Neural Substrates of Working Memory in Addiction: Meta-analysis of fMRI studies

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Abstract

Addiction is a multifarious brain disease characterised by poor self-regulatory behaviour. Working memory, the capacity to monitor information in pursuit of long-term goals, is compromised by, and is believed to contribute to, substance abuse. Functional brain imaging offers the opportunity to examine the neurological substrates underlying the impaired cognitive functions observed in substance use disorder. Many neuroimaging studies of working memory report inefficient neural patterns in substance addicts when compared to healthy controls. The results across these studies are difficult to compare, given the heterogeneous patient groups across studies and fact that different studies use different working memory tasks. The goal of this paper is to quantitatively review functional neuroimaging studies that contrasted brain activity in individuals with substance use disorder against that of healthy participants during a working memory task. I conducted an activation likelihood estimation meta-analysis to examine which brain regions are consistently implicated across studies of substance use disorder, as well as separate exploratory analyses of sample-specific components. The primary analysis, comprised of 17 case-control studies, found increased activity in bilateral clusters of the superior parietal cortex in individuals with substance use disorder relative to controls. A similar activation cluster was identified in the left hemisphere amongst the sub-group studies featuring individuals diagnosed with alcohol use disorder. These regions are typically activated during visuospatial processes associated with the majority of the tasks found in the present analysis, as well as during working memory tasks that demand greater attention and distraction resistance. I argue that the increased activity observed in these regions of substance addicts suggests a greater neural effort is required during task performance, which may reflect a compensatory attentional mechanism to reduce distractions.

Keywords: substance use disorder, self-regulation, working memory, attention, superior parietal cortex, inefficient neural processing

Introduction

Although current clinical interventions for SUD are more effective and empirically grounded than in the past, two key problems remain. Firstly, patients are more likely to drop out of treatment than to complete it, and, secondly, relapse rates remain high even after periods of prolonged abstinence (Brorson, Arnevik, Rand-Hendriksen, & Duckert, 2013). Hence, there is good reason to investigate cognitive deficits associated with SUD because this research may inform us about ways to decrease patient relapse and drop out.

Executive Control and Working Memory

The central executive system integrates and manages information to drive goal-directed behaviour. It is an interactive network comprised of domains including attentional control, cognitive flexibility, goal-oriented cognition, and working memory (WM). The addictive behaviour observed in substance use disorder (SUD) coincides with drug-reinforced changes in the brain's reward system, and with poor executive functioning that is linked to poor self-regulatory behaviour (Gould, 2010). Because the WM system, in particular, is involved in self-regulatory behaviour, it is one of the cognitive systems that is compromised in drug addicts (Wilson, 2015).

The neural substrates implicated in SUD overlay regions in the prefrontal cortex associated with executive functioning domains (Gould, 2010). Therefore, it is not surprising that poor executive control is a consistent feature of various substance addictions, as observed in dependencies pertaining to alcohol (Houston et al., 2014), cocaine (Hester & Garavan, 2004), cannabis (Lundqvist, 2005), heroin (Pau, Lee, & Shui-fun, 2002), methamphetamine (Rusyniak, 2013), and ecstasy (Wareing, Fisk, & Murphy, 2000). The deficits in executive functioning observed in SUD have been identified as a vulnerability factor associated with treatment drop-out and relapse (Teichner et al., 2002; Wilson, 2015).

Additionally, patients exhibiting high levels of impulsivity are associated with poor treatment outcomes (Stevens et al., 2014). Of particular concern here is that poor performance on WM tasks is strongly linked to impulsive behaviour (Bickel, Yi, Landes, Hill, & Baxter, 2011). Components of impulsivity can be conceptualised as antipodes to executive functions on a spectrum (Bickel, Jarmolowicz, Mueller, Gatchalian & McClure, 2012). The link between poor WM and impulsive behaviour may be explained by the role played by WM in focusing attention and keeping long-term goals in mind when faced by impulses and cravings (Kane & Engle, 2002). The relationship between WM, executive

control, and drug-seeking behaviour can be understood by cognitive models of substance abuse.

The Top-Down System and Working Memory

Current models of SUD suggest that addiction and impulsivity arise from an asymmetry between two competing neural systems. The first of these, the bottom-up system, is a more biologically primitive network that involves subcortical dopamine signalling areas that give rise to reward-seeking behaviour (Heatherton & Wagner, 2011). In contrast, the top-down system, found in the prefrontal cortex, is more evolutionarily recent and facilitates self-control and goal-directed behaviour. By regulating the functioning of the bottom-up system, the top-down system has the capacity to bend one's will in favour of long-term goals. Characterised as such, the impulsive behaviour observed in substance abusers can be explained as a result of a weakened top-down system.

WM plays a crucial role in the successful operation of the top-down system (Gazzaley & Nobre, 2012). WM functions as a dynamic short-term memory system, in which chunks of exteroceptive and interoceptive data are held, manipulated, and processed for use in more elaborate or higher-order cognitive tasks (Baddeley, 1992). WM is not exclusively involved in memory, as its name would suggest, but also in attentional stability and the integration of information. As such, the construct is measured by tasks wherein pieces of information are kept in mind while performing an engaging task. These tasks may tap into auditory, visual, or tactile sensory systems. Each task is composed of items that range in difficulty, gauged by changes in WM load and the complexity of the required operations.

The WM system comprises three components; two subsystems are governed by the third (Baddeley, 2012). The phonological loop and visuospatial sketchpad are subsystems that function as short-term memory stores that allow rehearsal of incoming information for a matter of seconds. The phonological loop deals with verbal and auditory information, whereas the visuospatial sketchpad deals with nonverbal data. The central executive governs the two subsystems by drawing from long-term memory, allocating attention, and executing a decision (Wilson, 2015).

Working Memory and Self-Regulation

Performance on WM tasks co-varies with measures of attentional control (McNab et al., 2009). This association may be explained by the considerable overlap in the respective constructs' neural correlates (Gazzaley & Nobre, 2012). Because attention is a key ability that underlies advanced cognition, it makes sense that WM correlates with various aspects of

high-level cognition, such as advanced learning (Kyllonen & Stephens, 1990), fluid intelligence, and self-regulatory behaviour (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). Indeed, myriad studies converge to suggest that WM and attentional operations are necessary for core elements of healthy self-regulation (Hofman, Schmeichel, & Baddeley, 2012), namely: (a) the active representation of long-term goals in light of immediate urges; (b) the focus of attentional resources amongst distracting stimuli during early processing; and (c) goal shielding, or the ability to resist rewarding cravings while focusing on goal-relevant information. Psychological measures thus suggest that poor WM may undermine self-regulation, and hence may contribute towards SUD. Brain imaging research in addicts may explain the neural mechanisms driving this association.

Neural Patterns of Working Memory in Substance Use Disorder

In healthy populations, functional magnetic resonance imaging (fMRI) during WM tasks typically activates regions in a distributed fronto-parietal network (Rottschy et al., 2012). Several studies have observed inefficient neural processing during WM tasks amongst SUD populations. Inefficient neural processing during a task occurs when increased activity is required in network-related regions (Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011), or when atypical brain structures are employed (Audoin et al., 2006), or when there is a compromised capacity to share resources between different cognitive domains (Wagner et al., 2006).

During abstinence, cocaine addicts have abnormally high WM network activation at low levels of WM load; when that load increases, the cerebellum is recruited (Hester & Garavan, 2004). In a study of nicotine addicts, WM neural activity was higher than controls on low levels of a task, and the same regions remained constantly activated as WM load increased (Xu et al., 2005). Similarly, when compared with controls, abstinent cocaine users showed less responsive activity in the medial frontal gyrus and postcentral gyrus as WM load increased (Tomasi et al., 2007). In relation to controls, increased frontal and parietal activity has been found in cannabis users (Schweinsburg et al., 2008 Padula, Schweinsburg, & Tapert, 2007), and in ecstasy users (Moeller et al., 2007).

Many of the aforementioned studies have focused particularly on brain regions that are typically associated with WM in healthy participants. However, by selectively focusing on such regions, researchers fail to consider the possible role of other structures that may be involved in an altered brain network. Meta-analysis of whole-brain studies provides a method to detect altered brain activity in non-typical brain structures (e.g., altered WM networks

identified in schizophrenia patients; Glahn et al., 2005). Additionally, meta-analysis offers other benefits to brain-imaging research. For instance, most published studies of WM in SUD have used small samples. The statistical 'power failure' of brain imaging studies with small samples may be ameliorated by data pooling techniques (Button et al., 2013). Synthesizing and summarizing neuroimaging results using meta-analysis is useful to overcome the problem of the small sample sizes that characterise single empirical studies in this field, and the consequent low reliability that is found in most brain imaging studies (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2011). Therefore, in the current paper, I provide a systematic review of neural activation in response to performance on WM tasks across different SUDs.

Although there are some meta-analyses of fMRI studies of addiction and substance abuse (see, e.g., Chase, Eickhoff, Laird, & Hogarth, 2011; Schacht, Anton, & Myrick 2013), none have examined WM functioning. Given that abnormal neural activations patterns while performing WM tasks have been observed in meta-analyses of other clinical populations such as schizophrenics (Glahn et al., 2005), and patients with multiple sclerosis (Kollndorfer et al., 2013), it is worth investigating WM brain activation patterns in drug-dependent individuals. Hence, in the present paper I meta-analyse cross-sectional fMRI studies that compare brain activity in SUD against that in healthy controls (i.e., SUD > controls, controls > SUD), as well as studies that report activations for healthy controls and SUD participants as a single group.

Methods

Primary Searching

Primary studies were acquired by entering the following combination of terms and Boolean separators into the PubMed FLink online search engine: *fMRI* AND *working memory* AND *substance use disorder* OR *addiction* OR *drug abuse* OR *opiate* OR *cocaine* OR *amphetamine* OR *cannabis* OR *alcohol* OR *nicotine* OR *ecstasy*. The initial search produced 183 papers, after duplicates were removed (see Appendix A for the PRISMA diagram illustrating the steps in study selection).

Selection Criteria

All papers appearing in the online search from the period January 2000-August 2016 were included. Studies involving behavioural addictions (e.g., gambling or gaming addiction), or treatments for SUD, or binge substance use were excluded. Inclusion criteria were that studies (a) contained at least one sample of people with a SUD or drug dependency

that were abstinent at the time of study (i.e., they were not under the influence of a psychoactive substance during scanning), (b) administered a WM task to measure activation patterns for a single group with SUD, or for between-group contrast activations (i.e., SUD > controls, or SUD < controls), (c) employed fMRI techniques, (d) were original papers written in English, (e) were published in peer-reviewed journals, (f) used a 1.5 or 3 Tesla strength fMRI scanner – all other functional imaging techniques (e.g., PET, resting state fMRI) were excluded, (g) reported data from Whole-Brain and not Region of Interest analysis, and (h) reported neural coordinates in Talairach or Montreal Neurological Institute space (Talairach & Tournoux, 1988).

Study Selection

Basic details from each study, including date retrieved, title, abstract, year of publication, type of SUD and details regarding fMRI statistical analyses were extracted from converted text files of each paper using EndNote X7 software and saved in an MSExcel spreadsheet during identification. After screening, 81 of the 183 studies were assessed in more detail to determine eligibility (see Appendix A). Some papers featured multiple studies, including between-group contrasts and analysis of single groups. A total of 18 separate papers met the aforementioned inclusion criteria and were thus included in the current meta-analysis (see Table 1 for the complete list of included papers). Most of the included papers reported between-group contrasts for case-control studies, as either increased activation in SUD (n = 17) or decreased activation in SUD (n = 13), while while fewer papers reported coordinates for single groups of people with SUD (n = 6) or controls (n = 4). During eligibility assessment, two papers describing eligible analyses were identified that did not report coordinates (Daumann, Fimm, Willmes, & Gouzoulis-Mayfrank, 2003; Falcone et al., 2014). The corresponding authors from these papers were contacted via email and asked to provide the relevant data. Only Daumann and colleagues (2003) provided data that were subsequently included in the current analysis.

Table 1

Neuroimaging Studies of Working Memory in Substance Use Disorder

Author, year	Type of SUD	Duration drug taking /Notes	Abstinence period (time)	SUD subjects		Controls		Task, Modality	Task contrast	No. of foci		No. of foci		Reference space
				N	Age	*N*	Age			SUD>C	C>SUD	SUD	C	
Bustamante et al., 2011	Cocaine	11 years	15.6 months	15	34	15	32	N-back, Auditory	Task > baseline	0	1	8	12	Talairach
Caldwell et al., 2005	Alcohol	2 years	16 days	18	16	21	17	SWM[a], Visual	Task > baseline	7	–	–	–	Talairach
Chanraud et al., 2011	Alcohol	15 years	67 days	15	40	15	48	SWM, Visual	Load effects	5	2	–	–	MNI
Charlet et al.,	Alcohol	9 years	198 days	40	45	40	44	N-back task, Visual	Task > baseline	32	–	–	–	MNI
Daumann et al., 2003 (a)	Ecstasy	5 years	At least 7 days	11	27	11	23	N-back, Visual	Task > baseline	1	1	–	–	Talairach
Daumann et al., 2003 (b)	Ecstasy	24 months	23 days	8	25	8	25	N-back, Visual	Task > baseline	1	6	–	–	Talairach
Desmond et al., 2003	Alcohol	Not reported	732-32 days	10	50	13	56	SVWM[b], Visual	Load effects	29	3	27	14	Talairach
Hester & Garavan, 2004	Cocaine	14 years	41 hours	15	40	15	31	N-back, Visual	Load effects	2	3	–	–	Talairach
Hester & Garavan, 2009	Cocaine	13 years	50 hours	16	41	–	–	N-back, Visual	Task > baseline + Load effects	–	–	22 + 4	–	MNI
Moeller et al., 2010	Cocaine	Currently dependent	47 hours	19	41	14	35	Delay memory task, Visual	Load effects	6	17	–	–	Talairach
Padula et al., 2007	Cannabis	477 lifetime episodes	28 days	17	19	17	18	SWM, Visual	Task > baseline	3	–	–	–	Talairach
Park et al., 2011	Alcohol	5.9 years	At least 1 day	11	24	10	24	N-back, Visual	Task > baseline	1	22	8	23	MNI
Pfefferbaum et al., 2001	Alcohol	–	5917-30 days	7	58	10	60	N-back, Visual	Task > baseline	3	24	21	12	MNI
Schweinsburg et al., 2008	Cannabis	481 lifetime episodes	61 days	15	18	17	18	SWM, Visual	Task > baseline	1	1	–	–	Talairach
Schweinsburg et al., 2005	Cannabis and alcohol	135 lifetime episodes	8 days	15	17	19	17	SWM, Visual	Task > baseline	1	2	–	–	Talairach
Smith et al., 2010	Cannabis	4.5 years	7 days-1 hour	10	20	14	20	N-back, Visual	Task > baseline	3	–	–	–	Talairach
Tapert et al., 2004	Alcohol	129 lifetime episodes	17 days	15	17	19	17	SWM, Visual	Task > baseline	2	8	–	–	Talairach
Tapert et al., 2001	Alcohol	–	72 hours	10	20	10	22	SWM, Visual	Task > baseline	1	8	–	–	Talairach

[a]*Spatial Working Memory Task*

[b]*SVWM Sternberg Verbal Working Memory Task*

Statistical Analyses

A coordinate-based meta-analysis was conducted using an activation likelihood estimation (ALE) algorithm that is facilitated by accepted standards of spatial normalisation and foci reporting of peak activation coordinates. Once all data from studies meeting the inclusion criteria were collected, they were compiled in compatible text files that were processed using GingerALE Version 2.3.5 software (http://brainmap.org/ale/).

The analysis includes the representation of entered foci not merely as single points, but as spatial probability distributions located at the specific coordinates. The breadth of a distribution is determined by empirical approximations of the dimensional uncertainty associated with between-study variability in sampling and experimentation (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012).

The coordinates and sample size of each study were grouped in text files according to certain variables of interest (see the following section for details on independent variables). Studies reporting coordinates in Montreal Neurological Institute space were converted into Talairach foci using GingerALE software to ensure spatial standardisation. Talairach space is a standardised grid of the brain that consists of 3 axes: the *x*-axis points from left to right, the *y*-axis runs anterior to posterior (front to back), and the *z*-axis runs rostral to dorsal (bottom to top) (Talairach & Tournoux, 1988).

Once all data were added to the program, 3-dimensional Gaussian distributions were summed to produce a statistical map of the brain that approximates the likelihood of activity, at every voxel, across the contrasts in the study, thus resulting in an activation likelihood statistic for every voxel (Eickhoff et al., 2012).

The ALE algorithm compares the distribution of observed scores to those of a null distribution of random spatial associations. The null distribution map is computed by the number of studies that are included within the meta-analysis. A cluster-level inference with $p = .05$ was implemented using a cluster-level forming threshold of $p = .001$ with 1000 threshold permutations with a minimum cluster size of $200mm^3$, as recommended by Eickhoff and colleagues (2012, 2016). This threshold helps to correct for publication bias relating to reported activation coordinates. In order to visualise the meta-analytic findings, whole-brain maps of the thresholded ALE images were imported into Mango Version 4 (http://ric.uthscsa.edu/mango), an anatomical image overlay program, and superimposed onto a standardised anatomical template in Talairach space.

The outcome variables in the current analysis include coordinate-based peak

neuronal activation, also known as brain foci, which are regions correlated in real time with a WM task. The number of foci from each study, as well as values for other variables of interest, are presented in Table 1.

Primary analyses. Deficits in WM are a common feature across various forms of substance addictions (Wilson, 2015). The primary analyses aimed to quantify convergence in WM-related neural activity across various drug classes, in line with previous coordinate-based meta-analyses of substance-using populations (see García-García et al., 2014; Hanlon, Dowdle, Naselaris, Canterberry, & Cortese, 2014; Konova, Moeller & Goldstein, 2013).

Primary meta-analyses were conducted for studies reporting between-group differences (i.e., separately for SUD > controls and SUD < controls), and for studies reporting activations for single groups (i.e., separately for SUD and controls). In the latter case, subtraction analyses were computed to determine between-group differences using the single-group ALE maps.

Secondary analyses of between-group studies. Secondary analyses were conducted on different groups within the sample of case-control studies. The reduction in the number of experiments for each of these sub-analyses compromised the statistical power and interpretability of these results – a minimum of 15 studies is needed for the ALE method (Eickhoff et al., 2012). All secondary analyses contained fewer than 10 studies, and were thus carried out for exploratory purposes. Secondary analyses involved dividing studies according to types of drugs, WM tasks, and fMRI task contrasts.

Type of substance addiction. There were 9 alcohol-, 4 cannabis-, 3 cocaine-, and 2 ecstasy-dependent groups. A meta-analysis was conducted on alcohol-related activity only, given that there were fewer than 5 studies present in the other drug classes.

Task type. Studies were categorised according to the modality (e.g., auditory) tested in the task and the type of WM task used (e.g., N-back task). All studies used visual WM tasks, except for one that used auditory stimuli. Most studies used either variants of the N-back task (n = 8) or a Spatial Working Memory task (n = 7), while one study used the Delayed Memory task. Although all these tasks assess WM functioning, the N-back and Delayed Memory tasks involve the memorisation of object features pertaining to presentations of numbers and letters on a centred screen, whereas Spatial Working Memory tasks require the online storage of shapes presented at varying locations on a screen. In a meta-analysis of WM-related brain neural activity, dorsal regions of the premotor cortex and areas within the parietal cortex were identified during WM tasks involving the memorisation

of spatial locations (e.g., Spatial Working Memory task), while the ventral premotor cortex was more active during tasks requiring memorisation of object features (e.g., N-back) (Rottschy et al., 2012). Therefore, separate exploratory analyses were conducted for N-back and Spatial Working Memory task studies.

fMRI task contrast. A distinction between experimental task contrasts focusing on 'task' effects and 'load' effects was drawn, in line with a previous WM meta-analysis (Rottschy et al., 2012). Task effect contrasts compare brain activity during the WM task to a resting baseline or a non-related task, thus showcasing WM-related brain activity. On the other hand, studies of load effects compare brain activity during a high level of WM difficulty to that of low level WM difficulty (e.g., 3-back versus 1-back, or parametric modulation of brain activity associated with changes in WM load). There were 13 task effect contrasts and 4 load effect contrasts in the present meta-analysis (Hester & Garavan, 2009, conducted both forms of contrasts on the same sample). Studies of task effects are more strongly related to activation in the left hemisphere including the left lateral prefrontal cortex, the postcentral sulcus, and the posterior superior frontal gyrus, while load effect contrasts are more strongly associated with a bilateral network encompassing Broca's region, the ventral premotor cortex, and the caudal prefrontal cortex (Rottschy et al., 2012). In a conjunction analysis, the same researchers found that the summed network activity from all task and load effect studies displayed a bilateral fronto-parietal network similar to the core WM network. Hence, exploratory analyses in the current paper were conducted separately for studies of load effects and task effects.

Results

Data from studies reporting regions of changed (either increased or decreased) activation in SUD in relation to healthy controls (i.e., SUD > controls or SUD < controls) were used for between-group analyses. Separate analyses were conducted on coordinates reported for single groups (i.e., individuals with SUD or controls) comparing an experimental condition (e.g., 1-back) versus a neutral condition (e.g., rest), the data from which were used for subtraction analysis to determine differences between the SUD and control group.

Primary Analyses

Between-group studies. A total of 17 studies reported regions of greater activation (foci $n = 98$) in those with SUD relative to controls (sample size $n = 551$), whereas 16 studies

found areas of decreased activation (foci $n = 98$, sample size $n = 427$) in those with SUD relative to controls.

Greater brain activity in SUD during the performance of a WM task was found in two clusters encompassing the right postcentral gyrus (weighted centre $x = 6$, $y = -48$, $z = 68$, cluster size = 808mm^3) and the left superior parietal lobule (weighted centre $x = -12$, $y = -44$, $z = 58$, cluster size = 760mm^3). Figure 1 and Table 2 present these results. The analysis detected no significantly deactivated regions.

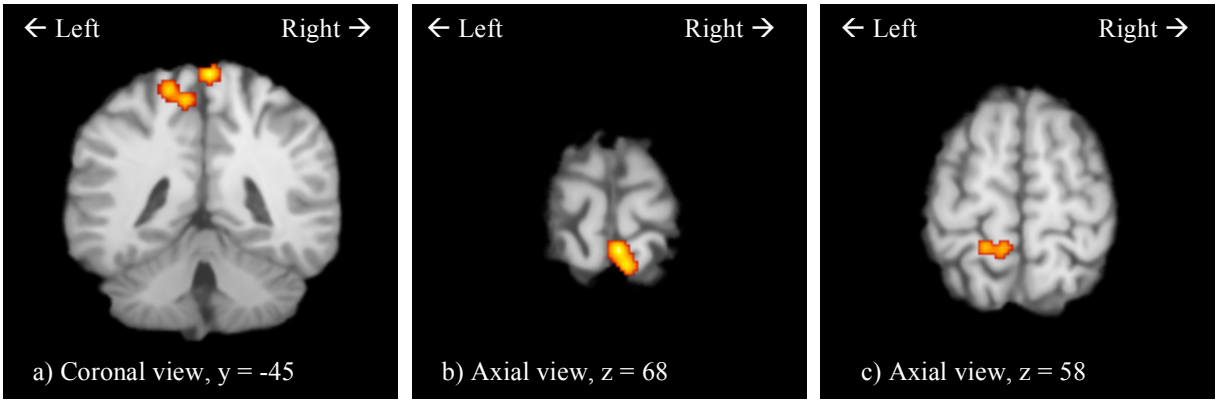

Figure 1. Images depicting increased activation in substance use disorder relative to healthy controls during WM tasks. Panel (a) shows both cluster one (right postcentral gyrus) and cluster two (left superior parietal lobule). Panel (b) shows cluster one (right postcentral gyrus), and panel (c) shows cluster two (left superior parietal lobule).

Table 2
Significant ALE Clusters for Primary and Secondary Meta-Analyses

Cluster Number	Volume (mm^3)	Weighted center x	y	z	Extrema value (x10^2)	Talairach coordinates x	y	z	Anatomic label	Brodmann area
Between-group contrasts, Activations in SUD (SUD > controls)										
1	808	6	-48	68	2.07	4	-46	68	Right postcentral gyrus	5
					1.87	8	-52	68	Right postcentral gyrus	7
2	760	-12	-44	58	1.87	-16	-44	60	Left superior parietal lobule	7
					1.71	-8	-44	56	Left frontal paracentral lobule	5
Between-group contrasts, Activations in alcohol use disorder (alcohol use disorder > controls)										
1	816	-12	-44	58	1.87	-16	-44	60	Left superior parietal lobule	7
					1.71	-8	-44	56	Left frontal paracentral lobule	5
2	552	0	-33	57	1.86	0	-34	56	Left frontal paracentral lobule	5
					1.13	-6	-34	60	Left frontal paracentral lobule	4
Single group contrasts, SUD activations										
1	1328	-33	-50	-26	1.6	-30	-44	-26	Left cerebellum culmen (anterior lobe)	-
					1.34	-36	-58	-26	Left cerebellum culmen (anterior lobe)	-
Single group contrasts, Healthy controls										
1	608	35	48	17	1.29	36	48	18	Right superior frontal gyrus	10

Single-group studies.

SUD. Six studies reported activated regions during increasing WM load, or during a WM task relative to a baseline measure in those with SUD (foci $n = 90$, participants $n = 75$). The analysis detected a large cluster of activation in the left cerebellum spanning the anterior lobe culmen (weighted centre $x = -33$, $y = -50$, $z = -26$, cluster size = 1328mm^3; see panels (a) and (b) of Figure 2).

Healthy controls. The analysis detected a significantly activated cluster in the right superior frontal gyrus in the sample of healthy controls (weighted centre $x = 35$, $y = 48$, $z = -17$, cluster size = 608mm^3; see panel (c) of Figure 2). However, few studies ($n = 4$) were included in this analysis, reducing the associated statistical power.

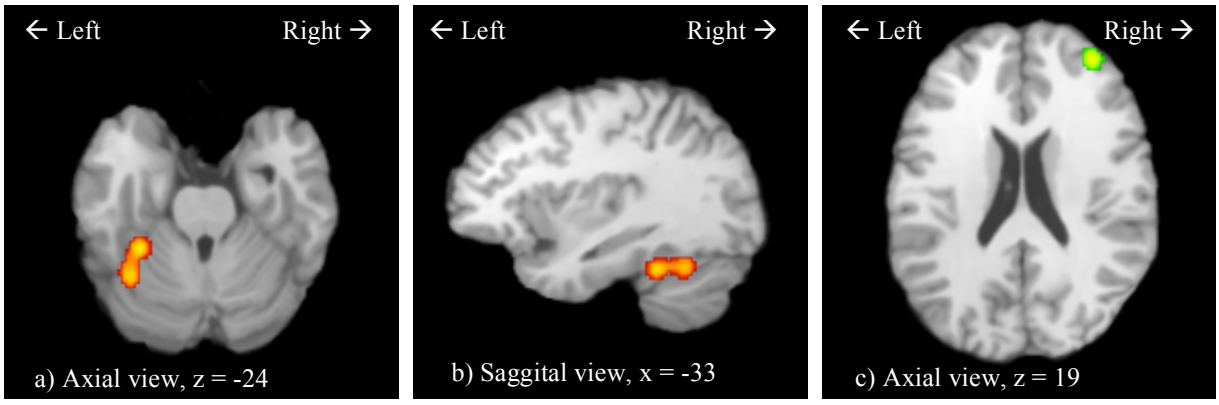

Figure 2. Illustrations of increased activation for single groups during WM tasks. Both panels (a) and (b) depict the same cluster encompassing the left culmen anterior lobe of the cerebellum of the SUD group. Panel (c) illustrates increased activity in the right superior frontal gyrus of healthy controls.

Subtraction analysis. Only papers that reported separate results for both a control group and a group with SUD were eligible for this analysis. Hence, the data from 4 case-control studies were included in this analysis. The analysis detected no significant-between-group differences in any region, even when a more liberal threshold was applied (uncorrected $p = .10$). However, ALE subtraction analyses with fewer than 15 studies have reduced statistical power and are unlikely to find significant differences, regardless of the degree of convergence between foci (Eickhoff et al., 2013).

Secondary Analyses

Types of SUD versus controls. In contrast studies between alcohol use disorder and healthy controls ($n = 9$ reporting activations, and $n = 6$ reporting deactivations), the analysis detected significant activation clusters in similar regions to the primary analysis of between-

group studies, including the left superior parietal lobule (weighted centre x = -12, y = -44, z = 58, cluster size = 816mm^3) and the left paracentral lobule (weighted centre x = 0, y = -33, z = 57, cluster size = 552mm^3). The analysis detected no significant deactivation clusters.

Analyses also detected no significant activations for task type or task contrast method.

Discussion

The present study examined neural patterns associated with WM performance, comparing individuals diagnosed with SUD to healthy controls. It was pertinent to examine WM given its links to impulsivity (Wesley & Bickel, 2012) and self-regulation (Hofman, Schmeichel, & Baddeley, 2012), both of which have been demonstrated to be impaired in individuals diagnosed with SUD (Grenard et al., 2008; Wilson, 2015).

Summary of Findings

The most robust finding of this paper is that individuals with SUD exhibited increased neural activation in bilateral clusters of the parietal cortex, including Brodmann areas 5 and 7. Significant activation in these regions was found across 17 case-control studies (participants n = 551), involving groups diagnosed with SUD pertaining to cocaine, ecstasy, alcohol or cannabis. All these studies used visual WM tasks. The parietal cortex has been implicated in various aspects of WM task performance, including visual attention (Corbetta, Kincade, & Schulman, 2002), attention shifting (Yantis & Serences, 2003), visual WM capacity (Todd & Marois, 2004), and the storage, maintenance, and rehearsal of verbal and visuospatial information (Smith & Jonides, 1998). Bilateral superior regions of Brodmann area 7 form part of the core WM network, while activation in Brodmann area 5 in the left hemisphere is associated with WM tasks involving the memorisation of object location (Rottschy et al., 2012).

In addition to the primary findings, secondary analyses (containing fewer than 10 studies) found increased activation in other areas, including the left anterior cerebellum, in single-group studies of SUD, and increased activation in the left superior parietal lobule in case-control studies of alcohol use disorder (similar to the primary analysis). No significant clusters were found in other sub-analyses (i.e., those involving task type and fMRI task contrast), which may be attributable to a lack of statistical power because of small sample sizes.

The current study shows that, in relation to controls, people diagnosed with SUD require additional parietal activity to complete WM tasks. While some of the literature on

WM in addicts has reported increased activity in the task-associated network (i.e., in the DLPFC), as well as decreased or increased activation in regions outside of the WM network, such patterns were not identified in the present meta-analysis. This may be due to several of these studies having conducted region of interest analyses, and as a result, these data were excluded from the current analysis.

Inefficient Neural Processing

Taken together, the findings reported here provide support for an inefficient processing model of WM in SUD, particularly in the visuospatial (as opposed to the verbal) WM domain. Efficient neural processing occurs when greater performance is facilitated by a more parsimonious brain network, or by less brain activity (Wilson, 2015). Increased activation of regions within and outside of the WM network may represent a compensatory neural response that facilitates task performance in people with SUD (e.g., Caldwell et al., 2005; Chang et al., 2006; Charlet et al., 2013; Jacobsen et al., 2007; Kanayama et al., 2004; Padula, Schweinsburg, & Tapert, 2007; Schweinsburg et al., 2007; Tomasi et al., 2007; Tapert et al., 2004). Based on a diverse sample, the current findings support an inefficient processing model of SUD during WM performance.

The studies included in the current analysis were highly variable in terms of design (e.g., in terms of task difficulty, some studies featured low WM load whereas others investigated high WM load) and population (e.g., mean age, type of substance addiction, duration of drug taking). Despite this variability, the primary meta-analysis found consistently increased activity in superior areas of the parietal cortex, including the bilateral precuneus, the right postcentral gyrus, the left superior parietal lobule, and the left frontal paracentral lobule (BA 5 and 7). Several WM studies have observed heightened activity in the parietal areas of substance addicts when compared to controls. For instance, greater activity in the right postcentral gyrus has been identified in alcoholics (Chanraud et al., 2011). Increased activity in the bilateral precuneus, superior parietal lobules, and the right postcentral gyrus has been observed in abstinent cannabis addicts (Padula et al., 2007). Hyperactivation in the right precuneus has also been found in adolescents with alcohol use disorder (Caldwell et al., 2005). Similarly, abstinent cocaine addicts display greater activation in parietal areas (including bilateral postcentral gyri) in relation to controls (Tomasi et al., 2007).

Additionally, the meta-analyses of single groups found convergence in the cerebellum for SUD, and in the right superior frontal gyrus for controls. Both of these areas are involved

in WM (Rottschy et al., 2012). No significant differences were found during subtraction analyses, most likely due to the small sample sizes featured in the studies under consideration (Eickhoff et al., 2012). It is worth noting, however, that studies of alcohol addicts, binge drinkers, and cocaine users have independently reported increased cerebellar activation associated with WM task performance (Campanella et al., 2013; Desmond et al., 2003; Hester & Garavan, 2004; Tomasi et al., 2007). Given the totality of these findings, it is worth speculating that the cerebellum may form part of a compensatory neural network in SUD.

It is worth noting, however, that some of the aforementioned studies investigated individuals with more than one form of substance addiction. The adverse effects of abstinence on WM may be more pronounced in polysubstance users. In a study comparing the effects of nicotine withdrawal on marijuana users and non-users, the former displayed increased parietal activity, including in the postcentral gyri, when compared to the latter after 2 weeks of nicotine abstinence (Jacobsen, Mencl, Constable, Westerveld, & Pugh, 2007). Additionally, marijuana users showed heightened activity in the same parietal regions during the abstinent condition when compared to the satiated condition (i.e., when they had recently used nicotine), in spite of poorer performance.

Implications of Results

It is worth comparing the current results to previous meta-analyses of WM to better understand the functional significance of the superior parietal cortex. In a meta-analysis of the executive components underlying WM in healthy individuals, the bilateral superior parietal lobules and precunei were associated with distractor resistance and spatial attention (Nee et al., 2013). Distractor resistance, a subdivision of the executive function known as inhibition, involves processes that moderate interference from the external world. In the study by Nee and colleagues (2013), superior parietal activity was more pronounced during visual WM tasks involving the simultaneous presentation of relevant and non-relevant items than during tasks presenting distractor (i.e., non-relevant) items alone. In addition, those researchers found that the same regions were also consistently activated during tasks involving spatial content and spatial attention. A separate meta-analysis of WM identified similar regions (BA 5 and 7) as being associated with the memorisation of object identification and object location (Rottschy et al., 2012); this is consistent with the observation that most studies included in the current analysis used such tasks (i.e., visual N-back, Spatial Working Memory). Given that areas in the superior parietal lobes are involved with spatial content and distractor resistance during WM tasks, spatial operations may be

involved in the process of filtering out distracting stimuli (Nee et al., 2013). Therefore, the hyperactivity observed in these regions in individuals with SUD suggests that addicts might require a greater neural effort to filter out distractions during WM tasks. The superior parietal lobules have also been associated with visual attention and attention shifting during WM tasks (Nee et., 2013), thus increased superior parietal activity may involve attentional mechanisms that promote distractor resistance.

Even though WM and attention can be differentiated as constructs, their underlying mechanisms interact considerably and are associated with overlapping brain networks (Gazzaley & Nobre, 2012). WM capacity moderates attentional control, and plays an important role in monitoring conflicting behaviour in light of long-term goals (Kane & Engle, 2002). The overlap between neural areas underlying attention and executive functions (e.g., WM) may explain the lack of self-regulation and poor higher-order cognition observed in SUD (Hofman et al., 2012).

Executive components of WM are generally associated with frontal circuitry, whereas the superior parietal cortex underlies attentional allocation and rehearsal (Diwadkar, Carpenter, & Just, 2000). In SUD, increased parietal activity may involve the recruitment of attentional resources to facilitate WM and other cognitive functions (Tomasi et al., 2007). Hester and Garavan (2004) argue that the allocation of additional attentional resources may compensate for the weakened executive functioning observed in SUD. This argument, taken together with the current findings, suggests that individuals with SUD may rely more on rehearsal and attention (i.e., distractor resistance) to perform tasks compared to healthy people, which in turn leads to the increased recruitment of the superior parietal cortex. The inefficient processing the WM network of substance addicts may contribute to the weakened top-down system observed in SUD. That is, hyperactivity in the WM network may have implications for other overlapping brain networks that are associated with cognitive impairments in SUD (i.e., attention, executive functioning).

It is worthwhile considering the interaction between the WM network and other large-scale brain networks. Evidence suggests that prominent neural networks sometimes work in unison to carry out certain tasks, and that, under these circumstances, these networks may compete for cognitive resources. These overlapping systems include the dorsal attentional network, the WM network, and the default mode network (Niendam et al., 2012; Koshino, Minamoto, Yaoi, Osaka, & Osaka, 2014; van den Heuvel, Stam, Kahn, & Pol, 2009). Neural inefficiency in SUD is characterised by the employment of compensatory neural networks

and the inability to efficiently allocate resources across different cognitive domains (Chanraud et al., 2011). In alcohol use disorder, neural inefficiency is also associated with a compromised capacity to isolate and ignore irrelevant information during processing, a mechanism similar to distractor resistance (Nixon, Tivis, Ceballos, Varner, & Rohrbaugh, 2002). The observed increase in brain activity required by individuals with SUD during WM tasks may be related to irregular neural patterns in other large-scale brain networks. Consistent with this line of thinking, alcoholics have shown inefficient processing in the default mode network that is linked to WM network activity (Chanraud et al., 2011). By investigating the relationship between large-scale brain networks (i.e., WM and attention) and the inefficient neural patterns (i.e., increased superior parietal activity) observed in SUD, future brain-imaging research may help understand the weakened top-down system and lack of self-regulation observed in substance addicts.

Although the current analysis focused on studies of SUD samples during abstinence, it should be noted that other phases of substance abuse, such as craving and satiation, have different effects on WM. For instance, acute drug administration in addicts has a temporary restorative effect on WM performance (Snyder, Davis & Henningfield, 1989) and improves neural efficiency in the WM network (Jacobsen et al., 2007). However, in most phases of SUD, and especially during abstinence, the WM system is compromised (Wilson, 2015). Nonetheless, some recent evidence suggests that WM functioning in recovering addicts is partially restored over long periods of abstinence (Jasper, 2016). Given the role of WM in constraining attention and monitoring conflicting behaviour in the pursuit of long-term goals (Kane & Engle, 2002), the WM construct can account for differences in the ability to keep abstinence goals in mind in the face of impulses and cravings. As such, the WM network presents a target of interest for clinical interventions.

There is some evidence to suggest that clinical interventions targeting WM, such as cognitive training, are useful in reducing impulsivity in recovering stimulant addicts (Bickel, et al., 2011), and in reducing consumption in alcoholics (Houben, Wiers, & Jansen, 2011). In methamphetamine addicts, cognitive training was found to reduce cerebellar volume (Brooks et al., 2016). Wilson (2015) argues that the positive outcomes observed in talk-based therapies for SUD, such as cognitive behavioural therapy and dialectical behavioural therapy, may occur because such treatments engage WM and the executive system. In a review of non-SUD clinical populations, Constantinides and Klingberg (2016) propose that WM training improves the strength in connections between fronto-parietal network structures and

increases prefrontal neural activity. Future research should investigate WM network changes over time in relation to abstinence and WM training, with particular focus on the superior parietal cortex.

Limitations of the Current Study

ALE meta-analyses have some limitations. Given the strong heterogeneity found across fMRI studies, it is important to investigate the effect of study characteristics on the outcome of the analyses. The ALE method does not consider some important statistical factors of brain-imaging studies, such as the statistical significance of single foci, cluster size, and blood-oxygen-level dependent signal strength (Brooks, Cedernaes, & Schiöth, 2013). Furthermore, given that different phases of SUD (i.e., abstinence, craving, satiation) are associated with changes in WM performance (Jacobsen et al., 2007; Wilson, 2015), and that WM performance may improve over prolonged periods of abstinence (Jasper, 2016), it is important to consider the duration of abstinence associated with each study under review. However, this was not possible in the current analysis due to the variability between studies (see Table 1).

Clinical and social science research is susceptible to the 'file drawer problem', that is, publication bias: In many fields and in many journals, only positive results are published and null findings are not reported (Franco, Malhotra, & Simonovits, 2014). In this regard, previous research that was eligible for this review may have found negative results and may therefore have remained unpublished. Assuming that such unpublished studies exist, and that they are inaccessible for this analysis, then these findings are not an accurate depiction of reality.

In a similar vein, differing levels of statistical power of each sampled study limits coordinate-based meta-analyses, although weighting for sample size addresses some of the problem. We should expect larger studies to have more statistical power, and to thus report more foci when compared to ones with smaller samples. Contrary to expectation, in an analysis of previous meta-analyses, David and colleagues (2013) found no correlation between reported foci and sample size. This unexpected finding may be explained by a selective reporting bias in studies with small samples. This bias is problematic because studies with smaller samples are more likely to commit Type I errors, and to thus have less predictive power. In an effort to reduce the error introduced by this bias, I employed a cluster-level forming threshold to lower the chances of committing a Type 1 error (Eickhoff et al., 2012). Moreover, the latest version of the GingerALE program considers a study's

sample size when calculating ALE values in such a way that studies with smaller samples generate weaker outcomes in the analysis.

Conclusion

The small sample sizes that characterise single brain-imaging studies in this field reduce the statistical power and reliability of individual analyses. Data pooling techniques provide a method to filter out consistent brain regions across neuroimaging studies. In an attempt to better understand the neural substrates of WM in addiction, I conducted a meta-analysis of fMRI studies that investigated WM brain activity in groups with SUD. The results showed that the recruitment of the bilateral superior parietal cortex during WM operations in SUD was a consistent feature across included studies. This recruitment may reflect a compensatory attentional mechanism to reduce distractions, or suggest that a greater neural effort is required during task completion.

The allocation of additional cognitive resources in the WM network may lead to fewer available resources for other overlapping large-scale brain networks. The overlap between these networks and the reduced availability of resources may explain the association between poor WM capacity and deficits in executive functioning observed in SUD populations. Few studies of SUD populations have assessed changes in the WM brain network over time in relation to abstinence and cognitive training. Questions that future research should address is the relation between WM network activity and the observed hyperactivity in the superior parietal cortex, and how this system is involved with other overlapping brain networks.

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APPENDIX A
PRISMA Diagram: Steps in study selection