pole, insula and supramarginal gyrus, and enhanced brain activity in the cerebellum during response inhibition in all addictions, compared with HCs. The SD subgroup showed additional hypoactivity in the precentral gyrus. The reduced brain activity in the VAN and FPN implicated altered attention to and inhibitory control for non-addiction-related stimuli during response inhibition tasks for adults with addiction, which may account for their repeated addictive behaviors. Additionally, the enhanced brain activity in the cerebellum may act as a compensatory mechanism to maintain the functional stability of an addicted brain. These results may help to understand the pathology of impaired response inhibition in adults with addiction.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291721000362

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Conflict of interest. The authors declare that they have no conflict of interests.

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