

Differential Activation of the Left and Right Cerebral Hemispheres of Individuals Who Use or are Dependent on Drugs of Abuse

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Abstract

Introduction: The left and right cerebral hemispheres are not equivalent in performance of cognitive functions associated with risk factors of drug abuse, nor is their development equivalently affected by drugs of abuse. The question addressed here is whether drugs of abuse affect cognitive function as assessed by brain activation, in particular related to impulsivity, and/or whether weaker brain activation associated with impulsivity increases the risk of drug abuse.

Methodology: Using PubMed and key words, articles were selected that addressed brain activation in individuals who used or abused one of the psychoactive drugs. Findings are summarized.

Results: For each of the drugs, hypoactivation was found. In some cases this reduced activation was reported predominantly for the right or both hemispheres. There were fewer reports for the left hemisphere.

Discussion and Conclusion: Rarely do authors focus on why only one or the other hemisphere is affected or why specific structures are affected. Neurobiological differences between the hemispheres and among various brain structures could provide clues to the specific effect of drugs. Increased attention to this gap in research will give additional insights into the etiology of drug abuse and provide direction for treatment.

Key words: Brain activation; Impulsivity; Drug abuse; Cerebral hemispheres

Received: June 28, 2018; **Accepted:** July 18, 2018; **Published:** July 25, 2018

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Citation: Gordon HW (2018) Differential Activation of the Left and Right Cerebral Hemispheres of Individuals Who Use or are Dependent on Drugs of Abuse. J Drug Abuse Vol.4 No.2:10

Introduction

The fact that the left and right cerebral hemispheres differ in cognitive perception and performance is well-accepted. Historically, various dichotomies were described in the literature as verbal/non-verbal, verbose/sequential/visuospatial, and approach/avoidance all of which were derived empirically. While dichotomies help focus attention on those specialized tasks that are associated with each hemisphere, it gives the false impression that each hemisphere is the sole processor of the cognitive functions attributed to it. Nevertheless, it is reasonable to conclude there is something neurobiologically different between the hemispheres that result in these differences. Neuroanatomical measures have also shown different sizes for paired structures and differences in intrahemispheric connectivity. While structural size differences and strengths of neural connections may contribute to the cognitive differences, there are also differences

in the distribution of neurotransmitters and their activity. Here it may be hypothesized that particular stimuli or cognitive activity may stimulate and favor a particular set of neurochemical actions and that these actions may be asymmetrically active between the left and right hemispheres. One way to assess this possibility is to observe the influence of exogenously administered psychoactive drugs to see their differential left/right hemisphere effect on brain activation and its subsequent effect on cognitive task performance. Individuals who regularly use, abuse, or are dependent on licit and illicit psychoactive drugs are appropriate cases to study in this regard.

Impulsivity is one of the risk factors underlying an individual's propensity to initiate the use of psychoactive drugs. Two of the most common experimental assessments of one's impulsive nature are the "go/no-go" and "stop signal" tests. These are easily adaptable to use with functional magnetic resonance

imaging (fMRI) to observe which structures of the brain are active while performing them. The generic procedure for the go/no-go task requires a subject to respond (e.g., by a button press) as quickly as possible (“go”) to serially-presented stimuli (e.g., a particular letter of the alphabet) but withhold responding for another letter (“no-go”) stimulus. The stop signal task requires the subject to respond rapidly to serially-presented stimuli but withhold the response if a “stop” signal (e.g., an “X” presented visually or a “beep” presented audibly) occurs immediately after one of the presented stimuli. In healthy individuals, the tasks overwhelmingly activate structures in the right hemisphere [1]. This observation, interpreted as impulse control, is related right hemisphere function. Since there is presumably less impulse control in those who participate in drug-taking, the activation in these subjects should either be less in the right hemisphere and/or distributed across both hemispheres. Accordingly, the goal of this review was to determine if hemispheric activation in performance of tests of impulsivity—most often “go/no-go” or “stop signal”—by drug-using individuals differed from the activation found in healthy, non-using individuals.

Methodology

PubMed was searched with appropriate key words. Search words included one of the drugs in question—cocaine, nicotine, cannabis, opioids, and alcohol—paired with “impulsivity” or “go/no-go” or “stop signal.” Articles were chosen in which drug-using individuals were compared to non-drug-using or, in some studies, abstinent individuals, where brain activation was assessed by fMRI. There were too few studies for each drug to perform statistical analyses. The results are presented as qualitative summaries of whether activations were less (hypo-) or greater (hyper-) than a comparison group, or comparison condition, with particular attention to hemispheric side.

Cocaine

There were nine studies with a total of 340 cocaine or stimulus-dependent individuals. Most study designs compared these subjects with non-using, healthy controls and/or with former users. Three of these studies compared subjects to themselves at follow-up. There were four studies that together compared 80 abstinent cocaine dependent individuals to healthy controls and two studies that compared 50 recreational users either to healthy controls or to stimulant dependent individuals. One study with 13 active users determined the effect on brain activation by comparing acute cocaine administration to saline.

Nicotine

There were 114 current smokers from eight studies and 43 adolescent smokers in one study. The smokers were variously described as “heavy,” “daily,” or “current”. Comparison groups included non- or never-smokers or former smokers. In two studies, smokers were compared to themselves either to be tested at follow-up (to predict relapse) or in a satiated versus deprived condition.

Marijuana/Cannabis:

There were two studies together that included 33 adolescent subjects and two studies that together included 25 adult subjects. Controls were non-users. There were two studies where together there were 27 subjects with some experience with marijuana who were assessed while exposed to THC.

Opioids

There were a total of five studies which, together, assessed 78 opioid-dependent individuals compared to healthy controls. Two studies together compared 41 abstinent opioid dependent subjects with healthy controls.

Alcohol

There were four studies that together had a total of 109 alcohol-dependent individuals which (together) were compared with 133 matched, healthy controls. There were two studies which together had a total of 103 non-treatment seeking individuals with alcohol dependence compared, in one study, with treatment-seekers, and in the other study, with social drinkers. There were two studies that together had a total of 58 subjects with a positive family history of alcoholism compared to subjects with a negative family history. There were two studies that together compared 55 heavy social drinkers to light or social drinkers. One study assessed early adolescents and determined at 4-year follow-up who had transitioned to heavy use.

Results

Cocaine

Current users

In fMRI tasks of impulsivity—commonly go/no-go or stop signal—most current users of cocaine have reduced activity (hypoactivity) in the anterior portions of the right hemisphere compared to healthy subjects. One of the early studies [2] using a go/no-go task—where activation is assessed during a successful stop for a no-go stimulus—showed hypoactivation to be in the right insula; hypoactivation was also in the anterior cingulate gyrus, more bilaterally distributed, but with the center of peak reduced activity was slightly greater in the right hemisphere. Stop failures in this study also resulted in hypoactivation in different structures, including the right medial frontal gyrus, bilaterally in the anterior cingulate although the peak was slightly to the right of midline, and in the left inferior frontal gyrus and left insula. Other studies replicated the early observations for successful stops in go/no-go tasks. In a study where the “no-go” stimulus was a repeated word, reduced activation was observed in the right superior frontal lobe, right pre-somatic motor area (pre-supplementary motor area), but bilaterally in the anterior cingulate cortex with the peak slightly to the left of midline [3].

The stop signal test is another measure of impulsivity producing right hemisphere activity, but not all in the same brain regions as for the go/no-go test [1]. In a study of cocaine- or amphetamine-dependent individuals, there was less activation for visual stop

signal in the right ventrolateral prefrontal cortex and in the right anterior cingulate cortex for an unsuccessful stop; unaffected sibs had no hypoactivations but had increased activation in the pre-supplementary motor area [4].

Another measure of impulsivity is delay discounting where a subject makes a choice to accept a smaller reward immediately or a larger reward at a later time. The choices can be “easy” or “hard” depending on the relative sizes of the two rewards and time delays. Individuals with cocaine dependence tend to make the impulsive choice for the earlier, smaller, reward rather than wait for the later, larger, reward. In a study comparing hard vs. easy choices [5], individuals with cocaine dependence had smaller increases in the right frontal pole and bilaterally in both the motor areas and the anterior cingulate cortex compared to non-dependent adults. For hard choices compared to no choice, cocaine patients had less activation in the right frontal pole, thalamus, and intra-parietal sulcus; for hard vs. single (i.e. no choice) option there was less activation in the left superior parietal and ventrolateral prefrontal cortex.

While the purpose of most studies of activation is to determine deficient brain regions in performance of cognitive tasks, one study in cocaine users sought to determine which regions were affected by acute (IV) administration of cocaine for a “standard” go/no-go task [6]. Compared to IV saline, cocaine administration increased activation in the right insula/inferior frontal gyrus and the right middle frontal gyrus, areas normally associated with hypoactivation in cocaine patients. Nevertheless, of interest, the increased activation in the right middle frontal gyrus was still less when compared to activation of non-using control subjects in a previous study [2].

Abstinent users

Some studies addressed the question of whether abstinence would eventually result in a return of brain activation to more healthy levels. In a study comparing individuals, abstinent for an average of 45 weeks to non-using subjects, there was no difference between the groups in a go/no-go task for activation to a successful stop, itself, (in this case, a repeated neutral image); however, in the abstinent individuals, there was a correlation between increased activation in the right inferior frontal gyrus and lower scores of a measure of attentional impulsiveness [7]. In addition, the left pre-supplementary motor area correlated with a decreased score for the same measure. In other words, those whose activation increased were less impulsive, supporting the negative observation among cocaine dependents of activation and impulsivity. Also, in another study in the same laboratory for the same go/no-go task [8], there were again no significant differences between individuals, abstinent for an average of 32 weeks and non-using subjects, for the planned analyses of any of the brain regions. Only when comparing the groups in a whole brain analyses uncorrected for multiple comparisons was there a significant increase in activation of the right superior temporal gyrus. Further, activation in the right insula in the abstinent patients was significantly correlated with duration of abstinence and with level of performance of the inhibition task, as might be expected if brain activation returned to levels of non-using subjects.

In a stop signal study of cocaine dependent men after only a two-week abstinence [9], there was less activation in the anterior cingulate cortex (with the peak slightly to the left of center). In a similar study (same abstinent period) by the same research group [10] relapse was predicted by reduced activation for unsuccessful stops in the left insula and dorsal anterior cingulate cortex for men and women but also in the left thalamus for women. It appears that activation may still be reduced even in subjects following a shorter abstinence period in these two stop signal studies though, in these studies, the correlations were with the left hemisphere loci.

Indeed, the situation involving recovering (abstinent) patients is quite variable. In another study [11] of patients with short-term abstinence (average: 2.4 weeks), activation following successful “no-go,” inhibition was greater than in non-using controls in the right middle frontal, precentral, superior frontal and middle temporal gyri, while patients with longer term abstinence (average: 69 weeks), had a greater activation for the right inferior frontal, middle frontal, and precentral gyri and the bilateral cerebellar tonsil but less activation in the left superior temporal gyrus. However, in contrast to the studies noted above, increases in the right precentral and middle temporal gyri were greater for the short term compared to the long-term abstinent patients.

False alarms, instead of successful stops, also produced activation. In one study comparing current users, former (abstinent) users, and non-using subjects [12], there was greater activation in the current users compared to non-users in the bilateral cingulate and left angular/submarginal gyrus but greater activation in the right inferior parietal and middle frontal/precentral gyri in abstinent individuals. And finally, instead of activation for stops, themselves, activation was positively correlated with years of cocaine use in the left insula and left inferior frontal gyrus [13]. As these studies with abstinent patients demonstrate, brain activation does tend to increase, perhaps toward pre-use levels, but increases are variable as to which hemisphere is affected: right or left.

FMRI assessments of activation to cocaine cues is a measure of craving and are often used to determine risk behavior and relapse. In a study of abstinent cocaine users, increased activation of the right ventral striatum when viewing cocaine stimuli was significantly associated with higher scores on a measure of compulsivity [7]. Relapse prediction—number of days of use in the three-month follow-up period—was correlated with greater activation in the right dorsal anterior cingulate cortex for an attentional bias test where cocaine words were contrasted with neutral words in a Stroop Test [14]. Similarly, cocaine dependent subjects with and without positive urine drug screens at 1 week were compared for activation following cocaine cue presentation [15]. Those with positive screens had greater activation for cocaine cues in the right putamen and insula and in bilateral occipital regions. These studies appear to be contradictory to a compilation of cue-activated craving that favored the left hemisphere [1]. The discrepancy could be due to the nature of these studies in which their aim was to predict relapse.

Recreational users

A few studies focused on recreational cocaine users. Unlike regular users of cocaine, recreational users had increased activation in the right pre-supplementary motor area and bilateral anterior cingulate cortex compared to non-using controls for the stop signal task [16]. In a study using a cocaine-word “Stroop” test, which assessed the distraction by the cocaine-related words, there was decreased activation for recreational users in the right inferior frontal cortex and orbitofrontal cortex [17]. It was suggested that less activation in the recreational users meant they were less distracted by the cocaine words than were dependent users.

Nicotine

In a previous report of risk factors of addiction [1], right or left asymmetry of brain activation for craving of nicotine was found to depend on whether the smokers were satiated or 24-hour deprived, whereas response inhibition (a measure of impulsivity) in non-smokers consistently activates the right hemisphere more than the left. The question in this review is how lateral asymmetry of activation for response inhibition is affected by smoking status. Only one study compared smokers in satiated to deprived condition in a go (respond to alternating letters)/no-go (withhold to repeated letters) study [18]. Results showed greater activation for the abstinent condition in the right inferior frontal cortex, which was interpreted as subjects needing greater effort to accomplish the task.

Most other fMRI studies of impulsivity tasks were done in subjects who had recently smoked within minutes of imaging; in other words: satiated. Nevertheless, the results for response inhibition in these subjects tend to support the observation of reduced activation compared to non-smoking controls. In the same go/no-go paradigm used in the satiated/deprived study above, satiated smokers had reduced activation compared to non-smokers in several regions mostly in the right hemisphere—superior frontal gyrus, precentral gyrus, anterior cingulate cortex and superior and middle temporal gyrus—but also in the left hemisphere—middle, inferior frontal, parahippocampal and post-central gyri, and bilaterally in the inferior parietal lobule and insula [19]. Right hemisphere hypoactivation was seen in a study of heavy smokers and gamblers compared to controls for the stop signal task in several areas including the dorsolateral prefrontal cortex and the dorsal anterior cingulate gyrus [20]. In 19-year-old adolescent smokers, reduced activation for a stop signal task was correlated with smoking severity, bilaterally, in the medial frontal gyrus, cingulate cortex and pre-supplementary motor area as well as the left orbitofrontal cortex and right superior frontal gyrus [21]. For the most part, these studies show hypoactivation for response inhibition tasks in the right hemisphere, supporting the suggestion that the right hemisphere may be compromised in smokers leading to increased impulsivity. By contrast, a recent study [22] failed to find hypoactivations in either current or former smokers for successful “no-go’s.” If anything, increases in the left cerebellum and increases in other left hemisphere structures in areas of the parietal lobe were seen for false alarms (inability to

withhold a response). Although not suggested in the discussion, perhaps these were due to motor response of the right hand.

A study with a modified go/no-go paradigm that included money rewards and punishments [23] contrasts with the usual response inhibition tasks. In this study, there was enhanced activation in right hemisphere structures (interior and middle frontal gyrus, dorsolateral prefrontal cortex, inferior parietal lobe and anterior insula). The authors pointed out that this was counter to expectations and suggested the subjects may need to recruit additional brain resources to do the task. Perhaps the additional effort was due to the monetary incentive aspect of the test. In a go/no-go study, where the aim was to predict craving, there was increased activation for “no-go” compared to “go” activations in target regions of interest (bilateral inferior frontal gyrus, pre-supplementary motor area, basal ganglia) that correlated with reduced craving and smoking after treatment [24]. This result seems to suggest that the increased ability to inhibit responses influenced craving following treatment.

A study to determine whether dopamine depletion was responsible for hypoactivation, a D2/D3 antagonist (haloperidol) was administered comparing smokers to non-smokers in a go/no-go task [25]. Across all subjects (smokers and controls), haloperidol reduced activation in the bilateral anterior cingulate cortex, right superior frontal gyrus, left inferior frontal gyrus, posterior cingulate cortex, and left middle temporal gyrus. In the placebo condition, smokers had less activation in the right medial frontal gyrus and left inferior frontal gyrus, but increases in the right temporal-parietal junction. Within groups, haloperidol reduced activation in the smokers in the right posterior cingulate cortex and, in the non-smokers, in the right medial frontal gyrus and left inferior frontal gyrus. These results suggest that dopamine depletion may influence activation, but apparently the influence is different among affected brain structures and between smokers and non-smokers.

Marijuana/Cannabis

For the few studies in marijuana users, reduced brain activity can be inferred just as has been observed in cocaine and nicotine users but conclusions are indirect. For example, in a go/no-go task, 28-day abstinent marijuana smokers had no difference in task performance compared to controls, but brain activity was increased for the no-go stimuli in the right superior and middle frontal gyrus extending to the insula and in the right lingual and middle occipital gyri and in several bilateral areas, including the middle and superior frontal gyri and in the inferior and superior parietal lobules [26]. For the “go” stimuli, only right hemisphere structures were increased relative to controls. Since there was no difference in performance accuracy, the authors’ explanation was that more brain activation was needed by marijuana users to achieve the same behavioral results as for non-users. Correlation analyses in these subjects seemed to support this conclusion. Smokers who had longer duration of involvement, earlier age of onset, and more lifetime use had less activation in many of the same brain areas. In other words, marijuana smokers were decreasingly activated relative to their increased use history, and

therefore needed to use more activation effort to perform the task. In another study where there was no activation differences in any brain area, marijuana users had poorer performance [27]. Using the same logic, these subjects presumably did not put forth additional effort—i.e., did not increase brain activation.

In a more complicated go/no-go paradigm [28], activation in cannabis users was greater in the right inferior parietal lobe, putamen, and middle cingulate gyrus. Again, there were no performance differences between groups. The go/no-go task differed from most because it was based on a Stroop test where the subject was required to withhold a response (i.e., “no-go”) in the conflict situation (color word printed in a different color font) which occurred when either two words were presented in succession or when the color and word did not match. The paradigm additionally required the subject to press twice if (s) he realized (s)he made an error. In this case, when the subjects were aware of their errors, marijuana users had greater activity in the left putamen and bilateral precuneus, but less activation in the left caudate and hippocampal regions. Finally, in a “standard” Stroop test [29], activation for the conflict situation was mixed for the marijuana users. There was decreased activation in the right anterior cingulate gyrus and a middle portion of the right dorsolateral prefrontal gyrus and greater activation in more distributed and bilateral regions of the frontal areas. Once again there were no performance differences between the groups, suggesting each group used different cortical circuitries to perform the task.

In order to answer the question of whether marijuana differentially affects specific areas of the brain, THC or placebo was orally administered to non-marijuana-using subjects (but with some, minimal experience) [30]. Since THC can evoke psychosis in some individuals, the subjects were divided into two groups—those who did, or did not, develop transient psychotic symptoms after THC administration. Regardless of whether drug or placebo was onboard, those developing psychotic symptoms had less activation in the right mid-temporal gyrus and vermis of the cerebellum in the “no-go” situation. Also in these subjects with psychotic symptoms, THC additionally reduced activation in left hemisphere structures including the parahippocampal gyrus, mid-temporal gyrus, and superior temporal gyrus as well as the right area of the cerebellum. In contrast, THC increased activation for all these same areas in the non-psychotic symptom group. The opposite was true for the right mid-temporal gyrus where THC increased activation in the psychotic symptom group and decreased it in the group without symptoms. It is apparently the case that those individuals who develop psychotic symptomatology are differentially affected by THC in terms of brain activation and, in opposite directions, from those who do not develop symptomatology. However, the same research group did essentially the same study with different results two years later (without referencing the previous study) [31]. In the latter study, subjects were not divided according to psychotic symptomatology. This time THC was associated with attenuated activation in the left inferior frontal gyrus extending to the insula and precuneus, but with increased activation relative to placebo

in the right hippocampus and caudate. The results for these two studies do not seem confirmatory, but may support the unsatisfying conclusion that there is “simply” individual variation in the brain activation effects of THC.

Opioids

Several studies in people with opioid dependency support the observation of reduced brain activation, as well as reduced connectivity, in most comparisons, among key brain structures. In one go/no-go study [32] in currently-using opioid dependent individuals, there was reduced activation in the anterior cingulate cortex, bilaterally, compared to matched controls, but only for false alarms (i.e., button presses when the no-go stimulus was presented). However, there was no activation differences between groups for successful inhibition of responses. In a more complicated go/no-go task in which the subjects had to respond to up-arrows unless the word “reverse” preceded the arrow in which case they were to respond to down-arrows, heroin addicts had reduced activation in the left anterior cingulate and inferior frontal gyrus but increased activation in the right angular gyrus region [33]. In a go/no-go study, former heroin addicts, abstinent for several weeks, showed reduced activation compared to never-using controls in several bilateral structures (medial prefrontal cortex, anterior cingulate cortex, inferior frontal gyrus), left hemisphere structures (mid frontal cortex, insula, uncus/parahippocampal gyrus), and right hemisphere structures (precuneus, superior parietal lobule, middle temporal gyrus) [34]. Another go/no-go study [35], to determine the effect of acute heroin administration (in heroin-using patients) on brain activation, focused only on the right inferior frontal gyrus. The result was an increase in activation after both saline and heroin administration, but the activation was attenuated after heroin administration relative to saline. In summary, it appears that activations in opioid-dependent patients are reduced for the most part but contrary to cocaine, nicotine, and marijuana, they do not appear to favor either the left or right hemisphere.

Studies of resting state connectivity among brain nodes report some left/right sidedness but authors never discuss the implications of the asymmetry. One study did try to attribute the effect on cognitive function, however [36]. Connectivity was compared between opioid-dependent patients and non-users using five left/right pairs of seeds originating in structures associated with cognitive functions related to drug abuse: nucleus accumbens (reward), amygdala (memory and learning), anterior cingulate (cognitive control) and lateral and medial orbital frontal cortices (drive and motivation). Weaker connections were observed between the left and right lateral orbital frontal cortices (the seeds) and the left and right dorsolateral prefrontal cortices. This was interpreted to be consistent with the notion that the opioid-dependent subjects had weaker cognitive control. By contrast, there was stronger connectivity between the left and right nucleus accumbens (the seeds) to the left, only, anterior cingulate cortex and medial orbitofrontal cortex, and from the right amygdala to the left, only, lateral orbitofrontal cortex. This was interpreted to be consistent with the notion

that opioid-dependent subjects have stronger craving and motivation connections. While not mentioned, this result also supports the observation that craving preferentially activates the left hemisphere [1]. Another study [37] showed reduced connectivity between the posterior cingulate cortex (the seed) and both the right cerebellum and the left dorsolateral prefrontal cortex, and between the rostral anterior cingulate cortex and several structures including the left orbitofrontal cortex, the left dorsolateral prefrontal cortex, and the right medial temporal lobe. There were also significant, negative correlations among these structures and duration of heroin use. Finally, in a study in patients dependent on opioids due, originally, to prescriptions [38], decreased functional connectivity was found for in pathways specific to the amygdala, insula, and nucleus accumbens accompanied by volumetric loss in the amygdala as well.

Alcohol

Perhaps the best example of hypoactivity related to alcohol use is a go/no-go study [39] where young adolescents were tested at baseline and retested after four years. Those who transitioned to heavy alcohol use had several areas of hypoactivation when compared to adolescents who had not transitioned to heavy use. These areas included the inferior frontal gyri of the right hemisphere, and the dorsolateral prefrontal cortex, as well as the cingulate, superior and middle frontal gyri and putamen of the left hemisphere. Bilaterally, there was hypoactivation in the medial frontal, middle frontal, paracentral and inferior parietal gyri. Therefore, heavy alcohol use could be predicted early in adolescence (before onset of drinking) by hypoactivation throughout the brain but not predominantly in one hemisphere of the other.

In a stop signal task with non-alcohol dependent heavy drinkers compared to light drinkers [40] hypoactivation was seen in the right superior frontal gyrus and left caudate. And in a go/no-go study with teenaged heavy versus light drinkers [41], hypoactivation was seen in the right hippocampus, the left supplementary-motor area and superior temporal gyrus as well as several bilateral structures including frontal and parietal lobes, the thalamus and putamen.

In a stop signal task with adult alcohol-dependent patients [42] hypoactivation was seen in the medial prefrontal cortex and superior temporal gyrus of the right hemisphere and superior frontal gyrus, as well as the hippocampus, and paracentral gyrus of the left hemisphere. Additionally, there was hyperactivation in the inferior parietal lobule and pre-supplementary-motor area of the right hemisphere. In another stop signal task [43], alcohol-dependent subjects had hypoactivation in the left supplementary-motor area but hyperactivation in the right ventral nucleus, right thalamus and the left putamen. The pattern of increased activation was also seen in non-alcoholic subjects who had a positive family history of alcoholism where there was hyperactivation in a go/no-go task in the bilateral insula and inferior frontal gyrus when compared with subjects without family history of alcoholism [44].

Another measure of impulsivity can be obtained with a delay discounting task in which subjects choose whether they want a

small sum of money immediately or a larger sum at some later time. In non-treatment-seeking subjects, activation was assessed in the “now” (impulsive) vs. “later” situation [45]. For this type of study, several brain regions were activated including the right orbitofrontal gyrus, as well as the lingual, precentral, and middle occipital gyri in the left hemisphere. Bilaterally, there were also activations in the cuneus, precuneus, cerebellum, and middle temporal, inferior frontal, and superior temporal gyri. By contrast, in another incentive delay task [46] alcohol-dependent subjects had hypoactivation in the right ventral striatum. Finally, a delay discounting task using positron emission tomography supported the hypoactivation by showing the measure of impulsive choice was correlated with reduced dopamine receptor availability in the same right ventral striatum [47].

Similar to impulsivity, increased expectation of receiving a potential reward is a risk factor for addiction. A study that examined “win” vs. “loss” found hypoactivation in alcoholic dependent subjects (vs. controls) in the dorsolateral prefrontal cortex where the peak was slightly toward the right hemisphere, in the left striatum, and in the bilateral lateral orbitofrontal cortex [48]. The authors concluded that subjects’ alcohol dependency was the cause of “less engagement of prefrontal cortical regions” leading to “weak or disrupted regulation of ventral striatal response.”

Thus, for individuals who had developed alcohol dependency, most studies of various methodologies reported hypoactivation in multiple brain structures, but not favoring either the left or right hemisphere. And in a few studies, increased activation for a few structures was reported.

Discussion

The results of this survey demonstrate that individuals using psychoactive drugs have shown reduced activation for response inhibition tasks bilaterally or unilaterally in one or the other hemisphere relative to those who do not use drugs. For current cocaine users, hypoactivation was most often in the right hemisphere. Since non-drug-using and non-impulsive individuals have strong right hemisphere activation when performing tasks of response inhibition, this observation supports the notion that those taking cocaine have weaker responses which may contribute to their greater impulsivity. However, studies of individuals abstinent from cocaine do not necessarily support the idea that impulsivity was causative of cocaine use. Those who had been abstinent for several weeks had activation equivalent to controls. This suggests that activation had returned to normal levels when the subjects stopped taking cocaine. Furthermore, the longer they were abstinent or the better they performed on the task of impulsivity, the larger activation. Nevertheless, it was also true that, on the average, the abstinent, former users still showed greater impulsivity in questionnaires than controls. By contrast, those with shorter abstinence had increased activation compared to non-using controls. These observations seem to suggest there may be a compensation mechanism of increased activation in order to perform the response inhibition tasks soon after abstinence. By the time of long-term abstinence, the

increased activation equalized to that of non-users. It is unknown whether there was hypoactivation prior to taking cocaine as would be expected from the impulsive measures on questionnaires. And unfortunately, there are no studies that followed subjects with repeated testing throughout their abstinence.

The results for smokers are more complicated to interpret due to the observation, reported previously [1] that cue-activated responses (presumably an index of craving) favored the left or right hemisphere depending on whether the subjects had just smoked (satiated) or were 24 hr deprived. Only one study compared smokers in both conditions. Increased right hemisphere activation was found for the deprived subjects which was interpreted to be due to increased effort needed to perform the task. But greater right hemisphere activation in that area is the norm for non-smokers on that task. Is it possible that nicotine on board reduced this activation in the satiated smokers? In most other studies where subjects had just smoked before entering the magnet, there was hypoactivation most often, but not always, in the right hemisphere, except for an increased activation in the right hemisphere when the go/no-go task included a monetary reward. In the study where haloperidol was used to determine whether dopamine depletion was responsible for reduced activation, the results were inconsistent. Hypoactivity was differentially distributed among various brain structures in the left and right hemispheres and between the smokers and non-smokers. However, it is reasonable to suggest that dopaminergic mechanisms are not equivalent in the two hemispheres nor functional in the same structures [49]. Accordingly, the presence or absence of nicotine exposure may affect hemispheric structures differently in smokers compared to non-smokers.

In marijuana smokers, reduced activation could only be deduced by indirect reasoning. Increased activation in the right or both hemispheres was needed for task performance to be equal to that of controls. Presumably, "brain power" was subnormal when the subjects were not performing a task. This was borne out when there was no increased activation resulting in poorer performance by users. In support of this reasoning, subjects whose activation was lower were those with greater marijuana use involvement. Two studies in one laboratory tried to determine if THC, administered acutely, would affect activation. The answer was, "yes," but the interpretation was obscured because the results were inconsistent: some brain areas had decreases in activation; other areas had increases. Only a few studies suggest the right hemisphere may be more affected in marijuana smokers, but differences among studies prevent a definitive conclusion.

In the few response inhibition studies in patients with opioid dependence, activation was generally lower, consistent with other studies. However, unlike studies in cocaine and nicotine, the reduced activations did not occur in one hemisphere; most results were reported for bilateral structures. Also, contrary to other substances, activation was still decreased in long-time abstinent individuals, not increased. That is, there was no evidence of compensatory increases in cortical activity as seen more clearly in abstinent cocaine individuals, for example.

Some studies with opioid individuals focused on connectivity

rather than activation. Results included outcomes of both weaker and stronger connectivity among a variety of structures. In some cases, authors attempted interpretation of these findings in terms of cognitive function, but it is not clear that the state-of-the-art has been definitive enough for such interpretations [50]. For the purposes of this review, it is notable that some circuits of connectivity—weaker or stronger—were reportedly lateralized to the left or right hemisphere, and not bilaterally.

Performance on response inhibition tasks in alcohol-dependent patients as well as in heavy drinkers compared to light drinkers resulted in a general pattern of hypoactivation. But, similar to individuals with opioid dependence, there was no clear lateralization to either the left or right hemisphere. In addition, there were a couple of studies where there was hyperactivation in some structures in the same subjects where there was hypoactivation in other structures. One delay discounting task showed increases in activation in both hemispheres. But two other studies with incentive delay tasks found hypoactivation only in the right hemisphere. The most notable study was the one that showed that reduced activation was predictive of adolescents who would transition to heavy alcohol use at follow-up. Thus the most consistent reports are that individuals with alcohol involvement tend to have reduced brain activation for tasks of impulsivity.

Conclusion and Recommendations

The studies reviewed here show there is a relationship between drugs of abuse and hemispheric activation for cognitive tasks such as response inhibition—a measure of impulsivity. In particular, users of these drugs are associated with lower activation. What is not entirely clear is whether hypoactivation of specific brain structures predated drug use. That is, did individuals have weaker activation that turned out to be a risk factor? A few studies suggest that this does occur. Adolescents with hypoactivation on a task of impulsivity were likely to transition to heavy drinking. Individuals with low scores on impulsivity had lower brain activation. An epidemiological recommendation to clarify these relationships of brain activation, cognitive function, and addiction vulnerability would be to leverage large-scale projects such as the Adolescent Brain and Cognitive Development (ABCD) initiative led by the National Institute on Drug Abuse which is now under way. Here, children and adolescents can be assessed by functional magnetic resonance imaging (fMRI) prior to any drug involvement to document brain activation and cortical connectivity. The important focus of these assessments would be on cognitive control or on the reward system. In particular, an example question could be: How do individual differences in activation and connectivity during adolescence relate to factors such as stress reactivity or personality that are predictors of drug use vulnerability?

Lateralization of hypoactivation was reported more for the right hemisphere, at least for users of cocaine and nicotine and, to some extent, marijuana. This pattern also suggests a causative factor since weak right hemisphere activation is related to increased impulsivity. A neurocognitive recommendation is to pursue hypothesis-driven

research that asks what the unique mechanisms are in the right hemisphere that would differentially affect drug risk.

Reduced activation in bilateral structures as well as specific structures in the left and right hemispheres were noted for all drugs, but more often for opioid and alcohol users. There were virtually no studies where only the left hemisphere was affected by tasks of impulsivity. Differences in brain activation whether they are only in the right hemisphere, or in equivalent or non-equivalent structures in the left and right hemispheres, are telling us something about the specific effect of drugs on the brain. We do not understand why this is the case. Several neurophysiological recommendations to investigate this question are to determine 1) how neurobiological mechanisms differ between the left and right sides of the brain during early, and during late, neurodevelopment, 2) which neurotransmitter mechanisms are the same, and which are different between the two hemispheres, 3) how exposure to psychoactive substances differentially interact with the unique, lateralized neurotransmitter mechanisms.

In a previous review [1], it was pointed out that two different risk factors for drug abuse are associated with opposite hemispheres. Response inhibition—a test of impulsivity—is consistently related to right hemisphere function in non-drug-using individuals. There is some evidence presented here—either with reduced activation in the right hemisphere or bilaterally (including the right hemisphere)—that drug users are impulsive due to reduced brain function. It was also observed that craving—brain reaction to an appetitive cue—activates areas more often in the left hemisphere. This was the case for most drugs and even for food craving. These observations of cognitive asymmetry have not been explained at the neurobiological level. For example, there are several models of impulsivity and risk-taking in both the rodent and human literature. There are undoubtedly one or more neurobiological mechanisms driving the cognitive and behavioral manifestations of them. It is also likely that these mechanisms differ between the hemispheres. The obvious research recommendation is to discover and define these neurobiological differences. Even animal models may well display neurobiological differences of neurotransmitter systems that may underlie models of impulsivity and other risk-taking behavior. Studies in rodents rarely, if ever, look for potential left/right asymmetries of these mechanisms at the neurobiological level. It is recommended that they do so now.

Exposure to drugs of abuse were shown in another review [51] to have direct influence on neuroanatomic development. Development was affected differently depending on whether the exposure was in utero or during adolescence or later. In the

case of cocaine exposure, left hemisphere structures tended to be more affected for in utero exposure while the reverse was true for adolescent/adult exposure. For alcohol, more right hemisphere structures were affected in utero while there was no hemisphere difference for adult/adolescent exposure. Why should this be the case? A recommended study would be to determine the interaction of cocaine—the cocaine molecule—with the neurobiological milieu in each hemisphere during early development and, similarly, the interaction during late development or even changes in the mature brain. Once these mechanisms are understood, interventions can more easily be derived to correct or ameliorate their deleterious effects. Similar sets of investigations would focus on alcohol and other abused psychoactive substances.

Many factors affect differential right/left development throughout the animal kingdom; the advantages can be specified according to species [52]. Humans are the most complex and, accordingly, the lateral development and function of neural structures are equally complex. This leads to “infinite” variation of behavior and skills. For the most part, this is a good thing. But dysfunction in one hemisphere or the other can accompany mental disorders [53]. For drug abuse, there are two factors. One is that some developmental variation—say, increased impulsivity—not influenced by drug exposure may increase risk for drug use. Secondly, exposure drugs themselves may adversely affect development. These observations highlight the fact that neurobehavioral and neurocognitive effects are often lateralized to the right or left hemisphere and affect specific structures. It is hoped that research such as that recommended here will take note of these observations in determining underlying risk factors and potential treatments for drug abuse.

Disclaimer

The views and opinions expressed in this manuscript are those of the author only and do not necessarily represent the views, official policy, or position of the U.S. Department of Health and Human Services or any of its affiliated institutions or agencies.

Acknowledgement

I thank Khushi Soni for hard work in compiling and summarizing the articles used in this paper.

Conflict of Interest

The author has no conflict of interest.

References

- 1 Gordon HW (2016) Laterality of Brain Activation for Risk Factors of Addiction. *Curr Drug Abuse Rev* 9: 1-18.
- 2 Kaufman JN, Ross TJ, Stein EA, Garavan H (2003) Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. *J Neurosci* 23: 7839-7843.
- 3 Hester R, Garavan H (2004) Executive dysfunction in cocaine addiction: Evidence for discordant frontal, cingulate and cerebellar activity. *J Neurosci* 24: 11017-11022.
- 4 Morein-Zamir S, Simon Jones P, Bullmore ET, Robbins TW, Ersche KD (2013) Prefrontal hypoactivity associated with impaired inhibition in stimulant-dependent individuals but evidence for hyperactivation in their unaffected siblings. *Neuropsychopharmacology* 38: 1945-1953.

- 5 Meade CS, Lowen SB, MacLean RR, Key MD, Lukas SE (2011) fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. *Psychiatry Res* 192: 167-175.
- 6 Garavan H, Kaufman JN, Hester R (2008) Acute effects of cocaine on the neurobiology of cognitive control. *Philos Trans R Soc Lond B Biol Sci* 363: 3267-3276.
- 7 Bell RP, Garavan H, Foxe JJ (2014) Neural correlates of craving and impulsivity in abstinent former cocaine users: Towards biomarkers of relapse risk. *Neuropharmacology* 85: 461-470.
- 8 Bell RP, Foxe JJ, Ross LA, Garavan H (2014) Intact inhibitory control processes in abstinent drug abusers (I): A functional neuroimaging study in former cocaine addicts. *Neuropharmacology* 82: 143-150.
- 9 Li CS, Huang C, Yan P, Bhagwagar Z, Milivojevic V, et al. (2008) Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. *Neuropsychopharmacology* 33: 1798-1806.
- 10 Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, et al. (2013) Error processing and gender-shared and specific neural predictors of relapse in cocaine dependence. *Brain* 136: 1231-1244.
- 11 Connolly CG, Foxe JJ, Nierenberg J, Shpaner M, Garavan H (2012) The neurobiology of cognitive control in successful cocaine abstinence. *Drug Alcohol Depend* 121: 45-53.
- 12 Castelluccio BC, Meda SA, Muska CE, Stevens MC, Pearlson GD (2014) Error processing in current and former cocaine users. *Brain Imaging Behav* 8: 87-96.
- 13 Prisciandaro JJ, Joseph JE, Myrick H, McRae-Clark AL, Henderson S, et al. (2014) The relationship between years of cocaine use and brain activation to cocaine and response inhibition cues. *Addiction* 109: 2062-2070.
- 14 Marhe R, Luijten M, van de Wetering BJ, Smits M, Franken IH (2013) Individual differences in anterior cingulate activation associated with attentional bias predict cocaine use after treatment. *Neuropsychopharmacology* 38: 1085-1093.
- 15 Prisciandaro JJ, Myrick H, Henderson S, McRae-Clark AL, Brady KT (2013) Prospective associations between brain activation to cocaine and no-go cues and cocaine relapse. *Drug Alcohol Depend* 131: 44-49.
- 16 Morein-Zamir S, Simon Jones P, Bullmore ET, Robbins TW, Ersche KD (2015) Take it or leave it: Prefrontal control in recreational cocaine users. *Transl Psychiatry* 5: e582.
- 17 Smith DG, Simon Jones P, Bullmore ET, Robbins TW, Ersche KD (2014) Enhanced orbitofrontal cortex function and lack of attentional bias to cocaine cues in recreational stimulant users. *Biol Psychiatry* 75: 124-131.
- 18 Kozink RV, Kollins SH, McClernon FJ (2010) Smoking withdrawal modulates right inferior frontal cortex but not presupplementary motor area activation during inhibitory control. *Neuropsychopharmacology* 35: 2600-2606.
- 19 Nestor L, McCabe E, Jones J, Clancy L, Garavan H (2011) Differences in "bottom-up" and "top-down" neural activity in current and former cigarette smokers: Evidence for neural substrates which may promote nicotine abstinence through increased cognitive control. *Neuroimage* 56: 2258-2275.
- 20 de Ruiter MB, Oosterlaan J, Veltman DJ, van den Brink W, Goudriaan AE (2012) Similar hyporesponsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. *Drug Alcohol Depend* 121: 81-89.
- 21 Galván A, Poldrack RA, Baker CM, McGlennen KM, London ED (2011) Neural correlates of response inhibition and cigarette smoking in late adolescence. *Neuropsychopharmacology* 36: 970-978.
- 22 Weywadt CR, Kiehl KA, Claus ED (2017) Neural correlates of response inhibition in current and former smokers. *Behav Brain Res* 319: 207-218.
- 23 Luijten M, O'Connor DA, Rossiter S, Franken IH (2013) Hester R Effects of reward and punishment on brain activations associated with inhibitory control in cigarette smokers. *Addiction* 108: 1969-1978.
- 24 Berkman ET, Falk EB, Lieberman MD (2011) In the trenches of real-world self-control: Neural correlates of breaking the link between craving and smoking. *Psychol Sci* 22: 498-506.
- 25 Luijten M, Veltman DJ, Hester R, Smits M, Nijs IM, et al. (2013) The role of dopamine in inhibitory control in smokers and non-smokers: A pharmacological fMRI study. *Eur Neuropsychopharmacol* 23: 1247-1256.
- 26 Tapert SF, Schweinsburg AD, Drummond SP, Paulus MP, Brown SA, et al. (2007) Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology* 194: 173-183.
- 27 Behan B, Connolly CG, Datwani S, Doucet M, Ivanovic J (2014) Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users. *Neuropharmacology* 84: 131-137.
- 28 Hester R, Nestor L, Garavan H (2009) Impaired error awareness and anterior cingulate cortex hypoactivity in chronic cannabis users. *Neuropsychopharmacology* 34: 2450-2458.
- 29 Gruber SA, Yurgelun-Todd DA (2005) Neuroimaging of marijuana smokers during inhibitory processing: A pilot investigation. *Brain Res Cogn Brain Res* 23: 107-118.
- 30 Atakan Z, Bhattacharyya S, Allen P, Martín-Santos R, Crippa JA, et al. (2013) Cannabis affects people differently: Inter-subject variation in the psychotogenic effects of Delta9-tetrahydrocannabinol: A functional magnetic resonance imaging study with healthy volunteers. *Psychol Med* 43: 1255-1267.
- 31 Bhattacharyya S, Atakan Z, Martín-Santos R, Crippa JA, Kambeitz J (2015) Impairment of inhibitory control processing related to acute psychotomimetic effects of cannabis. *Eur Neuropsychopharmacol* 25: 26-37.
- 32 Forman SD, Dougherty GG, Casey BJ, Siegle GJ, Braver TS, et al. (2004) Opiate addicts lack error-dependent activation of rostral anterior cingulate. *Biol Psychiatry* 55: 531-517.
- 33 Lee TM, Zhou WH, Luo XJ, Yuen KS, Ruan XZ, et al. (2005) Neural activity associated with cognitive regulation in heroin users: A fMRI study. *Neurosci Lett* 382: 211-216.
- 34 Fu LP, Bi GH, Zou ZT, Wang Y, Ye EM, et al. (2008) Impaired response inhibition function in abstinent heroin dependents: An fMRI study. *Neurosci Lett* 438: 322-326.
- 35 Schmidt A, Walter M, Gerber H, Schmid O, Smieskova R, et al. (2013) Inferior frontal cortex modulation with an acute dose of heroin during cognitive control. *Neuropsychopharmacology* 38: 2231-2239.
- 36 Ma N, Liu Y, Li N, Wang CX, Zhang H, et al. (2010) Addiction related alteration in resting-state brain connectivity. *Neuroimage* 49: 738-744.
- 37 Yuan K, Qin W, Dong M, Liu J, Liu P, et al. (2010) Combining spatial and temporal information to explore resting-state networks changes in abstinent heroin-dependent individuals. *Neurosci Lett* 475: 20-24.

- 38 Upadhyay J, Maleki N, Potter J, Elman I, Rudrauf D, et al. (2010) Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain* 133: 2098-2114.
- 39 Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP, et al. (2011) Neural activation during inhibition predicts initiation of substance use in adolescence. *Drug Alcohol Depend* 119: 216-223.
- 40 Bednarski SR, Erdman E, Luo X, Zhang S, Hu S, et al. (2012) Neural processes of an indirect analog of risk taking in young nondependent adult alcohol drinkers-an fMRI study of the stop signal task. *Alcohol Clin Exp Res* 36: 768-779.
- 41 Ahmadi A, Pearlson GD, Meda SA, Dager A, Potenza MN, et al. (2013) Influence of alcohol use on neural response to Go/No-Go task in college drinkers. *Neuropsychopharmacology* 38: 2197-208.
- 42 Hu S, Ide JS, Zhang S, Sinha R, Li CS (2015) Conflict anticipation in alcohol dependence - A model-based fMRI study of stop signal task. *Neuroimage Clin* 8: 39-50.
- 43 Sjoerds Z, van den Brink W, Beekman AT, Penninx BW, Veltman DJ (2014) Response inhibition in alcohol-dependent patients and patients with depression/anxiety: A functional magnetic resonance imaging study. *Psychol Med* 44: 1713-1725.
- 44 DeVito EE, Meda SA, Jiantonio R, Potenza MN, Krystal JH (2013) Neural correlates of impulsivity in healthy males and females with family histories of alcoholism. *Neuropsychopharmacology* 38: 1854-1863.
- 45 Claus ED, Kiehl KA, Hutchison KE (2011) Neural and behavioral mechanisms of impulsive choice in alcohol use disorder. *Alcohol Clin Exp Res* 35: 1209-1219.
- 46 Beck A, Schlagenhaut F, Wüstenberg T, Hein J, Kienast T, et al. (2009) Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics. *Biol Psychiatry* 66: 734-742.
- 47 Oberlin BG, Albrecht DS, Herring CM, Walters JW, Hile KL, et al. (2015) Monetary discounting and ventral striatal dopamine receptor availability in nontreatment-seeking alcoholics and social drinkers. *Psychopharmacology* 232: 2207-2216.
- 48 Forbes EE, Rodriguez EE, Musselman S, Narendran R (2014) Prefrontal response and frontostriatal functional connectivity to monetary reward in abstinent alcohol-dependent young adults. *PLoS One* 9: e94640.
- 49 Molochnikov I, Cohen D (2014) Hemispheric differences in the mesostriatal dopaminergic system. *Front Syst Neurosci* 8: 110.
- 50 Nielsen JA, Zielinski BA, Ferguson MA, Lainhart JE, Anderson JS (2013) An evaluation of the left-brain vs. right-brain hypothesis with resting state functional connectivity magnetic resonance imaging. *PLoS One* 8: e71275.
- 51 Gordon HW (2017) Hemispheric Asymmetry of Development Due to Drug Exposure. *J Syst Integr Neurosci* 3:3.
- 52 Rogers LJ (2014) Asymmetry of brain and behavior in animals: Its development, function, and human relevance. *Genesis* 52: 555-571.
- 53 Gordon HW (2016) Putting Hemispheric Asymmetry to Use in Understanding Brain Diseases. *Journal of Systems and Integrative Neuroscience* 3: 1-2.