Laterality of Brain Activation for Risk Factors of Addiction

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Abstract: *Background*: Laterality of brain activation is reported for tests of risk factors of addiction - impulsivity and craving - but authors rarely address the potential significance of those asymmetries.

Objective: The purpose of this study is to demonstrate this laterality and discuss its relevance to cognitive and neurophysiological asymmetries associated with drug abuse vulnerability in order to provide new insights for future research in drug abuse.

Method: From published reports, brain areas of activation for two tests of response inhibition or craving for drugs of abuse were compiled from fMRI activation peaks and were tabulated for eight sections (octants) in each hemisphere. Percent asymmetries were calculated (R-L/R+L) across studies for each area.

Results: For impulsivity, most activation peaks favored the right hemisphere. Overall, the percent difference was 32% (X^2 = 16.026; $p < 0.0001$) with the greater asymmetry for anterior peaks (46.8%; X^2 = 17.329; $p < 0.0001$). The asymmetries for cue-induced craving were opposite, favoring the left hemisphere by 6.7% (X^2 = 4.028; $p < 0.05$). The consistency of left asymmetry was found for almost all drugs. For nicotine, studies where subjects were not allowed to smoke (deprived) prior to measurement had the same left hemisphere activation but those who smoked (satiated) before the fMRI measure showed right asymmetry.

Conclusion: Brain activation studies demonstrate different left/right hemispheric contributions for impulsivity *versus* craving - factors related to addiction. Failure to take laterality into consideration is a missed opportunity in designing studies and gaining insight into the etiology of drug abuse and pathways for treatment.

Keywords: craving, fMRI, impulsivity, laterality, response inhibition.

INTRODUCTION

Although lateralization of brain function has been intensively investigated for a number of years in a variety of contexts, the role of lateralized function has not been a prominent topic in substance abuse research. Yet, brain activation asymmetries between the left and right hemispheres are often reported for measures of impulsivity and craving - both of which are risk factors for addiction. This disconnect is a missed opportunity to apply known hemispheric differences for specialized cognitive function to understand the underlying neurosystems of addiction. The purpose of this report, then, is to highlight these asymmetries of activation and to couple those data with cognitive, neuroanatomical, neurophysiological and pharmacological systems. Accordingly, new research on the vulnerabilities and consequences of addiction can incorporate these factors into study designs and functional models.

Hemispheric Specialization

Hemispheric specialization for specific cognitive functions has been known for over a century and a half dating from the attribution of speech production in the left hemisphere by Paul Broca in 1864 and singing in the right hemisphere by Hughlings Jackson soon thereafter. Additional verbal abilities and other cognitive functions emerged from studies in patients with unilateral brain damage. Such damage was either traumatic - from gunshot wounds, for example, as studied by Teuber and others in the 1950's and 1960's - or due to tumors or strokes as studied by several authors (*e.g.*, DeRenzi, Faglioni, and others) in the 1960's. Attribution of lateralized function in these studies was inferred from *deficits* following cerebral damage. Specialized functions were confirmed by *positive* evidence when the hemispheres could be studied independently after surgical disconnection of the corpus callosum in patients with intractable epilepsy. Not only were seizures significantly reduced for most patients, but to the casual observer there appeared to be no functional deficits resulting from the surgery. Nevertheless, pioneering work by Roger Sperry and his students and colleagues in the 1960's-1970's using lateralized visual, haptic, or olfactory inputs, allowed each hemisphere to be queried individually as to its specialized abilities. (Sperry won the Nobel Prize for this work in 1981.) Also, at this time, techniques were being developed that could assess functioning in healthy individuals primarily by means of competition between the right and left visual fields with tachistoscopically-presented stimuli or competing auditory perception with dichotic listening. Thus originated a glossary of "left-right" functional dichotomies: analytic/synthetic, verbal/spatial,

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temporal/non-temporal, or verbosequential/visuospatial. The dichotomies were a two-edged sword. On the one hand, they served a useful purpose in trying to understand the specific and specialized functions of each half of the brain. But they also generated invented asymmetries by the popular press and others that had no validation for brain function.

Brain Activation

Measurement of brain activity by means of changes in blood flow was developed in humans by Ingvar and Risberg [1]. Their crude methodology involved intracarotid injection of radioactive xenon that was used to measure the changes in regional blood flow by means of radiation counters contained in large collimating tubes adjacent to the head of pre-surgical patients as they processed auditory stimuli. With this technique the first asymmetry for perception of speech and music were reported for the left and right hemispheres, respectively [2, 3]. With faster computers and sophisticated algorithms (*e.g.*, correcting for peripheral blood flow), xenon could be inhaled and thus safely used with non-pre-surgical subjects. Other imaging techniques of cognitive function continued to be developed including Single Proton Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI). With increasing strength of magnets, fMRI has greater temporal and spatial resolution to measure, noninvasively, the minute changes in blood flow at the time of cognitive processing. Studies with fMRI are the basis of the analyses of localized brain activation in this report. Newer techniques such as Diffusion Tensor Imaging (DTI) and fMRI measures of resting state have begun to provide additional information, especially with respect to the connectivity of systems and circuits.

Dichotomy of Emotion

Motivated behavior –working toward a reward or avoiding punishment - was first studied in animals. J.A. Gray [4] was among the most influential theorists to develop these concepts in humans. The aversive system (avoiding punishment) was termed the Behavioral Inhibition System (BIS); reward (or non-punishment) was termed by Fowles [5] the Behavior Activation System (BAS). For some, behavioral inhibition implied anxiety about receiving punishment; while behavioral activity implied action. Fowles [5] redefined this dichotomy in terms of aversive and appetitive. "Aversive" implied a negative affect while "appetitive" implied a positive one. From this dichotomy, the labels, "avoidance" and "approach," respectively, were derived and later applied to studies of addiction vulnerability in animals and humans.

Validation of the behavioral inhibition and activation dichotomy (BIS/BAS) in humans was accomplished with a short assessment instrument [6]. Compared to other predictive measures of personality, this instrument seemed to be the best for predicting aversion in the form of nervousness in response to impending punishment and happiness in response to an impending reward. Factor analyses among the various personality measures invariably led to a two-factor solution: one termed "avoidance temperament" that included BIS, introversion, and negative emotionality; the other termed "approach temperament" that included BAS, extraversion and positive emotionality. While it was not considered in early studies, addiction researchers adopted the BIS/BAS dichotomy to demonstrate "impulsiveness" or lack of inhibition correlated with BIS. Craving might be considered to be an act or desire for approach.

Laterality of Emotion

Specific aspects of emotion are lateralized. For example, depressive affect was most often reported in patients with damage to the anterior left cerebral hemisphere (*e.g.*, from stroke); euphoria followed right hemisphere damage. In accordance with left/right hemispheric differences in emotion but relevant to the data presented here, Richard Davidson demonstrated left/right asymmetries for approach and avoidance behavior, respectively. The anterior (temporal) left hemisphere was more active in response to happy stimuli; the anterior right was more active in response to the stimuli evoking disgust [7]. Subsequent studies demonstrated similar right/left asymmetry for measures of BIS/BAS [8]. Thus, it was concluded from these various studies that left hemisphere activation is associated with approach, pleasant (happy) scenes, or reward, while right hemisphere activation is associated with sad or aversive reactions.

However, approach and positive, or avoidance and negative, are not equivalent concepts. Approach and avoidance are action-oriented - movement toward or away - likely due to motivation. By contrast, positive and negative are valence qualities that do not necessarily invoke action *per se*. To check this, an fMRI study assessed eating habits in a culture in which individuals would "approach" something appetizing to eat that they might normally avoid (*e.g.*, insects) and avoid something tasty they might normally approach (*e.g.*, steak) [9]. There was left dorsolateral prefrontal activation for approach but no significant laterality for valence (*i.e.*, a positive or negative inclination for the stimuli). In addition, there was a significant correlation between overall BAS and left activation; there was no correlation for BIS. The concept that motivation, and not valence, is the most important feature for lateral specialization was also demonstrated in a series of articles where aggression, especially caused by anger, was, in fact, an *approach* behavior [10]. There was a significant correlation between anger assessments and left frontal brain activation. The more that anger aggression could be shown to be associated with heightened motivation, the stronger the left frontal activation. Thus, these studies support the contention that left hemisphere activity is associated with approach regardless of the pleasantness or unpleasantness of the valence. By face value, craving could be considered a desire to approach. This is discussed in more detail, together with relevant studies, in the Discussion.

Laterality of Drug Effects on Morphology and Activation

There are studies reporting lateralized drug effects on the brain and behavior. However, the studies do not specifically intend to determine if there are hemispheric differences per se; such differences are usually reported as part of the full accounting of the results in response to the purposes of the

individual studies. Review of the literature reveals mixed results. While most, if not all, studies report bilateral involvement, there are a number of studies that also demonstrate that specific psychoactive drugs may affect one hemisphere more or differently than the other. The following sections summarize the evidence for the laterality of drug effects derived from a wide range of studies designed for purposes other than laterality.

Alcohol. The effects of alcohol on brain development and anatomy are assessed by magnetic resonance imaging (MRI) and most commonly focused on one of three conditions: fetal alcohol exposure, binge or heavy drinking in adolescents, or adult alcoholics. In general, the consequences are reported as reduced gray matter volume, or reduced cortical thickness, bilaterally. However, in studies of development, cortical thickness is sometimes *greater* than a comparison group because alcohol exposure interferes with age-related neuronal pruning together with increased myelination. A comprehensive MRI study of children with fetal alcohol syndrome reported smaller frontal lobes, bilaterally, as well as smaller basal ganglia and hippocampus [11] and a study, using magnetic resonance spectroscopy (MRS), reported metabolic effects of reduced choline concentrations [12]. There are a few studies of fetal exposure where the damage is more to the left hemisphere in a variety of structures [13, 14, 15, 16]. While most studies are cross-sectional, as to age, one study assessed children with fetal exposure at two time points in development. Here, the natural thinning (synaptic pruning) of white matter development was arrested in the left medial superior frontal gyrus [17]. Studies of binge-drinking adolescents also showed more involvement of the left hemisphere either in terms of increased gray matter volume in frontal regions including the mid-dorsolateral prefrontal cortex [18] or other frontal structures that differed between males and females [19]. In adolescents with alcoholic use disorder, hippocampal volume was reportedly reduced bilaterally [20] or in the left hippocampus [21]. In adult alcoholics, the effects may be opposite: while gray matter reduction is usually reported for both hemispheres, one study implicated only the right hippocampus [22]. In addition, in a study of cortical thickness, several structures of the right hemisphere were affected while those in the left were not, with the caveat that a minority of the subjects had abused other substances [23]. And finally, in an MRI study with verbal (words) and non-verbal (faces) memory encoding tasks that should favor left and right hippocampi respectively, alcohol did not affect performances by the left hemisphere but did affect activity in the right hemisphere [24]. In summary, it appears that in developing brains (prenatal exposure, adolescent use), alcohol affects the left hemisphere (or both hemispheres) more than the right, while in the mature brain (alcoholics), structures in the right hemisphere are more affected.

Nicotine. In general, maternal smoking during pregnancy results in reduced gray matter volume or cortical thinning in the offspring. The reductions are most often bilateral but when there is an asymmetry, it is usually the left side that was most affected. In addition, it appears that females are more vulnerable than males. In adults, measurement of gray matter volume or density in heavy smokers typically reveals bilateral reductions in the frontal cortical areas and/or basal ganglia or insula. However, several studies reported reduced gray matter volume in specific structures of the left hemisphere including the insula [25], nucleus accumbens [26], dorsal anterior cingulate cortex [27], and lower density in the left prefrontal cortex, but increased density in the (left) insula [28]. Unilateral reduction in right hemisphere structures was rarely mentioned but has been reported for the olfactory gyrus and anterior cingulate cortex [25] and the cerebellum [27]. A study of brain activation following nicotine infusion showed increased activity bilaterally in several structures but also decreased activity in some structures including the left hippocampus, which was the only unilateral structure mentioned [29]. Overall, nicotine seems to affect the left hemisphere structures more than the right.

Cocaine. Gray matter volume is usually reported to be bilaterally reduced in individuals exposed to cocaine *in utero* [30]. However, specific structures vary among reports. Volume reduction measured in exposed infants is associated with deficits in prefrontal and frontal regions (dorsal prefrontal cortex is specifically cited) [31]. In teenagers exposed *in utero*, reductions are reported but in one study only the thalamus and putamen are mentioned [32] while in a similar population, several structures were mentioned including the putamen, amygdala, insula, hippocampus and several cortical structures but *not* the thalamus [33]. And yet another study cited thinner cortical thickness only in the right dorsolateral prefrontal cortex [34]. A plausible explanation as to why frontal and striatal areas are affected more than posterior cortical areas is that they are richer in dopamine, a neurotransmitter system directly affected by cocaine.

In adults with cocaine use disorders, reductions in gray matter volume are regularly reported. Most reports show bilateral reduction in various cortical structures [35], often including reward areas. However, there is a preponderance of specific volume reductions reported for structures of the right hemisphere, notably the dorsolateral prefrontal cortex [36]. These areas include the anterior cingulate [37], amygdala [38], putamen and insula [39, 40]. The orbitofrontal cortex was the one structure in which a few reports found more volume reduction in the left hemisphere [36, 40]. It is important to point out that differences in gray matter reduction for specific structures may, in part, be due to sex differences [41]. This interaction was strikingly clear in a study where there was a bilateral thinning in the insulae of substance dependent individuals but when compared to same-sex controls, females had smaller insulae whereas males' insulae were larger [42]. Thus for the most part, laterality effects due to prenatal exposure is rarely reported while the right hemisphere appears to be more affected in adults.

Opiates. There are considerably fewer studies that assess the effect of long-term heroin use on brain morphology or physiology. One comprehensive study of prenatal exposure albeit with few (n=10) opiate-exposed children reported several structures of reduced volume both in cortical and basal ganglia areas. However, cortical thinness was found only in the right anterior cingulate and right lateral orbitofrontal cortices [43]. In adult heroin addicts, frontal areas have reduced gray matter density or volume either bilaterally [44] or more on the right; posterior structures are more affected on the left [45, 46]. In a SPECT study of

regional cerebral blood flow (rCBF), there was bilateral increase in rCBF in the dorsal cortical areas in opiate-dependent patients but there were areas of lateral increase that differed between subject groups: in healthy controls rCBF increased in the right hemisphere, whereas increases in the patients were in the left hemisphere [47]. In a study on patients with opiate addiction Diffusion Tensor Imaging (DTI) was used to assess the integrity of (white matter) fiber tracts. Three tracts were found to have decreased fractional anisotrophy (FA) in both the left and right hemispheres, but only the superior longitudinal fasciculus of the right frontal tract was significantly correlated with years of use [48]. Taken together, these diverse studies suggest that opiates seem to asymmetrically affect the right hemisphere more than the left.

Cannabis. The effect of cannabis on the brain was summarized in two comprehensive reviews: one on structure and function in chronic users [49] and another on acute effects on brain activation in occasional users or non-users [50]. The most often reported effect on gray matter volume was bilateral reduction in the hippocampus, but several reports also demonstrated effects in the amygdala, cerebellum and frontal cortex. These latter effects were not always decreases; increases were also noted, which may be due to failure of synaptic pruning during development. Functional neuroimaging studies generally showed reductions in resting state blood flow that the authors suggest may be due to down-regulation of CB1 (cannabinoid) receptors. Performance of cognitive tasks in chronic users did not differ from non-using subjects, but different brain areas were activated. Whether or not the structures in one hemisphere were affected more than the other during functional imaging, was not addressed. However, results cited in their review indicated the right hemisphere, especially prefrontal cortex, was the most affected. In contrast to the chronic users, the acute effect of resting state in occasional users was an increase in blood flow particularly in regions rich in CB1 receptors. Presumably, down-regulation of these receptors had not occurred in these subjects. Also in contrast to chronic users, there appears to be a decline in cognitive processes, especially memory, though the differences in activated areas of the brain differed, again reflecting recruitment of different mechanisms. No laterality was reported and none was evident by examining individual results. A few studies report sex differences in morphology and activation. One study reported *increased* gray matter in the right amygdala for females only - no effect for males [51]. Another study reported slightly larger volumes in the prefrontal cortex for female marijuana smokers; slightly smaller for males [52]. An important genetic study assessed the effect of polymorphisms of the COMT gene (*val/val, val/met, met/met*) on brain volumes in male heavy cannabis users with early age (<14 yrs) onset [53]. The results showed that a higher copy number of the *val* allele was associated *lesser* volume in the bilateral ventral caudate nucleus in chronic users and *larger* volumes in controls. By contrast, the opposite effect was seen for the left amygdala where a greater number of the *val* alleles resulted in *increased* volume in chronic users and *lesser* volume in controls. A possible explanation involves the dopamine system and the effect cannabis has on brain development during adolescence. In summary, it appears there are fewer effects on laterality due to cannabis, but there are provocative reports of sex differences and genetic variation.

Laterality of Activation

This report highlights left/right hemisphere activation asymmetries for two important behavioral risk factors associated with addiction: impulsivity and craving. Theoretically, impulsive individuals are more likely to be vulnerable to initiate drug-taking and, being unable to restrain themselves, continue to abuse and become addicted. Two tasks (*Stop Signal* and *Go/No-Go*) assessing impulsivity - the *in*ability to restrain action (called response inhibition) were designed to be administered in a brain scanner so as to assess associated brain activation. Brain areas associated with control of impulsive actions would presumably be associated with control of addiction vulnerability. A similar justification drives research in craving. If brain areas involved in craving can be discovered, they will provide possible targets for intervention. While studies usually report left and right activation, the great majority of these studies report the results without explanation or speculation as to why they are so lateralized. Outlined above are theoretical constructs for specialized function for the two hemispheres as well as the influence of the drugs themselves. In the Discussion, the consequences of differential brain activation for risk factors of addiction are presented in the context of cognitive function and neurophysiological systems. The hope is that discussion of these data and associated factors will stimulate new paradigms of study focusing on laterality differences to better understand the underlying factors of addiction.

METHODS

Strategy of Tabulation

Brain areas activated by tests of response inhibition or induction of craving are tabulated in fMRI studies where central coordinates (peaks) are reported. While Talairach or MNI coordinates were acceptable, MNI coordinates were transcribed into Talairach coordinates using one of the formula sets published online by M. Brett (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Conventional analyses would not work in this analysis because studies differ in selections of locations and names as well methodologies for imaging and morphing algorithms [54]. Importantly, for this analysis, the main interest was to compare activation peaks between the left and right hemispheres, so methodological confounds across studies are not a factor. Activation peaks are located in an arbitrary way by subdividing each hemisphere into eight sections which we have termed “octants” (eighths) defined by the following coordinates: $0 \leq |X| < 30$ or $30 \geq |X|$; $\pm Y$; and $\pm Z$. Thirty was arbitrarily chosen in the “X” direction because it is about halfway along this axis, thereby distinguishing medial from lateral. Positive and negative values of Y and Z located the coordinates into anterior/posterior and superior/inferior sectors, respectively. An initial attempt to tabulate specific structures across studies did not yield sufficient data to assess lateralization. Nevertheless, there are important structures associated with addiction which do not fit

uniquely into one of the arbitrary octants, so separate analyses were done on these structures defined by coordinates that would likely include them: Amygdala (|X|<35; |Y|<15; -30>Z>-10); Insula (|X|>30; |Y|<25; |Z|<15); Hippocampus (15<|X|<40; -40<Y<5; -30<Z<-10). However, as important as these structures are for addiction only a few categories of studies - response inhibition, alcohol, or nicotine craving - had enough data points to analyze, highlighting the problem of analyzing individual structures according to left/right asymmetries.

Studies included in the tabulation were derived from key word searches in PubMed. The terms, "fMRI" or "imaging," were combined with either "go/no-go" or "stop signal" for the measures of impulsivity or names of individual substances (*e.g.*, nicotine, alcohol, *etc*.) for craving. Studies were included regardless of their method of analysis (*e.g.*, ROI, whole brain, *etc*.) since methodology would not affect the left/right comparison. Studies were excluded if their paradigms did not provide a clear, direct inducement of brain activation. For example, some paradigms focused on attention bias whereby subjects were required to attend or ignore a secondary (distracting) stimulus while doing a Go/No-Go task. Similarly, some studies of craving had multiple experimental paradigms rather than straight-forward visual cues presented to induce craving. In studies where medications were being assessed, only the placebo group or condition was included.

The data are presented in tabular form - the number of peaks in the left and right hemispheres subdivided into octants as defined above. Laterality measures were given as percent differences: the difference between the number of peaks in the right and left side divided by the total number of peaks: R-L/R+L.

Characteristics of Studies Included (Studies are Referenced in Supplementary Material)

Go/No-Go. Response inhibition - a measure of the ability to inhibit an impulsive, prepotent action is assessed. A total of fifteen studies included 409 subjects and 218 peaks. A typical task required the subject to press a button as quickly as possible whenever there was a (experimenter-designated) positive stimulus and refrain from pressing for a non-positive stimulus. The stimuli were typically letters but some were geometric figures, pictures, or words. Activation peaks for correct inhibition were included in the tabulation.

Stop Signal. Response inhibition - a measure of the ability to inhibit an impulsive, prepotent action is assessed. A total of twelve studies included 274 subjects and 156 peaks. A typical task required the subject to press a button as quickly as possible after stimuli were each presented one at a time, but refrain from pressing when a "stop" signal was presented. The stop signal was given in close succession to one of the presentation stimuli to see if the subject could suppress a prepotent response. The stimuli and the stop signal could be either in the visual or auditory modality. Activation peaks for successful stops were included in the tabulation.

Nicotine. A total of eighteen studies included 437 subjects and 254 peaks. Among the studies, subjects were described either as "smokers" or "nicotine dependent." To induce craving in smokers, either visual (pictures or videos) or tactile cues were used. About half the studies allowed smokers to have their smokes prior to imaging; the other studies required abstinence for several hours to a day.

Alcohol. A total of twelve studies included 260 subjects and 95 peaks. The combined subjects included social drinkers as well as those with various clinical designations - alcoholics, alcohol use disorder, alcohol dependence. The studies were designed to induce craving by one of various methods - showing pictures, words, or listening to scripts. In all but two studies, subjects refrained from taking alcohol for one or more days. In one of the two studies where there was no drinking restriction, subjects were given a small taste of alcohol in an attempt to increase their craving. Cravings were usually assessed by questionnaire or with a Likert scale. Activation data reflected either cue-inducement directly or correlation with craving.

Cocaine. In total there were only five studies; 84 subjects and 66 peaks were included. All but one of the studies reported subjects to be abstinent at the time of the imaging. All subjects were described as cocaine dependent. Cue-inducing stimuli were either pictures or videos of cocaine paraphernalia or action of use, or scripts based on the subjects' experiences.

Heroin. A total of eight studies included 204 subjects and 158 peaks. All but one study included only males. The subjects were described as "temporarily abstinent" except for three studies where the subjects were on methadone maintenance. Cues to induce craving were pictures of paraphernalia or individuals using.

Cannabis. In total there were only five studies; 117 subjects and 65 peaks were included. Subjects were abstinent from marijuana use for a day or more, although one study required that subjects abstain only overnight; another study had no restrictions. Cues to induce craving were either visual or tactile.

Food. A total of fourteen studies included 206 subjects and 186 peaks. The subjects were generally healthy; three studies included obese (but otherwise healthy) subjects. For the most part, subjects were not deprived from eating; two studies required an overnight fast. Cue stimuli included food pictures of usually desirable foods, or scripts describing food. One study focused on chocolate. Some studies included only males, some only females, or both; overall there were about equal numbers of males and females.

Gaming. A total of seven studies included 149 subjects and 93 peaks. All but one study used various diagnostic instruments to assess internet gaming addiction. All but one study used only male subjects. Some subjects were recruited if they also smoked; others if they did not smoke. Cues were usually pictures of gaming situations and, in one case, a video.

RESULTS

Measures of Impulsivity (Response Inhibition)

Most activation peaks favored the right hemisphere for both impulsivity (Go/No-Go and Stop Signal) tasks. Of the

two, the Stop Signal tasks had the larger right hemisphere asymmetries. Overall, the percent difference - the number of right peaks minus the number of left peaks divided by the total number of peaks (R-L/R+L) - was 32% (X^2 = 16.026; p < 0.0001). However, this asymmetry was primarily for anterior peaks (Y>0) (46.8%; X^2 = 17.329; p < 0.0001). See Fig. (**1**); Table **1** for details. The largest asymmetries were in the two anterior, medial octants: |X|<30; Y>0; Z<0 which includes the orbital frontal cortex where all five of the activations were on the right side (X^2 = 5.00; p < 0.025), and |X|<30; Y>0; Z>0 which includes the anterior cingulate where there were 3 times as many peaks (21 right; 7 left) (X^2 = 7.00; p < 0.01). Interestingly, there was no significant asymmetry in those same two octants for the Go/No-Go tasks. The asymmetry in the octant that includes the dorsolateral prefrontal cortex was significant for both the Go/No-Go task (36.4%; X^2 = 5.818; p < 0.02) and the Stop Signal task (44.8%; X^2 = 5.828; p < 0.02). Apparently, the areas that contribute to the performance for the 2 tasks are somewhat different, implying different cognitive functions are operating. *Overall*, peaks in posterior regions (Y<0), favored the right hemisphere but not significantly because those in the superior regions (Y<0; Z>0) significantly favored the right hemisphere while those inferior (Y<0; Z<0) significantly favored the left. This pattern was most prominent in the medial octant (|X|<30; Y<0; Z<0) where there were more peaks were on the left side (two few to reach significance). There were enough peaks to assess the asymmetry for the insula which significantly favored the right hemisphere (Go/No-Go: 57.1%, X^2 = 4.571, p < 0.05; Stop Signal: 73.3%, X^2 = 6.721, p < 0.01). This means that the posterior octants favoring the left hemisphere are posterior to the insula and so more posterior than Y=-25, located in either the occipital or temporal cortices. There were very few reported peaks that fell in the region of the hippocampus or the amygdala.

Measures of Craving

The asymmetries for brain activations for cue-induced craving were opposite to the asymmetries for impulsivity. Across all studies, regardless of the substance craved, the

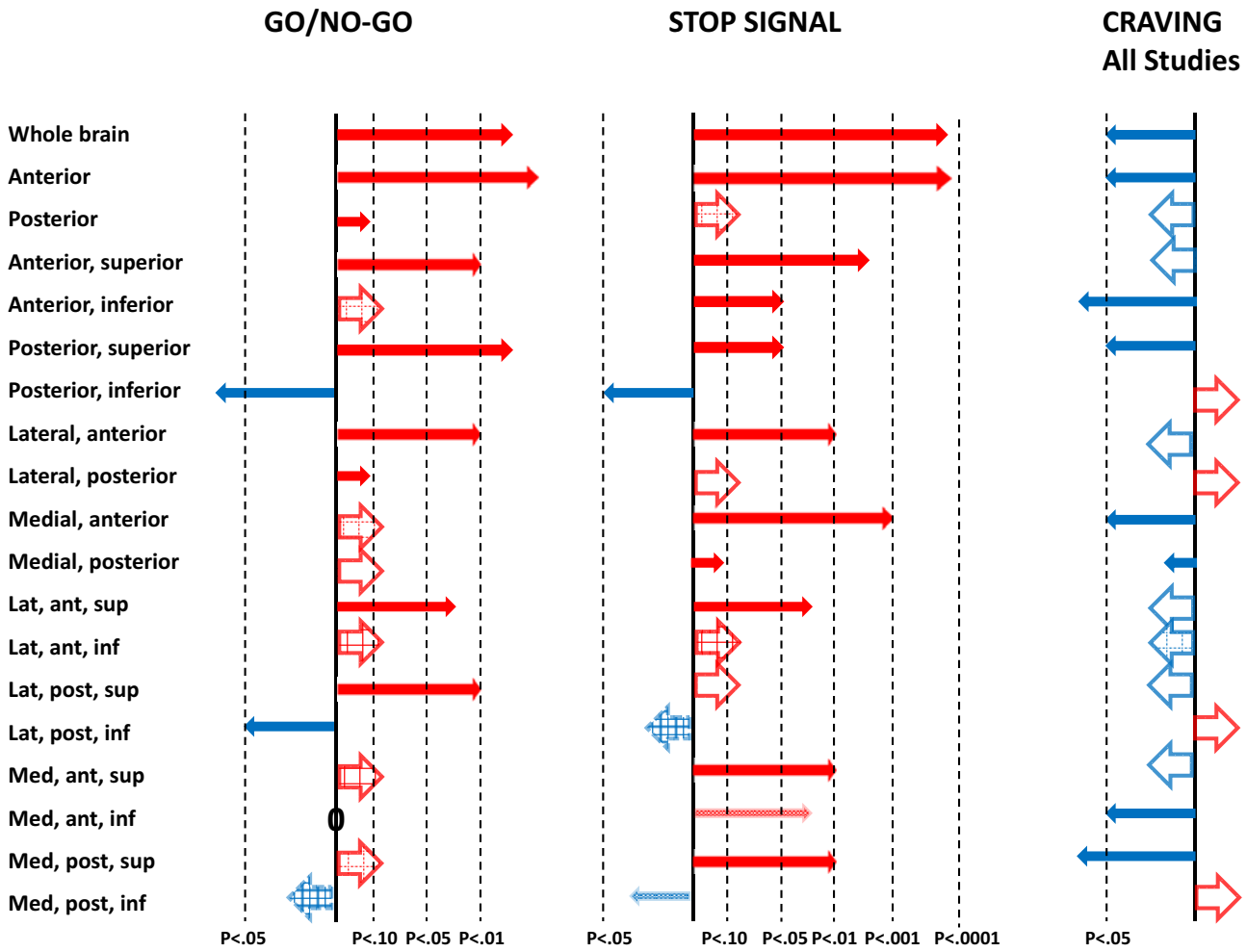

Fig. (1). Differential brain activation shows lateralization to areas of the left and right hemispheres for measures of impulsivity and craving. Solid arrows represent statistically significant differences (X) with arrow length ranging from marginally significant (P<0.1) to highly significant (P<0.0001); red, right preference; blue, left preference. Sections in which data are taken from fewer than 10 peaks are represented in fainter colors. Short, thick arrows represent activation differences in sections which were not statistically significant; the magnitude of percent differences are represented by 4 "fill" patterns from blank to increasingly dense grids: <10%, 10-24.9%, 25-49.0%, >50%. Where data are fewer than 10 peaks, arrow borders are dashes. See tables and supplementary material for details.

Table 1. Summary (R-L/R+L x 100).

Coordinates	GO/ NO-GO	Stop	Alcohol	Nicotine			Cocaine	Heroin	Marijuana	Food	Game
				All	Depr'd	Sati'd					
Total **# pks**	**+21.1†** 218	**+32.0‡** 156	**-9.7** 195	**+1.6** 254	**-13.1** 99	**+11.0** 155	**-18.2** 63	**-5.1** 58	**-4.6** 65	**-14.0** 186	**-1.1** 93
Y>0 **# pks**	**+26.9‡** 104	**+46.8‡** 79	**-16.3** 86	**-3.0** 97	**-25.0** 40	**+22.8** 57	**-13.3** 30	**-17.6** 51	**-16.7** 24	**-34.4†** 64	**+15.8** 38
Y<0 **# pks**	**+15.8** 114	**+17.9** 77	**-4.6** 109	**+0.1** 157	**-5.1** 59	**+4.1** 98	**-22.0** 36	**+1.0** 107	**+2.4** 41	**-3.3** 122	**-12.7** 55
Y>0; **Z>0**	**+32.8†** 68	**+47.4†** 57	**-17.6** 51	**+10.7** 56	**-18.5** 27	**+37.9*** 29	**-20.0** 20	**-20.0** 30	**+20.0** 10	**-25.5** 40	**+17.2** 29
Y>0; **Z<0**	**+16.7** 36	**+45.4*** 22	**-14.3** 35	**-7.3** 41	**-38.5** 13	**+7.1** 28	**0.0** 10	**-14.3** 19	**-42.8** 14	**-50.0*** 24	**+11.1** 9
Y<0; **Z>0**	**+28.0†** 100	**+27.5*** 69	**-5.6** 72	**-6.9** 101	**-17.1** 41	**0.0** 60	**-33.3** 21	**-12.7** 55	**+4.8** 21	**-10.3** 58	**-45.4*** 22
Y<0; **Z<0**	**-81.8*** 13	**-75.0*** 8	**-2.7** 37	**+14.3** 56	**+22.2** 18	**+10.5** 38	**-6.7** 15	**+15.4** 52	**0.0** 20	**+3.1** 64	**+9.1** 33
|X|>30; **Y>0**	**+32.8†** 68	**+39.1†** 46	**-14.3** 21	**-7.1** 28	**-33.3** 12	**+12.5** 16	**-14.3** 14	**+5.9** 17	**+50.0** 8	**-52.4*** 21	**+5.3** 19
|X|>30; **Y<0**	**+20.0** 75	**+3.7** 27	**-10.6** 47	**+4.9** 61	**-4.0** 25	**+11.1** 36	**-5.9** 17	**+5.0** 30	**+26.0** 19	**+3.2** 62	**+15.4** 26
|X|<30; **Y>0**	**+16.7** 36	**+57.6‡** 33	**-16.9** 65	**+7.2** 69	**-21.4** 28	**+26.8** 41	**-12.5** 16	**-29.4** 34	**-50.0*** 16	**-25.6** 43	**+26.3** 19
|X|<30; **Y<0**	**+7.7** 37	**+24.0** 50	**0.0** 62	**-2.0** 96	**-5.9** 34	**0.0** 62	**-36.8** 19	**-1.5** 67	**-19.0** 21	**-10.0** 60	**-37.9*** 29
|X|>30; **Y>0;** **Z>0**	**+36.4*** 34	**+44.8*** 29	**-23.0** 13	**+6.7** 15	**-42.8** 7	**+50.0** 8	**0.0** 10	**-20.0** 10	**+60.0** 5	**-46.7** 15	**+5.9** 17
|X|>30; **Y>0;** **Z<0**	**+25.0** 24	**+29.4** 17	**0.0** 8	**-23.0** 13	**-20.0** 5	**-25.5** 8	**-50.0** 4	**+42.8** 7	**+33.3** 3	**-66.7** 6	**0.0** 2
|X|>30; **Y<0;** **Z>0**	**+34.4†** 64	**+7.7** 26	**-7.7** 26	**-2.6** 39	**-14.3** 15	**0.0** 24	**-11.1** 9	**-14.3** 21	**+20.0** 10	**0.0** 32	**+14.3** 7
|X|>30; **Y<0;** **Z<0**	**-63.6*** 11	**-100** 1	**-14.3** 21	**+18.2** 22	**0.0** 10	**+33.3** 12	**-11.1** 9	**+26.3** 19	**+33.3** 9	**+3.2** 31	**+15.8** 19
|X|<30; **Y>0;** **Z>0**	**+25.0** 24	**+50.0†** 28	**-15.8** 38	**+12.2** 41	**-10.0** 20	**+33.3** 21	**-40.0** 10	**-20.0** 20	**-20.0** 5	**-12.0** 25	**+33.3** 12
|X|<30; **Y>0;** **Z<0**	**0.0** 12	**+100*** 5	**-18.5** 27	**0.0** 28	**-50.0** 8	**+20.0** 20	**+33.3** 6	**-42.5** 14	**-63.6*** 11	**-44.4** 18	**+14.3** 7
|X|<30; **Y<0;** **Z>0**	**+16.7** 36	**+39.5†** **43**	**-4.3** 46	**-9.7** 62	**-23.1** 26	**0.0** 36	**-50.0** 12	**-11.8** 34	**-9.1** 11	**-23.1** 26	**-73.3†** 15
|X|<30; **Y<0;** **Z<0**	**-100** 3	**-71.4** 7	**+12.5** 16	**+11.8** 34	**+50.0** 8	**0.0** 26	**0.0** 6	**+9.1** 33	**-27.3** 11	**+3.0** 33	**0.0** 14
Amygdala	**0.0** 2	**0.0** 0	**-27.2** 11	**+16.7** 12	**0.0** 4	**+25.0** 8	--	--	--	--	--
Insula	**+57.1*** 14	**+73.3†** 15	**-33.3** 9	**-22.2** 18	**-27.3** 11	**-14.3** 7	--	--	--	--	--
Hippocampus	**-33.3** 3	**0.0** 0	**+24.0** 8	**-5.3** 19	**-42.8** 7	**+16.7** 12	--	--	--	--	--

***p < 0.05; †p < 0.01; ‡p < 0.001.**

difference in over 1000 activation peaks favored the left hemisphere by 6.7% ($X^2 = 4.028$; $p < 0.05$). See Fig. (**1**); Table **2** for details. For peaks measured in the anterior half of the brain (Y>0), the difference was 11.3 % ($X^2 = 4.96$; $p < 0.03$). In fact, the asymmetry was consistently left for most of the brain sections. However, due to the small number of peaks, the differences were not always significant. The exceptions were posterior (Y<0) and inferior (Z<0) where the asymmetry favored the right side. These were the same octants that favored a *left* asymmetry for the impulsivity tasks! The brain octant that includes the orbitofrontal cortex (|X|<30; Y>0; Z<0) had the largest difference (20.7%; $X^2 = 4.766$; $p < 0.03$). The insula also favored the left side (25.9%) for alcohol and nicotine combined but, probably due to the few peaks, the asymmetry was not significant.

Importantly, the asymmetry of peak counts for most of the individual substance-specific study groups consistently favored the left hemisphere for areas of the brain. The most consistent groups showing left hemisphere asymmetry were alcohol, cocaine, and food, followed by heroin and marijuana, at least for the medial areas. However, in spite of these consistencies, most asymmetries did not reach significance - again, likely due to the smaller number of peaks in each brain section. The 2 groups that did not seem to show a consistent asymmetry pattern were nicotine and gaming. Interestingly, results in the nicotine group depended on whether the subjects were deprived of smoking prior to the fMRI study session. The deprived subjects had left hemisphere preferential responses, while the satiated subjects had relatively increased activation in the right hemisphere. When the satiated nicotine group and the gaming group were removed from remaining craving groups, the significant differences increased, as might be expected. For all points the difference favored the left hemisphere by 10.5% ($X^2 = 8.532$; $p < 0.01$ and for all the anterior peaks(Y>0): 21.3% ($X^2 = 13.454$; $p < 0.001$).

Alcohol*.* Cue-activated craving consistently activated sections of the left hemisphere. See Fig. (**2**); Table **1** for details. The larger asymmetries were located anteriorly (Y>0); the octant with the largest asymmetry (23%) included the (left) dorsolateral prefrontal cortex. The second largest asymmetries were the octants that included the orbitofrontal cortex (18.5%) and the anterior cingulate cortex (15.8%). While craving consistently activated the left hemisphere for most octants and for the amygdala and insula, no asymmetry was significant. The hippocampus had a slight right asymmetry, as did the posterior, inferior, medial octant (X<30; Y<0; Z<0).

Nicotine*:* There was virtually no asymmetry of peak activation overall (only a non-significant 1.6% favoring the right) and no obvious pattern for the individual octants. However, the pattern changed dramatically when the studies were divided into those where the subjects were allowed (satiated) or not allowed (deprived) to smoke prior to the fMRI session. See Fig. (**2**); Table **1** for details. Those who were deprived had consistently more brain activations in the left hemisphere for almost every brain section. The left hemisphere preference for the anterior sections (Y>0) tended to be larger in these deprived smokers than for all the other groups (except food). The largest differences were found in

Table 2. Craving: All Studies.

Brain Coordinates	Left	Right	R-L/R+L x 100
Total Brain	541	476	-6.7*
Y>0	217	173	-11.3*
Y<0	324	303	-3.3

All Studies (Y>0)

	Left	Right	R-L/R+L x 100
Z>0	126	110	-6.8
Z<0	91	63	-18.2*

All Studies (Y<0)

	Left	Right	R-L/R+L x 100
Z>0	195	155	-11.4*
Z<0	129	148	+6.8

All Studies (|X|>30)

	Left	Right	R-L/R+L x 100
Y>0	70	58	-7.0
Y<0	131	141	+3.7

All Studies (|X|<30)

	Left	Right	R-L/R+L x 100
Y>0	147	115	-12.2*
Y<0	193	162	-8.7

All Studies (|X|>30; Y>0)

	Left	Right	R-L/R+L x 100
Z>0	46	39	-8.2
Z<0	24	19	-11.6

All Studies (|X|>30; Y<0)

	Left	Right	R-L/R+L x 100
Z>0	74	70	-2.8
Z<0	59	71	+9.2

All Studies (|X|<30; Y>0)

	Left	Right	R-L/R+L x 100
Z>0	80	71	-6.0
Z<0	67	44	-20.7*

All Studies (|X|<30; Y<0)

	Left	Right	R-L/R+L x 100
Z>0	121	85	-17.5*
Z<0	70	77	+4.8

All Studies

	Left	Right	R-L/R+L x 100
Amygdala (|X|<35; | Y|<15; -30>Z>-10)	12	11	-4.3
Insula (|X|>30; |Y|<25; |Z|<15	17	10	-25.9
Hippocampus 15<|X|<40; -40<Y<5; -30<Z<-10	13	14	+3.7

***p < 0.05; †p < 0.01; ‡p < 0.001.**

the octants that includes the orbitofrontal cortex (50%) and the dorsolateral prefrontal cortex (42.8%) though, with too few points, not significant. The one exception for the deprived group, where there was a right asymmetry, was in the posterior/inferior/medial octant (X<30; Y<0; Z<0); but again, not significant.

By contrast, studies in which subjects were allowed to smoke (*i.e.*, satiated) prior to the fMRI session reported consistently more activations in the right hemisphere octants. Just like the deprived smokers, the largest asymmetry was in the dorsolateral prefrontal brain octant (50%), but in the opposite (right) direction.

For the most part, studies reported increased craving among their subjects whether or not they were deprived or allowed to smoke. It is not possible to compare the degree of craving between the deprived and satiated subject groups, but it is tempting to speculate that those who were deprived were more affected by the cues. That is, they likely had greater craving.

Cocaine. Peak activations for cue-induced cocaine craving consistently favored the left hemisphere in all but one octant. See Fig. (**3**); Table **1** for details. For this group, there were the fewest number of studies and therefore a few number of peaks reported. Though the left asymmetries are consistent, none was significant; the percent differences must be interpreted with caution. It is hard to speculate with so few peaks, but it is interesting to note that the only octant that had a few more peaks on the right side instead of the left included the orbitofrontal cortex which, as mentioned in the Introduction, was the only one where cocaine seemed to reduce gray matter in the left hemisphere.

Heroin. Asymmetry of peak counts for heroin cues was less consistent among brain sections. Like alcohol and deprived smokers, there were more peaks favoring the left side in the orbitofrontal cortex (42.5%) and in the dorsolateral prefrontal cortex (20%). See Fig. (**3**); Table **1** for details. And, as with both alcohol and cocaine studies, there was a greater left asymmetry (20%) in the superior, medial, frontal octant (X<-30; Y>0; Z>0) that includes the anterior

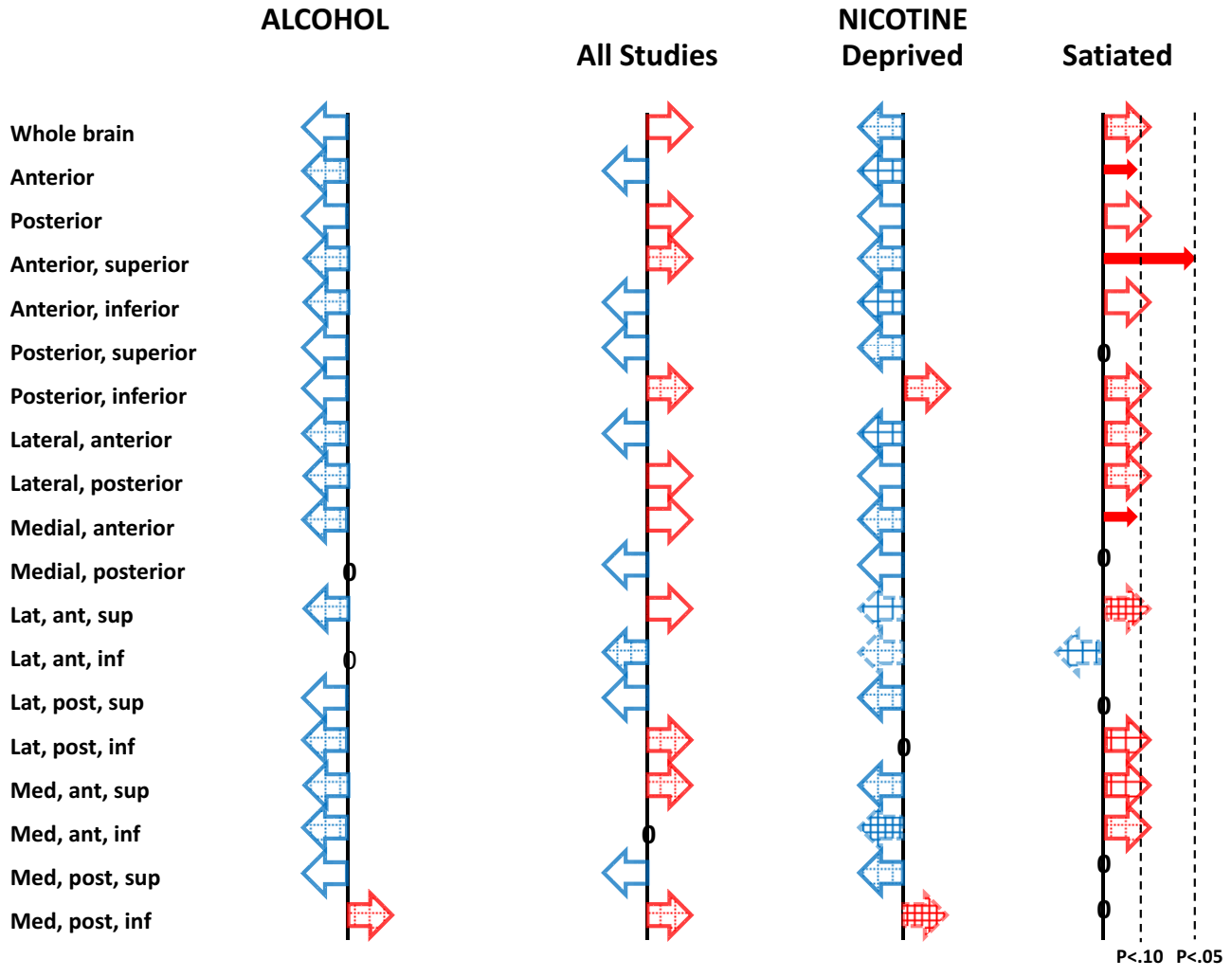

Fig. (2). Differential brain activation shows lateralization to areas of the left and right hemispheres for measures of impulsivity and craving. Solid arrows represent statistically significant differences (X) with arrow length ranging from marginally significant (P<0.1) to highly significant (P<0.0001); red, right preference; blue, left preference. Sections in which data are taken from fewer than 10 peaks are represented in fainter colors. Short, thick arrows represent activation differences in sections which were not statistically significant; the magnitude of percent differences are represented by 4 "fill" patterns from blank to increasingly dense grids: <10%, 10-24.9%, 25-49.0%, >50%. Where data are fewer than 10 peaks, arrow borders are dashes. See tables and supplementary material for details.

cingulate gyrus. Asymmetries favoring the right hemisphere were mostly posterior, inferior, both medial and lateral, although there was one asymmetry favoring the right hemisphere anteriorly (|X|>30; Y>0; Z<0). None reached significance.

Marijuana. Peaks for cue-induced craving in marijuana subjects gave a contrasting picture for peaks that were medial *versus* lateral. See Fig. (**3**); Table **1** for details. Overall there were more peaks in the left hemisphere for medial points but these were mostly attributed to those located anteriorly which reached significance in spite of the small numbers (|X|<30; Y>0; 50%; X^2 = 4.000; p < 0.05). This asymmetry was mostly due to the octant that included the orbitofrontal cortex (|X|<30; Y>0; Z<0; 63.6%; X^2 = 4.455; p < 0.05). However, by contrast, there was a consistent asymmetry toward the right hemisphere for peaks that were lateral and anterior both superiorly (which includes the dorsolateral prefrontal cortex) and inferiorly (which includes the ventrolateral prefrontal cortex). These few peak differences were not significant.

Food. Cue-induced craving for food produced essentially the same results as for the drugs, but with more peaks; some

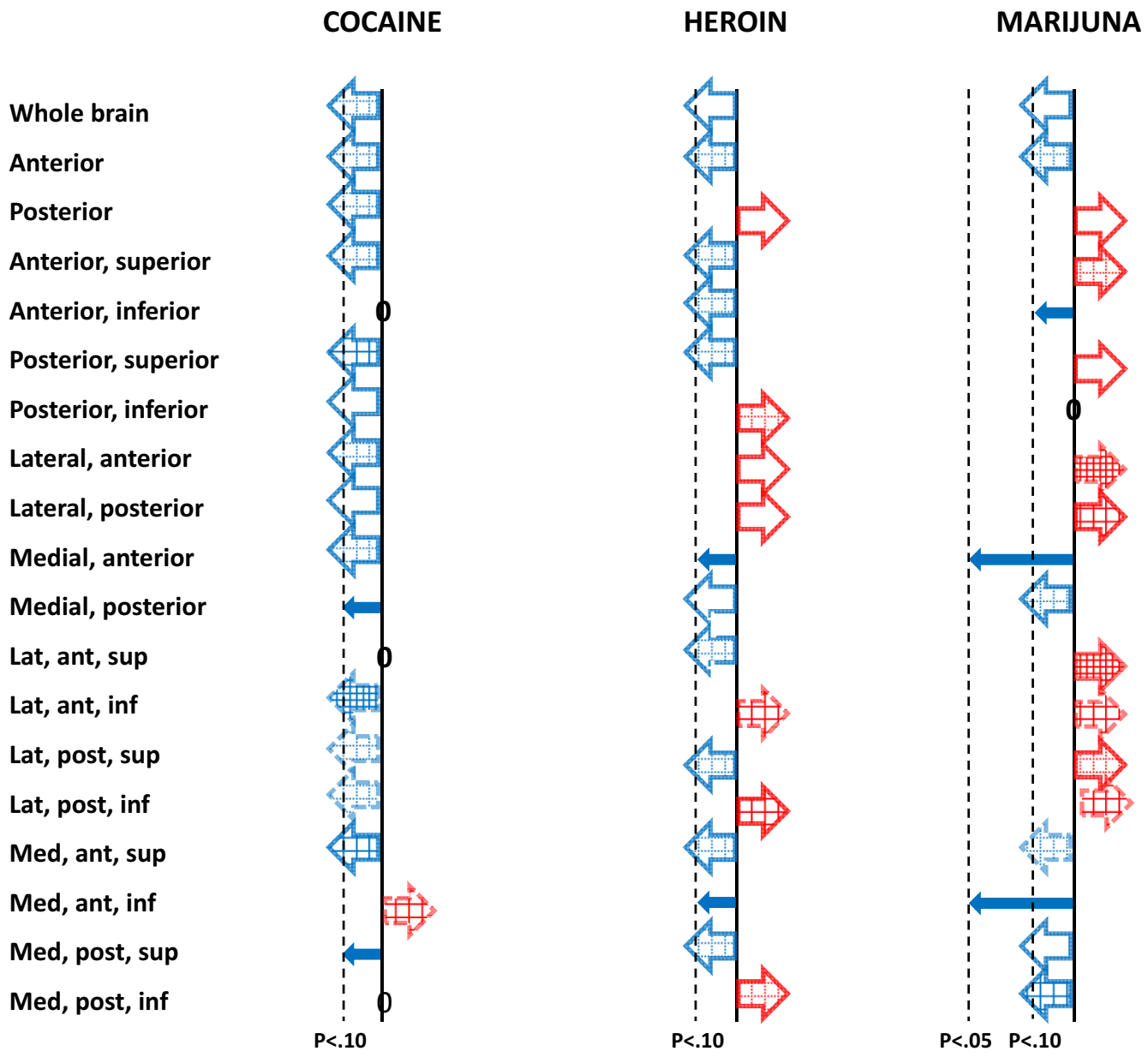

Fig. (3). Differential brain activation shows lateralization to areas of the left and right hemispheres for measures of impulsivity and craving. Solid arrows represent statistically significant differences (X) with arrow length ranging from marginally significant (P<0.1) to highly significant (P<0.0001); red, right preference; blue, left preference. Sections in which data are taken from fewer than 10 peaks are represented in fainter colors. Short, thick arrows represent activation differences in sections which were not statistically significant; the magnitude of percent differences are represented by 4 "fill" patterns from blank to increasingly dense grids: <10%, 10-24.9%, 25-49.0%, >50%. Where data are fewer than 10 peaks, arrow borders are dashes. See tables and supplementary material for details.

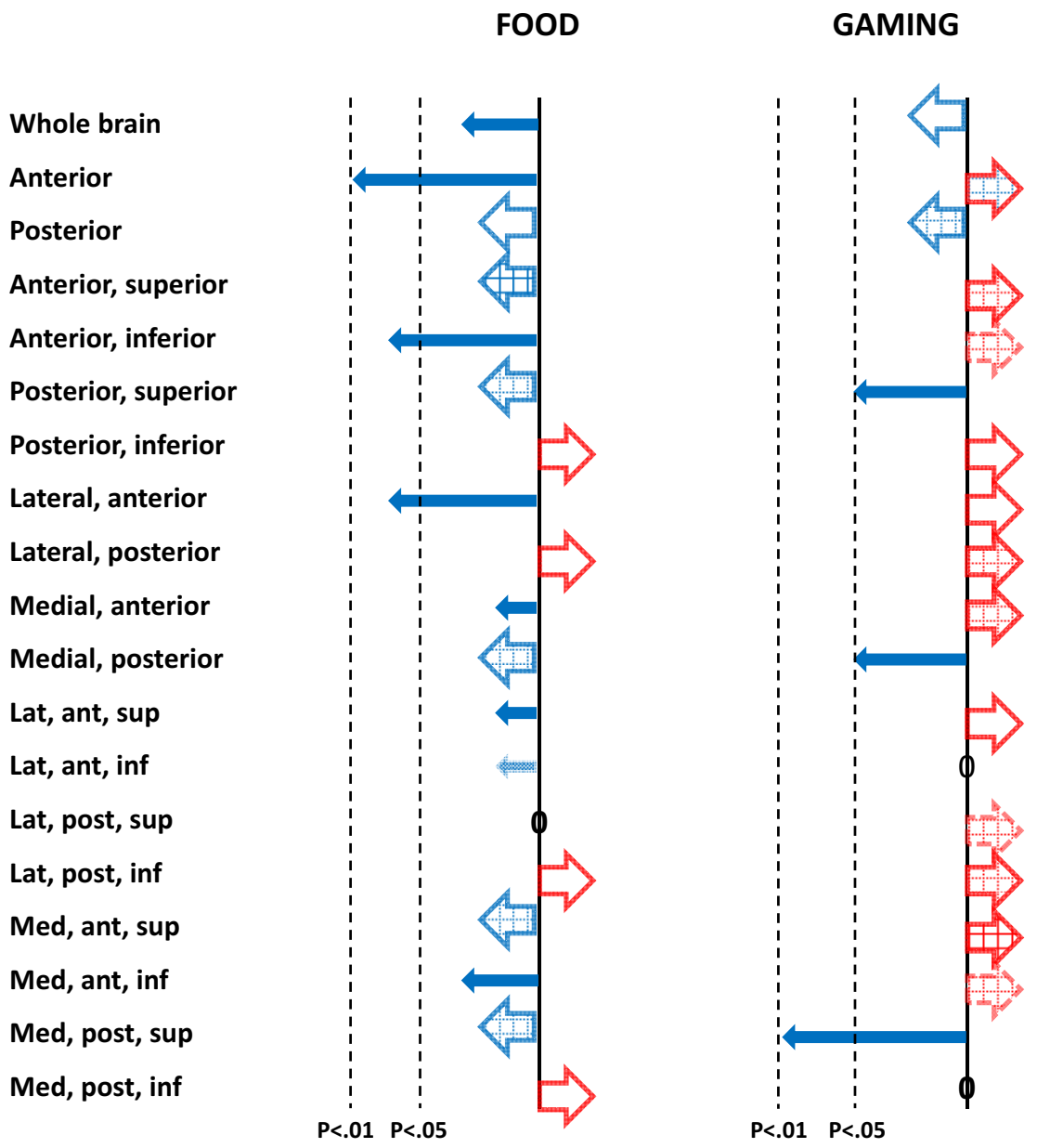

Fig. (4). Fig. (1). Differential brain activation shows lateralization to areas of the left and right hemispheres for measures of impulsivity and craving. Solid arrows represent statistically significant differences (X) with arrow length ranging from marginally significant (P<0.1) to highly significant (P<0.0001); red, right preference; blue, left preference. Sections in which data are taken from fewer than 10 peaks are represented in fainter colors. Short, thick arrows represent activation differences in sections which were not statistically significant; the magnitude of percent differences are represented by 4 "fill" patterns from blank to increasingly dense grids: <10%, 10-24.9%, 25-49.0%, >50%. Where data are fewer than 10 peaks, arrow borders are dashes. See tables and supplementary material for details.

asymmetries reached significance. See Fig. (**4**); Table **1** for details. For all peaks, the left hemisphere preference of 14% was marginally significant ($X^2 = 3.634$; $p < 0.06$). The large asymmetry of 34.4% for all anterior areas (Y>0) was significant: $X^2 = 7.563$; $p < 0.01$. The larger asymmetries in octants including the ventrolateral prefrontal cortex (66.7%), the dorsolateral prefrontal cortex (46.7%) and the orbitofrontal cortex (44.4%) were all marginally significant ($p < 0.10$) in spite of very few peaks. Indeed, it appeared the craving activations for food that favored the anterior sections of the left hemisphere were comparable if not larger (or more significant) than for any of the drugs. In contrast, activation slightly favored the right hemisphere for most posterior areas (Y<0).

Gaming. Cue-induced craving for internet gaming did not follow any of the other groups. If anything, it appears that the asymmetries were opposite to those of drug (or food) induced activations. Here, right hemisphere activations were more consistent especially in the anterior sections. Posterior sections had more peak activations on the left side. See Fig. (**4**); Table **1** for details. In fact, the largest left asymmetry (73.3%) in the medial, superior octant was significant ($X^2 = 8.067$; $p < 0.01$) in spite of the few peaks.

These results suggest that the type of craving induced by computer game cues is qualitatively different from the types induced for appetitive (drug and food) substances.

DISCUSSION

Impulsivity

Most activation peaks for the Go/No-Go and Stop Signal tasks favored the right hemisphere confirming the oft-reported asymmetry for these two impulsivity-related tasks. The Stop Signal task appeared to have larger asymmetries than the Go/No-Go task but, in general, both were larger anteriorly than posteriorly. Interestingly, there was a significant right asymmetry in the anterior medial areas (X<30, Y>0) for only the Stop Signal task while both tasks had a significant right asymmetry in the octant that includes the dorsolateral prefrontal cortex. Where it can be concluded that these right hemisphere areas are more active when a person needs to control (refrain from) an impulsive action or inhibit a prepotent response, the different octant location of the asymmetries suggests the neural mechanisms for the two tasks are different and therefore may assess different aspects of impulsivity.

The results raise two questions. First, what is it about the anterior right hemisphere that facilitates performance on these tasks? Second, since the tasks relate to impulsivity - which is a risk factor for addiction - what can be learned that will enable future understanding for the etiology of addiction and for designing treatment?

As discussed in the Introduction, the two labels that seem to describe specialized right hemisphere cognition are "avoidance" and "negative." The former appears to be action-oriented; the latter, a valence or psychological state. In performance of these impulsivity tasks, preventing or inhibiting a prepotent action is an action-oriented quality. While inhibition for these particular tasks may have questionable face value for the kind of inhibition needed to avoid drug-seeking, such an explanation is often invoked. To the extent that both types of inhibition share common brain components, it can be hypothesized that a well-functioning right hemisphere is a protection against drug-seeking and progressing to addiction. Control functions in the right hemisphere monitor the environment for the need to avoid a stimulus or situation - either at the immediate level in the response inhibition tasks or at the global level of harm avoidance in taking drugs. Therefore the brain needs to have the knowledge and understanding that, in spite of the physically and psychologically positive feelings associated with psychoactive drugs, it is necessary to avoid them because of the negative consequences.

To check this conclusion, supportive data should show that there are weaker activations in these right hemisphere areas for impulsivity measures in drug-dependent individuals. The logic is that weak activation would also mean they have reduced ability to inhibit urges to take drugs and/or to engage in drug-seeking behaviors. A number of studies demonstrate this. In a study of heavy smokers wanting to quit, activation was reduced relative to non-smokers in the right dorsomedial prefrontal cortex (which would fall into the X<30, Y>0, Z>0 octant) for a Stop Signal task [55]. Similarly, marijuana users who smoked longer, started earlier, and had more lifetime use exhibited reduced activation in the same octant [56]. In a different right hemisphere octant (the right inferior frontal gyrus (X>30, Y>0, Z<0)), low activation was related to increased cigarette use in subjects trying to quit [57]. In yet another anterior right hemisphere area (anterior cingulate and insula), hypoactivity was seen in cocaine users relative to non-users [58]. However, a different result was seen for cocaine users in a Go/No-Go study where *increased* activation was correlated with years of use in the *left* inferior frontal gyrus and the *left* insula [59]. Specialization of the anterior left hemisphere is associated with "approach." Could this mean there was an increase of craving rather than a reduction of inhibitory control? All in all, the pattern for reduced anterior right hemisphere activation in fMRI tests of impulsivity seems to occur in drug-dependent individuals.

This pattern of results begs the question of whether the reduced activity preceded drug use or was caused by it. A prospective study in early adolescents (ages 12-14) sheds light on this issue [60]. fMRI measures were obtained for a Go/No-Go task in these young subjects prior to any involvement with drugs. Then, in follow-up 4 years later, those who had reduced activation at baseline were more likely to be involved with problem behaviors and substance abuse, suggesting reduced impulse control led to drug use. In a complementary study, healthy subjects with some experience with marijuana use (but were neither dependent nor frequent users) performed a Go/No-Go task while being infused with each of two of the chemicals found in marijuana: THC and CBD and with [61]. The usual areas of the right hemisphere were most often activated as typical for the impulsivity task. However, relative to placebo, THC *reduced* activation in two anterior right hemisphere areas (and the left precuneus) while increasing activation in several posterior right hemisphere (Y<0) areas, either in temporal or visual cortices. CBD, on the other hand, reduced activation only in left temporal areas without increases in any area. Clearly these chemicals had differential effects on activation but only THC reduced activation in the area associated with impulsivity and presumably reduced cognitive inhibitory control.

Craving

Most activation peaks for cue-stimulated craving across all substances favored the left hemisphere. This observation is consistent with the left/right hemisphere dichotomy whereby the left hemisphere is associated with "approach" or "appetitive" behavior. The concept is that craving is a "wanting" of (previously experienced) pleasure from a particular drug and the cues induce a desire to obtain the drug to recreate the experience. Because not all those who experience pleasure will progress to heavy use or dependence, the question is whether those who do not progress have less left hemisphere activation for craving or stronger impulse control in the right hemisphere, or both.

The consistency of left hemisphere activation was apparent for most of the specific drugs (and food) being assessed. This overall finding is, in some sense, remarkable because of the wide variation among the factors modulating neural reactivity, not to mention the diverse motivations of

the participants as well as the effects of the drugs themselves [62]. While the response inhibition paradigms for impulsivity were more or less the same across studies - differing only in specific stimuli, for example - cues to induce craving varied in their modality of presentation - pictures, videos, personal scripts, and touch as well as the effects of the drug itself. Accordingly, these various stimuli and associated tasks would likely activate additional brain structures not specifically related to craving, complicating interpretation. Follow-up questions assured that craving was increased but the intensity of that craving was not always assessed. Moreover, it is not likely that the intensity of craving (as far as brain activation is concerned) is equivalent across substances. Is the strength of craving for a person who craves cocaine the same for a person who craves marijuana, even given the same diagnostic score?

It would be important to show that those who had the strongest craving would be those who had the most consistent asymmetry favoring left hemisphere activation. One hypothesis is that those who are abstinent at the time of fMRI assessment might crave more and thus have greater left hemisphere activation. The most dramatic support for this hypothesis are the two groups of smokers - those who were allowed to smoke (satiated) just prior to the imaging session, and those who were abstinent (deprived) for several hours or a day. Smokers, overall, had inconsistent hemispheric preferences, but those who were deprived activated the left hemisphere more often; the reverse for the satiated smokers (Fig. **2**; Table **1**). Abstinence arguably induced stronger craving following cue exposure, resulting in the left hemisphere activation. This issue was specifically addressed in a recent meta-analysis comparing deprived and non-deprived smokers across several studies (most of which were included in this survey as well [63]. The results reported here supported their analysis: deprived smokers had a activation peaks that would fall in left inferior frontal octants ($Y>0$; $Z<0$).

In addition to food, the other two strong left hemisphere asymmetries were for alcohol and cocaine. The subjects in both studies were abstinent from their drug at the time of imaging, supporting the contention that deprivation increased craving and, accordingly, left hemisphere activation for cue-activation. However, the marijuana users, whose left activation was not so strong, were also abstinent. In the marijuana groups, it remains an open question as to whether or not the failure of a consistent left hemisphere asymmetry was due to a lesser intrinsic craving vis-à-vis hemisphere activation. The methodology for the food studies usually included manipulations to increase craving - fasting, comparison to non-appetizing foods, or use of obese subjects - again supporting the strong left hemisphere activation. The heroin group with the exception of one group of former addicts was, for the most part, under treatment and it is not clear how their craving state affected the less strong left hemisphere asymmetry.

One of the other aspects that may be associated with, or similar to, craving is "expectancy." Expectancy of receiving a non-drug reward (*e.g.*, money) might induce activation similar to craving a drug or food. Three studies were designed to test this hypothesis and all three had more activation in the left frontal area. In one study, subjects were cued to expect (or not to expect) a cash reward if they responded correctly to a triggering cue. There were 3 activation peaks in the left and 1 in the right superior (2 lateral; 2 medial) pre-frontal cortex; 4 only in the left superior temporal cortex, and others in the left or right areas more posteriorly [64]. Another study designed to increase anticipation of a reward (to be received following 3 correct responses in succession) produced 1 peak in the left superior medial octant and bilateral peaks in the superior temporal gyrus [65]. Finally, a complex paradigm revealed left-sided ventral striatal involvement for reward magnitude contrasts, and medial prefrontal and left orbitofrontal cortex for reward uncertainty [66]. Across these studies, expectancy of a reward seemed to activate areas in the left hemisphere more often than the right.

Another aspect of craving related to the process of addiction is "wanting" as distinct from "liking" a drug. The brain networks associated with these psychological constructs are dissociable as first hypothesized in the rodent model [67]. In a study of healthy women under conditions of hunger and satiety, separate brain activations were obtained for a paradigm that assessed either wanting or liking [68]. Relevant to craving was the "wanting" session in which food and non-food odors were presented to hungry subjects and each was to indicate on a five-point scale how much she *wanted* to eat the food evoked by the odor. These scores were positively correlated with activation in the left medial orbitofrontal cortex - the same area activated by expectation of a monetary award. Taken together, it appears that studies of expectancy and wanting more often activate the left frontal areas as do studies of cue-activated craving of addictive substances, all of which are consistent with the approach or appetitive aspect of the left hemisphere.

Right/Left Differences for Connectivity and Neuro-transmitter Activity

The impulsivity (response inhibition) studies give credence to connection between anterior right hemisphere activation and earlier reports of right laterality for avoidance behavior. And, as discussed, evidence supports the notion that weakened activation in these right hemisphere areas increases risk for drug abuse. Similarly, the craving studies support the connection between the anterior left hemisphere and approach or appetitive behavior. And, accordingly, there are data that show increased left brain activity is related to increased craving together with "wanting" and "expectancy." These lateralized brain/behavior connections to risks of drug abuse have rarely, if ever, been posited. The next step is to determine how the right and left hemispheres differ neuroanatomically (*e.g.*, neuronal connectivity) or neurochemically (*e.g.*, neurotransmitter activity) to support these behaviors and how these differences might be manipulated to prevent or treat drug abuse.

Structural Connectivity. There are hemispheric differences in connectivity. Imaging technology and increasingly sophisticated statistical methods have explored the organization of myelinated fiber tracts within each hemisphere as well as the differences between them. One study [69], using three different tractography algorithms, determined that the right hemisphere was significantly more efficient and interconnected than the left hemisphere.

However, in terms of centrality which reflects connections that are more important for the regions assessed, the left hemisphere had more such measures. This was interpreted in functional terms whereby the right hemisphere has a leading role for more generalized functions while the left has a leading role in more specific functions such as language. In another study, proportions of fibers intersecting cortical regions differed significantly between the left and right hemispheres with an increase in the relative fiber density over time and small world effect (which reflects a global clustering coefficient and characteristic path length) favoring the right hemisphere [70]. The opposite results were reported where the left hemisphere was more efficient and, while efficiency declined with age in both sexes, the decline was greater for women compared to men [71]. The difference between the studies was explained by differences in the number of subjects and by differences in the methods of tractography.

Functional Connectivity. fMRI studies of resting state functional connectivity also demonstrate hemispheric differences which would be expected because of their different cognitive specialties, most notably language in the left hemisphere. A study of the default mode network, using independent component analysis which identifies regions of strong temporal coherence in low frequency fluctuations, reported greater leftward functional connectivity in the posterior cingulate and thalamus and rightward functional asymmetry in the middle frontal and middle/superior temporal gyri [72]. Similarly, another study on highly connected brain regions ("hubs") reported different connectivity measures in different areas of the left and right hemisphere [73]. Lateralized hubs in the left hemisphere encompassed the default mode network and language areas; whereas right lateralized hubs included regions of attention control networks. These studies establish differences in connectivity but do not address the functional or behavioral consequences of these differences except to indicate they are plausible in light of such cognitive asymmetries typically found in those hemispheres.

There are a few connectivity studies that focus on cognitive qualities, such as impulsivity or craving, relevant to drug abuse. One study addressed this question by studying white matter integrity using diffusion tensor imaging in cocaine-dependent subjects [74]. Interestingly, there were no left/right differences but there was reduced integrity, bilaterally, in the inferior frontal white matter as assessed by fractional anisotropy and more integrity in the white matter of the anterior cingulate compared to a control group. However, in spite of the lack of left/right asymmetry in connectivity, the fractional anisotropy of the inferior frontal white matter of *only* the right hemisphere was significantly correlated with a questionnaire assessment of impulsivity. While there does not appear to be any anatomical explanation for this, the result is consistent with reduced activation for response inhibition in the same brain area in addicted subjects.

Delay discounting is another paradigm that assesses impulsivity: For example, "Do you want $10 today or $20 next week?" As the dollar amounts and delay periods are manipulated, addicted and drug-dependent individuals will make the more immediate choice for lower amounts at an earlier receipt; that is, they discount the value of the delay. A comprehensive study that explores the network contributions and the connectivity to these choices was conducted in smokers *versus* non-smokers [75]. The paradigm included "hard" choices (where the individually determined value of the delay was about the same as the immediate reward) and "easy" choices. For the non-smokers only, the hard choices had a greater activation of the frontal-parietal network only in the right hemisphere compared to the activation of this network for the easy choices; there was no difference between the choice difficulties for the smokers. This result was interpreted as a less functional executive control network in the smokers - an interpretation not unlike the observation of reduced activation in the right hemisphere for response inhibition tasks. But in smokers, measures did show that the degree of *left* fronto-parietal network connection to the left fronto-insular cortex was significantly related to the steepness of discounting. That is, the subjects who wanted the immediate reward sooner had the stronger connectivity between these areas on the left side. While the interpretation was not stated, this result seems to suggest that this left hemisphere connection was related to craving - wanting the reward sooner.

Transcranial Magnetic Stimulation. Left/right differences in connectivity and their relationship to risk factors for drug abuse are a promising avenue to pursue for potential treatment strategies. It may be that some connectivity networks are facilitating drug abuse behavior while others are preventing addiction. In those who are addicted, disruption or enhancement of specific networks may reduce craving or strengthen cognitive control, respectively [76]. In support of this hypothesis are studies using repetitive transcranial magnetic stimulation (rTMS). This technique uses a frequency of 10 Hz to stimulate specific areas of the brain to affect the underlying circuitry. Accordingly, an early study of stimulation of the *left* dorsolateral prefrontal cortex in a single session significantly reduced cue-induced craving in cigarette smokers [77]. More dramatically, there were significant reductions in the number of cigarettes per day in treatment-seeking smokers following exposure to TMS in multiple sessions [78]. However, in this study, and contrary to the one-session study, the stimulation was bilateral and there was no significant reduction in craving. The authors speculated that the failure to reduce craving, which differed from other such studies, was due to the likelihood that many subjects had smoked prior to treatment. This explanation would be supported by the data for smokers summarized here. As for the effect of bilateral stimulation, the authors speculated that the TMS may have strengthened control networks, on the one hand, and disrupted networks related to craving, on the other. Data supporting this conclusion were generated in a preliminary study in non-treatment seeking cocaine users. Subjects were administered a continuous theta burst stimulation over the left medial prefrontal cortex [76] that resulted in a reduction in craving in half the subjects. Of interest, these subjects had lower evoked activity in the "craving" octants of the left hemisphere and higher evoked activity in "impulse control" octants of the right hemisphere. The results from this study suggest that either the decrease in left or increase in right (or both) contributed to reduce craving in cocaine patients. The preliminary evidence from these studies are encouraging for

future work that continues to focus on neural circuitry and connectivity underlying inhibitory and craving circuits leading to better understanding of factors underlying drug abuse and enabling more efficient designs of relevant treatment strategies.

Neurotransmitter Activity. Differences of behavior associated with the left or right hemisphere may be related to differential activation of neurotransmitter systems. There are data that support this. On a simple level, early observations in unilateral-lesioned rodents and later in schizophrenic patients [79]), showed that rotation or turning behavior was *toward* the lesion or *away* from the higher concentration of dopamine. In humans, a similar orientation bias to the side opposite to D2 receptor binding was demonstrated in a PET study [80]. Turning away from an active hemisphere was also implied in a study of left/right hemispheric specialization in healthy subjects [81]. Those who favorably turned towards the right performed better on verbosequential tasks (associated with the left hemisphere) while those who those who turned toward the left performed better on visuospatial tasks (associated with the right hemisphere). Neurotransmitter activity was not assessed.

Hemiparkinson patients provide a good model to relate asymmetry of dopamine activity to functions favoring the left or right hemispheres. In an early study, right and left groups of hemiparkinson patients were given a personality questionnaire to assess their novelty-seeking and harm avoidance profile [82]. Those with left lesions had reduced novelty-seeking which would fit the approach/avoidance model wherein novelty-seeking is an approach activation. Those with right lesions had increased harm avoidance which should reflect increased activity in the right hemisphere. To explain these results, the authors argued that the lesions in the right side were in the striatum which reduced inhibition in the more anterior areas thereby increasing avoidance activity. A subsequent PET study demonstrated more directly the effect on personality of neurotransmitter asymmetry [83]. There was a significant correlation between self-reported incentive motivation and higher D2 receptor availability in the left hemisphere of healthy volunteers.

It is a relevant question to ask how neurotransmitter asymmetries affect risk factors of drug abuse. Are there different neurotransmitter systems or different activation levels between the left and right hemispheres that underlie approach and avoidance behavior? If so, such differences could be related to craving and to impulsivity (response inhibition), respectively. This question was addressed directly in another PET study where D2 receptor binding (using [F18] fallypride) was compared to responses on the BIS/BAS questionnaire and on a reward/punishment learning task [84]. The reward/punishment task is a computer-generated classification learning paradigm where subjects make choices for reward trials for which there is positive feedback if correct or, for punishment trials, negative feedback if incorrect. A reward-punishment index reflects the individual differences among subjects where some tended to be more sensitive to gaining reward while others were more sensitive to avoiding punishment. Similarly, an approach-avoidance index can be calculated for the BIS/BAS questionnaire (a self-evaluation of motivation). When these behavioral indices were correlated with D2 binding asymmetry, higher binding in the left hemisphere was associated with preference for rewarding choices while higher right hemisphere binding was associated with a tendency to avoid punished choices. In addition, higher binding in the left hemisphere was associated with a relatively higher self-reported BAS ("approach") score while a higher binding in the right hemisphere was associated with a higher BIS ("avoidance") score. While these results indicate that asymmetries in baseline levels of D2 receptor binding relate to individual differences in these motivated behaviors, there is one caveat: The correlations of the dopamine D2 receptor asymmetries were in different locations for the BIS/BAS than for the reward/punishment measures. This is not unlike the different asymmetries among the octants reported here for the impulsivity tasks or the cue-induced craving paradigms. Nevertheless, these studies are relevant to understanding factors underlying drug abuse and addiction and should be followed in future work.

Left/right asymmetries for the serotonergic receptor exist, as well. A PET study using a ligand for the 5-HT_{1A} receptor demonstrated significantly higher binding in several areas of the anterior right hemisphere while the left hemisphere had higher binding only in more posterior (temporal) areas [85]. Furthermore there was a sex difference whereby women had greater binding in one area of the right inferior frontal gyrus; no asymmetries favoring men were found. These findings were not studied together with tests of cognitive function, though it was speculated that the anterior right hemisphere binding of serotonin supported a superiority of emotional processing while the greater temporal lobe left hemisphere binding supported superiority in language processing. The 5-HT_{1A} receptor has polymorphisms, one of which is a risk allele for depression. A study comparing EEG asymmetry as a function of the polymorphisms in patients with major depression, found significantly higher activation for the risk allele in the right hemisphere [86]. A review of evidence from several sources supports the right hemisphere lateralization for serotonin activation and goes further to also suggest that norepinephrine is related to increases in activation in the left hemisphere [87]. There is paucity of research in humans on asymmetric activity for norepinephrine. Another review, mainly in rodents, proposes that the drugs of abuse enhance norepinephrine signaling and induce reward effects [88]. These hypotheses need to be tested but to the extent they are true, they support the connection between cue-induced craving and left hemisphere activation.

Sex Differences

There are not enough data points in the studies reported here to determine whether the asymmetries for impulsivity or craving differ between men and women. The relevant literature is vast; an in-depth analysis would be beyond the scope of this discussion. Suffice it to say that there are sex differences in responses to taking drugs of abuse, in impulsivity, in neurotransmitter activity, in emotional stimuli, and in stress, as well as in differences in cortical structure. These facts suggest that the differences in hemispheric asymmetry for impulsivity and for craving need to be considered in both men and women. Since the

underlying factors of neurotransmitter systems, connectivity, and brain activity are likely to be different between males and females, different treatment strategies may be required with respect to the effect of psychoactive drugs and the risk factors leading to drug abuse and addiction.

CONCLUSION AND IMPLICATIONS FOR FURTHER RESEARCH

Impulsivity is a risk factor for drug-seeking leading to abuse, addiction and dependence. Successful inhibition in the Stop Signal and the Go/No-Go tasks, designed to assess impulsivity, consistently activates anterior areas in the right hemisphere. Reduced activation is found in drug-using individuals. Craving is also a risk factor for drug abuse, but cue-induced activation compiled from these studies consistently favors anterior areas of the left hemisphere across most substances. However, very few studies statistically compare this differential activation between hemispheres; they only report activation peaks for each hemisphere separately. More importantly, few authors offer hypotheses as to what is specialized in the right and left hemispheres to produce these results. The theories, reviewed here, offer some explanations. The right hemisphere is associated with inhibitory or avoidance behavior and the left hemisphere is associated with approach or appetitive behavior. These dichotomies seem to correlate with the risk factors - impulsivity measures and craving, respectively. Also, inhibition and craving functions are related to asymmetries of connectivity and neurotransmitter activation. Drugs of abuse also affect the two hemispheres differently. The purpose of this article is to bring all these factors into one narrative demonstrating the potential importance of considering the left/right differences in cognitive function and neurophysiology. Consideration of these several factors will stimulate new directions in research of the underlying etiology of drug abuse in order to inform new concepts for treatment. One promising strategy is to disrupt detrimental neural circuits and/or enhancement of favorable circuits. This requires a better understanding of the differential neuroanatomy of the circuity involved and the neurochemistry subserving them. With a broader understanding of the lateralization aspect of both cognitive and neurobiological factors, a much more refined understanding of drug addiction and treatment will result.

CONFLICT OF INTEREST

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

REFERENCES

[1] Ingvar DH, Risberg J. Increase of Regional Cerebral Blood Flow During Mental Effort in Normals and in Patients with Focal Brain Disorders. Exp Brain Res 1967; 3(3): 195-211.

[2] Carmon A, Lavy S, Gordon HW, Portnoy Z. Hemispheric differences in rCBF during verbal and non-verbal tasks. In: NA L, DH I, editors. Brain Work, Alfred Benzon Symposium VIII. Copenhagen, Denmark: Munksgaard; 1975. p. 414-23.

[3] Gordon HW. Music and the right hemisphere. In: Young AD, editor. Functions of the Right Hemisphere. London: Academic Press; 1983. p. 65-85.

[4] Gray JA. Perspectives on Anxiety and Impulsivity: A Commentary. J Res Personal 1987; 21: 493-509.

[5] Fowles DC. Application of a Behavioral Theory of Motivation to the Concepts of Anxiety and Impulsivity. J Res Personal 1987; 21: 417-35.

[6] Carver CS, White TL. Behavioral Inhibition, Behavioral Activation, and Affective Responses to Impending Reward and Punishment: The BIS/BAS scales. J Personality Social Psychol 1994; 67(2): 319-33.

[7] Davidson RJ, Ekman P, Saron CD, Senulis JA, Friesen WV. Approach-withdrawal and cerebral asymmetry: emotional expression and brain physiology. I. J Personality Soc Psychol 1990; 58(2): 330-41.

[8] Sutton SK, Davidson RJ. Prefrontal Brain Asymmetry: A Biological Substrate of the Behavioral Approach and Inhibition Systems. Psychol Sci 1997; 8(3): 204-10.

[9] Berkman ET, Lieberman MD. Approaching the bad and avoiding the good: lateral prefrontal cortical asymmetry distinguishes between action and valence. J Cognitive Neurosci 2010; 22(9): 1970-979.

[10] Harmon-Jones E, Gable PA, Peterson CK. The role of asymmetric frontal cortical activity in emotion-related phenomena: a review and update. Biol Psychol 2010; 84(3): 451-62.

[11] Astley SJ, Aylward EH, Olson HC, *et al*. Magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. Alcohol Clin Exper Res 2009; 33(10): 1671-89.

[12] Astley SJ, Richards T, Aylward EH, *et al*. Magnetic resonance spectroscopy outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. Magnetic Resonance Imaging 2009; 27(6): 760-78.

[13] Sowell ER, Thompson PM, Mattson SN, *et al*. Regional brain shape abnormalities persist into adolescence after heavy prenatal alcohol exposure. Cerebral Cortex 2002; 12(8): 856-65.

[14] Sowell ER, Thompson PM, Mattson SN, *et al*. Voxel-based morphometric analyses of the brain in children and adolescents prenatally exposed to alcohol. Neuroreport 2001; 12(3): 515-23.

[15] Zhou D, Lebel C, Lepage C, *et al*. Developmental cortical thinning in fetal alcohol spectrum disorders. Neuro Image 2011; 58(1): 16-25.

[16] Willoughby KA, Sheard ED, Nash K, Rovet J. Effects of prenatal alcohol exposure on hippocampal volume, verbal learning, and verbal and spatial recall in late childhood. J Internat Neuropsychol Society : JINS 2008; 14(6): 1022-33.

[17] Treit S, Zhou D, Lebel C, Rasmussen C, Andrew G, Beaulieu C. Longitudinal MRI reveals impaired cortical thinning in children and adolescents prenatally exposed to alcohol. Hum Brain Mapping 2014; 35(9): 4892-903.

[18] Doallo S, Cadaveira F, Corral M, Mota N, Lopez-Caneda E, Holguin SR. Larger mid-dorsolateral prefrontal gray matter volume in young binge drinkers revealed by voxel-based morphometry. PloS One 2014; 9(5): e96380.

[19] Squeglia LM, Sorg SF, Schweinsburg AD, Wetherill RR, Pulido C, Tapert SF. Binge drinking differentially affects adolescent male and female brain morphometry. Psychopharmacol 2012; 220(3): 529-39.

[20] De Bellis MD, Clark DB, Beers SR, *et al*. Hippocampal volume in adolescent-onset alcohol use disorders. Am J Psychiat 2000; 157(5): 737-44.

[21] Nagel BJ, Schweinsburg AD, Phan V, Tapert SF. Reduced hippocampal volume among adolescents with alcohol use disorders without psychiatric comorbidity. Psychiat Res 2005; 139(3): 181-90.

[22] Ozsoy S, Durak AC, Esel E. Hippocampal volumes and cognitive functions in adult alcoholic patients with adolescent-onset. Alcohol 2013; 47(1): 9-14.

[23] Momenan R, Steckler LE, Saad ZS, van Rafelghem S, Kerich MJ, Hommer DW. Effects of alcohol dependence on cortical thickness as determined by magnetic resonance imaging. Psychiat Res 2012; 204(2-3): 101-111.

[24] Yoon HW, Chung JY, Oh JH, *et al*. Differential activation of face memory encoding tasks in alcohol-dependent patients compared to healthy subjects: an fMRI study. Neurosci Lett 2009; 450(3): 311-16.

[25] Fritz HC, Wittfeld K, Schmidt CO, *et al*. Current smoking and reduced gray matter volume-a voxel-based morphometry study. Neuropsychopharmacol : Official Pub Am College Neuropsychopharmacol 2014; 39(11): 2594-600.

[26] Das D, Cherbuin N, Anstey KJ, Sachdev PS, Easteal S. Lifetime cigarette smoking is associated with striatal volume measures. Addict Biol 2012; 17(4): 817-25.

[27] Brody AL, Mandelkern MA, Jarvik ME, *et al*. Differences between smokers and nonsmokers in regional gray matter volumes and densities. Biol Psychiat 2004; 55(1): 77-84.

[28] Zhang X, Salmeron BJ, Ross TJ, Geng X, Yang Y, Stein EA. Factors underlying prefrontal and insula structural alterations in smokers. NeuroImage 2011; 54(1): 42-8.

[29] Yamamoto RT, Rohan ML, Goletiani N, *et al*. Nicotine related brain activity: the influence of smoking history and blood nicotine levels, an exploratory study. Drug Alcohol Depend 2013; 129(1-2): 137-144.

[30] Rivkin MJ, Davis PE, Lemaster JL, *et al*. Volumetric MRI study of brain in children with intrauterine exposure to cocaine, alcohol, tobacco, and marijuana. Pediatrics 2008; 121(4): 741-50.

[31] Grewen K, Burchinal M, Vachet C, *et al*. Prenatal cocaine effects on brain structure in early infancy. NeuroImage 2014; 101: 114-23.

[32] Akyuz N, Kekatpure MV, Liu J, *et al*. Structural brain imaging in children and adolescents following prenatal cocaine exposure: preliminary longitudinal findings. Develop Neurosci 2014; 36(3-4): 316-28.

[33] Rando K, Chaplin TM, Potenza MN, Mayes L, Sinha R. Prenatal cocaine exposure and gray matter volume in adolescent boys and girls: relationship to substance use initiation. Biol Psychiat 2013; 74(7): 482-9.

[34] Liu J, Lester BM, Neyzi N, *et al*. Regional brain morphometry and impulsivity in adolescents following prenatal exposure to cocaine and tobacco. JAMA Pediatrics 2013; 167(4): 348-54.

[35] Ide JS, Zhang S, Hu S, Sinha R, Mazure CM, Li CS. Cerebral gray matter volumes and low-frequency fluctuation of BOLD signals in cocaine dependence: duration of use and gender difference. Drug Alcohol Depend 2014; 134: 51-62.

[36] Alia-Klein N, Parvaz MA, Woicik PA, *et al*. Gene x disease interaction on orbitofrontal gray matter in cocaine addiction. Arch General Psychiat 2011; 68(3): 283-94.

[37] Franklin TR, Acton PD, Maldjian JA, *et al*. Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. Biol Psychiat 2002; 51(2): 134-42.

[38] Makris N, Gasic GP, Seidman LJ, *et al*. Decreased absolute amygdala volume in cocaine addicts. Neuron 2004; 44(4): 729-40.

[39] Gardini S, Venneri A. Reduced grey matter in the posterior insula as a structural vulnerability or diathesis to addiction. Brain Res Bull 2012; 87(2-3): 205-11.

[40] Moreno-Lopez L, Catena A, Fernandez-Serrano MJ, *et al*. Trait impulsivity and prefrontal gray matter reductions in cocaine dependent individuals. Drug Alcohol Depend 2012; 125(3): 208-14.

[41] Rando K, Tuit K, Hannestad J, Guarnaccia J, Sinha R. Sex differences in decreased limbic and cortical grey matter volume in cocaine dependence: a voxel-based morphometric study. Addict Biol 2013; 18(1): 147-60.

[42] Tanabe J, York P, Krmpotich T, *et al*. Insula and orbitofrontal cortical morphology in substance dependence is modulated by sex. AJNR Am J Neuroradiol 2013; 34(6): 1150-6.

[43] Walhovd KB, Moe V, Slinning K, *et al*. Volumetric cerebral characteristics of children exposed to opiates and other substances in utero. NeuroImage 2007; 36(4): 1331-44.

[44] Yuan Y, Zhu Z, Shi J, *et al*. Gray Matter Density Negatively Correlates with Duration of Heroin Use in Young Lifetime Heroin-dependent Individuals. Brain Cognition 2009; 71: 223-8.

[45] Liu H, Hao Y, Kaneko Y, *et al*. Frontal and cingulate gray matter volume reduction in heroin dependence: optimized voxel-based morphometry. Psychiat Clin Neurosci 2009; 63(4): 563-8.

[46] Wang X, Li B, Zhou X, *et al*. Changes in brain gray matter in abstinent heroin addicts. Drug Alcohol Depend 2012; 126(3): 304-8.

[47] Pezawas L, Fischer G, Podreka I, *et al*. Opioid addiction changes cerebral blood flow symmetry. Neuropsychobiol 2002; 45(2): 67-73.

[48] Bora E, Yucel M, Fornito A, *et al*. White matter microstructure in opiate addiction. Addict Biol 2012; 17(1): 141-8.

[49] Batalla A, Bhattacharyya S, Yucel M, *et al*. Structural and functional imaging studies in chronic cannabis users: a systematic review of adolescent and adult findings. PloS One 2013; 8(2): e55821.

[50] Batalla A, Crippa JA, Busatto GF, *et al*. Neuroimaging studies of acute effects of THC and CBD in humans and animals: a systematic review. Curr Pharmaceut Design 2014; 20(13): 2168-2185.

[51] McQueeny T, Padula CB, Price J, Medina KL, Logan P, Tapert SF. Gender effects on amygdala morphometry in adolescent marijuana users. Behav Brain Res 2011; 224(1): 128-34.

[52] Medina KL, McQueeny T, Nagel BJ, Hanson KL, Yang TT, Tapert SF. Prefrontal cortex morphometry in abstinent adolescent marijuana users: subtle gender effects. Addict Biol 2009; 14(4): 457-68.

[53] Batalla A, Soriano-Mas C, Lopez-Sola M, *et al*. Modulation of brain structure by catechol-O-methyltransferase Val(158) Met polymorphism in chronic cannabis users. Addict Biol 2014; 19(4): 722-32.

[54] Brett M, Johnsrude IS, Owen AM. The Problem of Functional Localization in the Human Brain. Nat Rev Neurosci 2002; 3: 243-9.

[55] de Ruiter MB, Oosterlaan J, Veltman DJ, van den Brink W, Goudriaan AE. Similar hyporesponsiveness of the dorsomedial prefrontal cortex in problem gamblers and heavy smokers during an inhibitory control task. Drug Alcohol Depend 2012; 121(1-2): 81-9.

[56] Tapert SF, Schweinsburg AD, Drummond SP, *et al*. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. Psychopharmacol 2007; 194(2): 173-83.

[57] Berkman ET, Falk EB, Lieberman MD. In the trenches of real-world self-control: neural correlates of breaking the link between craving and smoking. Psychol Sci 2011; 22(4): 498-506.

[58] Kaufman JN, Ross TJ, Stein EA, Garavan H. Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. J Neurosci 2003; 23(21): 7839-43.

[59] Prisciandaro JJ, Joseph JE, Myrick H, *et al*. The relationship between years of cocaine use and brain activation to cocaine and response inhibition cues. Addiction 2014; 109(12): 2062-70.

[60] Norman AL, Pulido C, Squeglia LM, Spadoni AD, Paulus MP, Tapert SF. Neural activation during inhibition predicts initiation of substance use in adolescence. Drug Alcohol Depend 2011; 119(3): 216-23.

[61] Borgwardt SJ, Allen P, Bhattacharyya S, *et al*. Neural basis of Delta-9-tetrahydrocannabinol and cannabidiol: effects during response inhibition. Biolog Psychiat 2008; 64(11): 966-73.

[62] Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov Y. Factors modulating neural reactivity to drug cues in addiction: A survey of human neuroimaging studies. Neurosci Biobehav Rev 2014; 38: 1-16.

[63] Wilson SJ, Sayette MA. Neuroimging craving: urge intensity matters. Addiction 2014; 110: 195-203.

[64] Ramnani N, Miall RC. Instructed delay activity in the human prefrontal cortex is modulated by monetary reward expectation. Cerebral Cortex 2003; 13(3): 318-27.

[65] Rowe JB, Eckstein D, Braver T, Owen AM. How does reward expectation influence cognition in the human brain? J Cognitive Neurosci 2008; 20(11): 1980-92.

[66] Abler B, Herrnberger B, Gron G, Spitzer M. From uncertainty to reward: BOLD characteristics differentiate signaling pathways. BMC Neurosci 2009; 10: 154.

[67] Robinson TE, Berridge KC. Addiction. Ann Rev Psychol 2003; 54: 25-53.

[68] Jiang T, Soussignan R, Schaal B, Royet JP. Reward for food odors: an fMRI study of liking and wanting as a function of metabolic state and BMI. Soc Cognit Affect Neurosci 2015; 10(4): 561-8.

[69] Iturria-Medina Y, Fernandez AP, Morris DM, *et al*. Brain Hemispheric Structural Efficiency and Interconnectivity Rightward Asymmetry in Human and Nonhuman Primates. Cerebral Cortex. 2011; 21: 56-67.

[70] Daianu M, Jahanshad N, Dennis EL, *et al*. Left *Versus* Right Hemisphere Differences in Brain Connectivity: 4-Tesla Hardi Tractography in 569 Twins. Proceedings / IEEE International Symposium on Biomedical Imaging: from nano to macro IEEE International Symposium o. 2012; 2012: 526-9.

[71] Caeyenberghs K, Leemans A. Hemispheric lateralization of topological organization in structural brain networks. Human Brain Mapping 2014; 35(9): 4944-57.

[72] Saenger VM, Barrios FA, Martinez-Gudino ML, Alcauter S. Hemispheric asymmetries of functional connectivity and grey matter volume in the default mode network. Neuropsychol 2012; 50(7): 1308-15.

[73] Nielsen JA, Zielinski BA, Ferguson MA, Lainhart JE, Anderson JS. An evaluation of the left-brain *vs* right-brain hypothesis with resting state functional connectivity magnetic resonance imaging. PloS One 2013; 8(8): e71275.

[74] Romero MJ, Asensio S, Palau C, Sanchez A, Romero FJ. Cocaine addiction: diffusion tensor imaging study of the inferior frontal and anterior cingulate white matter. Psychiat Res 2010; 181(1): 57-63.

[75] Clewett D, Luo S, Hsu E, Ainslie G, Mather M, Monterosso J. Increased functional coupling between the left fronto-parietal network and anterior insula predicts steeper delay discounting in smokers. Human Brain Mapping 2014; 35(8): 3774-87.

[76] Hanlon CA, Dowdle LT, Austelle CW, *et al*. What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals. Brain Res 2015; 1628(Pt A): 199-209.

[77] Li X, Hartwell KJ, Owens M, *et al*. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. Biol Psychiat 2013; 73(8): 714-20.

[78] Dinur-Klein L, Dannon P, Hadar A, *et al*. Smoking cessation induced by deep repetitive transcranial magnetic stimulation of the prefrontal and insular cortices: a prospective, randomized controlled trial. Biol Psychiat 2014; 76(9): 742-9.

[79] Bracha HS. Asymmetric rotational (circling behavior), a dopamine-related asymmetry: Preliminary findings in unmedicated and never-medicated schizophrenic patients. Biol Psychiat 1987; 22: 995-1003.

[80] Tomer R, Slagter HA, Christian BT, *et al*. Dopamine asymmetries predict orienting bias in healthy individuals. Cerebral Cortex 2013; 23(12): 2899-904.

[81] Gordon HW, Busdiecker EC, Bracha HS. The Relationship between leftward turning bias and bisuospatial ability in humans. International J Neurosci 1992; 65: 29-36.

[82] Tomer R, Aharon-Peretz J. Novelty seeking and harm avoidance in Parkinson's disease: effects of asymmetric dopamine deficiency. J Neurol Neurosur Psychiat 2004; 75(7): 972-5.

[83] Tomer R, Goldstein RZ, Wang GJ, Wong C, Volkow ND. Incentive motivation is associated with striatal dopamine asymmetry. Biol Psychol 2008; 77(1): 98-101.

[84] Tomer R, Slagter HA, Christian BT, *et al*. Love to win or hate to Lose? Asymmetry of dopamine D2 receptor binding predicts sensitivity to reward *versus* punishment. J Cognit Neurosci 2014; 26(5): 1039-48.

[85] Fink M, Wadsak W, Savli M, *et al*. Lateralization of the serotonin-1A receptor distribution in language areas revealed by PET. Neuro Image 2009; 45(2): 598-605.

[86] Bismark AW, Moreno FA, Stewart JL, *et al*. Polymorphisms of the HTR1a allele are linked to frontal brain electrical asymmetry. Biol Psychol 2010; 83(2): 153-8.

[87] Fitzgerald PJ. Whose Side Are You ON: Does Serotonin Preferentially Activate the Right Hemisphere and Norepinephrine the Left? Med Hypotheses 2012; 79: 250-4.

[88] Fitzgerald PJ. Elevated Norepinephrine May be a Unifying Etiological Factor in the Abuse of a Broad Range of Substances: Alcohol, Nicotine, Marijuana, Heroin, Cocaine, and Caffeine. Substance Abuse: Res Treatment 2013; 7: 171-83.

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