Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience
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Since the first study in stimulant-dependent individuals using structural MRI was published fifteen years ago, much evidence has accumulated on brain abnormalities associated with stimulant drug dependence. Here we conducted a voxel-based morphometry meta-analysis of published MRI data in stimulant-dependent individuals to clarify the most robust abnormalities underlying the disorder. We found that neuroimaging studies in stimulant-dependent individuals consistently report a gray matter decline in the prefrontal cortex regions associated with self-regulation and self-awareness. One of the next key questions that neuroimaging research today needs to address is the question of causality, namely to what extent these brain abnormalities are caused by the toxic effects of drug exposure, or the possibility that these may have predated drug-taking and even predisposed individuals for the development of drug dependence. Although the question of causality has not yet been answered completely, there has been significant progress made to date.

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Introduction
The United Nations estimates that one in every 200 people worldwide is affected by drug use problems [1,2], which in turn creates enormous costs for the affected individuals, their families, communities and society as a whole. An escalation in the adverse consequences of drug abuse, both personal and societal, necessitates the improvement of treatment options for people whose drug use has become problematic. Stimulant drugs such as cocaine and amphetamines are popular recreational drugs, but their chronic use can result in significant harm [2], and, most worryingly, dependence on stimulant drugs is still difficult to treat [3]. A better understanding of the neuropathology underlying the clinical symptoms of stimulant dependence may help to identify new targets for interventions; and the marked increase in neuroimaging studies over the past few years has partly been fuelled by this pressing need for the development of more efficient treatments for stimulant-dependent individuals [4].

The majority of published neuroimaging studies report significant structural abnormalities within fronto-striatal brain systems in stimulant-dependent individuals. This anatomical profile appears plausible given that the core clinical symptoms of addiction, the loss of control over drug use and the compulsive nature in which drugs are consumed, are known to be subserved by fronto-striatal neural networks [5]. However, the knowledge gained from these neuroimaging studies in stimulant dependence has not yet been translated into better treatments. One reason for this might be that the structural abnormalities identified across studies have been relatively inconsistent. For example, several studies reported significant enlargement of the basal ganglia in stimulant-dependent individuals [6–10], while others found a significant reduction in basal ganglia volume in these patients [11–13], and two studies could not identify any structural abnormalities in cocaine-dependent individuals at all [14,15]. Another reason may be the lack of clarity about the extent to which the observed neurobiological abnormalities in stimulant-dependent individuals are caused by the toxic effects of drug exposure, and whether these are potentially reversible. It is also conceivable that the observed abnormalities are not caused by drug exposure, but instead may have predated drug-taking, rendering individuals vulnerable for dependence. Further clarification of the health risks associated with stimulant abuse would help to improve therapeutic strategies for prevention and treatment in the future.

In this review, we aim to discuss this basic question of causality with regard to structural brain abnormalities associated with stimulant drug dependence. In order to determine the most robust brain abnormalities associated
with stimulant drug dependence, we performed a voxel-based meta-analysis of the structural neuroimaging studies. For this analysis, we aimed to be comprehensive and inclusive without restricting publication dates, but in the discussion we will focus on the most recent developments in the field.

Meta-analysis of structural abnormalities in stimulant drug dependence

We searched the scientific databases of PubMed, Web of Knowledge and Science Direct for neuroimaging studies comparing individuals with chronic stimulant use and matched healthy control volunteers using the terms: voxel-based morphometry (VBM), structural magnetic resonance imaging (MRI), brain, cocaine, amphetamines, methamphetamine, stimulants. We only included studies that contained original data in a complete article (not abstracts), used voxel-based morphometry for the analysis of structural MRI brain scans, and analyzed the whole brain. We excluded studies in which individuals did not satisfy the diagnostic criteria for cocaine, amphetamine or methamphetamine dependence according to DSM-IV.

On the basis of these criteria, we identified 16 studies suitable for the meta-analysis, listed in Table 1. Two further studies did not identify any significant structural differences between cases and controls [14,15].

The meta-analysis of regional gray matter differences was performed using GingerALE software [16]. Co-ordinates reported in Montreal Neurological Institute format were converted to Talairach stereotactic space [17]. Probability maps were generated and thresholded, controlling the False Discovery Rate (FDR) at $q < 0.01$. The minimum cluster size was set at 25 voxels. MRIcron software [18] was used to visualize brain areas with significantly altered gray matter on an MRI template image. The effect of duration of stimulant drug use was also assessed by meta-regression using SDM software (http://www.sdmproject.com) [19].

The sample for the voxel-based meta-analysis comprised 494 stimulant-dependent individuals and 428 healthy control volunteers. The mean sample size across the 14 studies that provided data was 32 for stimulant-dependent individuals and 34 for control volunteers. The majority of participants were male (79% stimulant group; 69% control group). Overall there were no significant age differences between the groups ($t = -1.81, P = 0.82$) with a mean age of 35.6 years. As shown in Table 1, the average duration of stimulant use was 12.1 years ($\pm 4.5$ standard deviations) and in four of the 14 studies patients were drug abstinence for more than one month at the time of scanning.

For the meta-analysis of gray matter decreases in patients compared to controls there were 62 sets of coordinates included from the primary studies; for the meta-analysis of gray matter increases in patients there were seven sets of coordinates included from the primary literature. One study compared two cocaine groups with the same control group [11], and so the cocaine abinent subgroup was excluded from the analysis to avoid overlapping subgroups.

The meta-analysis revealed significant decreases in gray matter in stimulant-dependent individuals in five regions: the insula, ventromedial prefrontal cortex, inferior frontal gyrus, pregenual anterior cingulate gyrus, and anterior thalamus (for details see Table 2 and Figure 1). No regions of gray matter increases in patients were significant.

The identified areas of gray matter decreases were part of a neural network previously implicated in the processing of drug-related cues [20], and more generally in the regulation of emotional, cognitive and behavioral responses. For example, the anterior cingulate gyrus, in concert with the insula and the right inferior frontal gyrus plays an important role in the awareness of cognitive, affective and physical states [21**]. The right inferior frontal gyrus is critically implicated in inhibitory response control functions [22] while the ventromedial prefrontal/orbitofrontal cortex is specifically concerned with the assessment of value and the evaluation of outcomes associated with behavioral choices [23**,24]. Given that the prefrontal cortex, partly through cortico-striatal circuitries, influences many aspects of human behavior, dysfunction typically manifests as poor decision-making and maladaptive behavior, traits which are frequently observed in people with stimulant drug dependence [25,26,27**]. Insufficient top-down control from the prefrontal cortex may also lead to a predominance of habitual behaviors, which are mediated by dorsolateral parts of the striatum (putamen) [28]. In the context of drug use, such an imbalance between top-down and bottom-up control may result in deleterious consequences, as drug-taking habits are decoupled from the regulatory influences of the prefrontal cortex.

The brain abnormalities identified by this meta-analysis in prefrontal brain regions concur well with the perfusion and metabolic alterations frequently described in stimulant-dependent individuals [29,30]. However, our analysis did not detect abnormalities in basal ganglia structures. At first glance, this may seem surprising in light of the close interconnections between the prefrontal cortex, the striatum and the compulsive patterns of drug-taking which are a hallmark of addiction. Yet, there are a number of plausible reasons that may account for the lack of striatal abnormalities identified in this meta-analysis. The most obvious reason lies in the inconsistencies in the directions of reported striatal change in the primary literature. Thus in the search for commonalities in
Table 1

Details about the studies considered for the meta-analysis in alphabetical order. Although the studies by Narayana et al. [14] and Weller et al. [15] met criteria for inclusion, they did not identify significant group differences between cases and controls at whole brain level, and were thus not included in analysis.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size (N)</th>
<th>Males (%)</th>
<th>Mean age (±SD)</th>
<th>Diagnosis</th>
<th>Years of use (±SD)</th>
<th>Duration of abstinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alia-Klein et al.</td>
<td>40 42</td>
<td>100 100</td>
<td>45 (±6.3) 39 (±6.5)</td>
<td>Cocaine dependence</td>
<td>19.0 (±1.4)</td>
<td>Not abstinent</td>
</tr>
<tr>
<td>Barros-Loscertales et al.</td>
<td>20 16</td>
<td>100 100</td>
<td>33.3 (±6.4) 33.4 (±9.2)</td>
<td>Cocaine dependence</td>
<td>13.2 (±6.0)</td>
<td>&gt;4 days</td>
</tr>
<tr>
<td>Ersche et al. [8]</td>
<td>60 60</td>
<td>88 77</td>
<td>32.5 (±8.5) 32.3 (±8.3)</td>
<td>Cocaine dependence</td>
<td>10.0 (±7.1)</td>
<td>Not abstinent</td>
</tr>
<tr>
<td>Ersche et al. [37]</td>
<td>47 50</td>
<td>92 64</td>
<td>34.5 (±7.4) 32.8 (±8.9)</td>
<td>Cocaine dependence (94%) Amphetamine dependence (6%)</td>
<td>16.3 (±7.6)</td>
<td>Not abstinent</td>
</tr>
<tr>
<td>Franklin et al.</td>
<td>13 16</td>
<td>– –</td>
<td>42 (±6.3) 32 (±6.9)</td>
<td>Cocaine dependence (6%)</td>
<td>13.0 (±6.5)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Hanlon et al. [11]</td>
<td>24 25</td>
<td>63 48</td>
<td>38.9 (±0.9) 36.2 (±1.0)</td>
<td>Cocaine dependence</td>
<td>11.1 (±1.2)</td>
<td>Not abstinent</td>
</tr>
<tr>
<td>Jan et al. [9]</td>
<td>17 20</td>
<td>71 65</td>
<td>35.1 (±6.6) 30.9 (±8.2)</td>
<td>Methamphetamine dependence</td>
<td>10.2 (±5.8)</td>
<td>Not abstinent</td>
</tr>
<tr>
<td>Kim et al. [63]</td>
<td>29 20</td>
<td>93 75</td>
<td>36.75 33.2 (±6.5)</td>
<td>Methamphetamine dependence</td>
<td>5.4 (±3.7)</td>
<td>&gt;4 weeks</td>
</tr>
<tr>
<td>Morales et al. [64]</td>
<td>39 43</td>
<td>51 49</td>
<td>34.8 (±1.5) 32.8</td>
<td>Methamphetamine dependence</td>
<td>11.5 (±1.5)</td>
<td>4-7 days</td>
</tr>
<tr>
<td>Moreno-Lopez et al. [13]</td>
<td>38 38</td>
<td>100 100</td>
<td>29.6 (±6.5) 31.1 (±5.1)</td>
<td>Cocaine dependence</td>
<td>4.1 (±3.1)</td>
<td>&gt;1 month</td>
</tr>
<tr>
<td>Narayana et al. [14]</td>
<td>29 29</td>
<td>72 72</td>
<td>41.0 (±9.1) 34.3 (±10.2)</td>
<td>Cocaine dependence</td>
<td>12.7 (±7.7)</td>
<td>Not abstinent</td>
</tr>
<tr>
<td>Parvaz et al. [65]</td>
<td>22 17</td>
<td>82 59</td>
<td>42.9 (±6.2) 40.3 (±6.7)</td>
<td>Cocaine dependence (82%)</td>
<td>17.8 (±6.9)</td>
<td>4.5 days</td>
</tr>
<tr>
<td>Schwartz et al. [66]</td>
<td>44 61</td>
<td>68 51</td>
<td>33.4 (±8.4) 34.1 (±10.7)</td>
<td>Cocaine abuse (18%)</td>
<td>Not reported</td>
<td>&gt;2 weeks</td>
</tr>
<tr>
<td>Sim et al. [67]</td>
<td>40 41</td>
<td>67 63</td>
<td>41.4 (±6.9) 38.7 (±8.8)</td>
<td>Cocaine dependence</td>
<td>15.3 (±6.2)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Tanabe et al. (2009)</td>
<td>19 20</td>
<td>53 30</td>
<td>35 (±7) 33 (±11)</td>
<td>Cocaine dependence (73%) Amphetamine dependence (63%) Cocaine abuse or amphetamine abuse (15%)</td>
<td>Not reported</td>
<td>&gt;2 years</td>
</tr>
<tr>
<td>Weller et al. [15]</td>
<td>9 8</td>
<td>100 100</td>
<td>41.0 (±5.7) 39.5 (±5.4)</td>
<td>Cocaine dependence</td>
<td>Not reported</td>
<td>1-19 days</td>
</tr>
</tbody>
</table>

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published case-control comparisons, studies with increased and decreased striatal volume (e.g., [9,11]) may have simply negated each other in the meta-analysis. It is also conceivable that subcortical abnormalities in stimulant-dependent individuals are not so reliably measured by computational techniques as the cortical changes, and therefore may not be captured by VBM techniques. Indeed, several studies reporting striatal enlargement in stimulant-dependent individuals used manual or semi-automatic volumetry [6,7,10], not VBM, and were thus not included in our analysis. It is also of note that volume increase in the striatum has frequently been reported in both animal and humans following blockade of dopamine D2 receptors by antipsychotic drugs [31–35]; and methylphenidate has shown to normalize the reduced striatal volume in children with ADHD [36]. One may speculate as to whether volume changes in the striatum of stimulant-dependent individuals are particularly susceptible to individual differences in the recent history of stimulant abuse (or abstinence) compared with the changes observed in cortical brain regions. Finally, one also needs to bear in mind that healthy volunteers in most of the published studies were not selected on the basis of their family histories, that is, it is possible that some healthy control volunteers have a family history of addiction and thus share with the dependent group the enlargement of the putamen, amygdala and hippocampus that has been reported in first-degree relatives of people with stimulant dependence [37]. Consequently, the absence of these limbic-striatal abnormalities in stimulant-dependent individuals in this meta-analysis should be considered with caution.

We further conducted a meta-regression to identify which of the abnormal brain regions were associated with the duration of stimulant use. As shown in Table 3, the longer the individuals had been using stimulants, the greater the decline in gray matter in the inferior and frontal middle frontal gyri. Conversely, gray matter volume in the parahippocampal gyrus appeared to be differentially related to the duration of stimulant use, with the left parahippocampal gyrus being associated with an increase in volume the longer individuals had been using stimulants, whilst the right parahippocampal gyrus showed the opposite relationship. In light of the important roles of the frontal cortex and the limbic system in the development of addiction, the relationship between the changes in their structure and the duration of stimulant abuse seems

### Table 2

Locations of abnormally reduced gray matter volume in chronic users of cocaine and amphetamines compared to healthy volunteers; identified by meta-analysis of 14 MRI studies in the primary literature.

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Volume (mm$^3$)</th>
<th>Weighted centre (x, y, z)</th>
<th>P-value</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Anatomical label</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>416</td>
<td>−42.46 −6.56 −0.18</td>
<td>0.015312</td>
<td>−42</td>
<td>−10</td>
<td>0</td>
<td>Left insula</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.011523</td>
<td>−42</td>
<td>0</td>
<td>−2</td>
<td>Brodmann area 13</td>
</tr>
<tr>
<td>2</td>
<td>232</td>
<td>−6.03 −1.65 5.29</td>
<td>0.014608</td>
<td>−6</td>
<td>−2</td>
<td>6</td>
<td>Left insula</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.014043</td>
<td>−20</td>
<td>24</td>
<td>−10</td>
<td>Anterior nucleus</td>
</tr>
<tr>
<td>3</td>
<td>184</td>
<td>−20.03 23.99 −9.97</td>
<td>0.012401</td>
<td>6</td>
<td>46</td>
<td>8</td>
<td>Left thalamus</td>
</tr>
<tr>
<td>4</td>
<td>104</td>
<td>5.23 46.35 7.65</td>
<td>0.010912</td>
<td>26</td>
<td>24</td>
<td>−10</td>
<td>Right anterior cingulate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.010637</td>
<td>26</td>
<td>20</td>
<td>−8</td>
<td>Brodmann area 47</td>
</tr>
<tr>
<td>5</td>
<td>88</td>
<td>25.1 22.91 −9.09</td>
<td>0.010637</td>
<td>26</td>
<td>20</td>
<td>−8</td>
<td>Brodmann area 13</td>
</tr>
</tbody>
</table>

### Table 3

Positive and negative correlations between the years of stimulant drug use and gray matter volume.

<table>
<thead>
<tr>
<th>Talairach</th>
<th>Z</th>
<th>P</th>
<th>Voxel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>−22, −8, −18</td>
<td>2.308</td>
<td>0.000012845</td>
<td>361</td>
<td>Left parahippocampal gyrus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Talairach</th>
<th>Z</th>
<th>P</th>
<th>Voxel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>−24, 26, −12</td>
<td>−2.429</td>
<td>0.000064226</td>
<td>114</td>
<td>Left inferior frontal gyrus, Brodmann area 11</td>
</tr>
<tr>
<td>36, 16, 30</td>
<td>−1.954</td>
<td>0.001130379</td>
<td>16</td>
<td>Right middle frontal gyrus, Brodmann area 9</td>
</tr>
<tr>
<td>32, −16, −12</td>
<td>−1.905</td>
<td>0.001323087</td>
<td>28</td>
<td>Right parahippocampal gyrus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Talairach</th>
<th>Z</th>
<th>P</th>
<th>Voxel</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>−24, 26, −12</td>
<td>−2.429</td>
<td>0.000064226</td>
<td>114</td>
<td>Left inferior frontal gyrus, Brodmann area 11</td>
</tr>
<tr>
<td>36, 16, 30</td>
<td>−1.954</td>
<td>0.001130379</td>
<td>16</td>
<td>Right middle frontal gyrus, Brodmann area 9</td>
</tr>
<tr>
<td>32, −16, −12</td>
<td>−1.905</td>
<td>0.001323087</td>
<td>28</td>
<td>Right parahippocampal gyrus</td>
</tr>
</tbody>
</table>
Reduction in gray matter volume in stimulant-dependent individuals (controlling the False Discovery Rate at $q < 0.01$), as identified by the meta-analysis shown (a) on a rendering of the cortical surface, and (b) in axial slices. The left side of the brain is shown on the left side of each slice; the blue numbers denote z-coordinates for each slice in Talairach stereotactic space.
plausible. However, in order to discuss these changes in view of the chicken and egg question, additional approaches would be necessary.

The ‘chicken-and-egg’ dilemma
The question as to whether the neurobiological abnormalities frequently observed in stimulant-dependent individuals reflect a predisposing cause for their addiction, or an effect of their long-term exposure to potentially neurotoxic drugs, is difficult to address in human drug addiction research. In clinical settings, there are a growing number of studies investigating the long-term effects on structural brain development in children who have been prenatally exposed to stimulant drugs. However, as in the adult literature, the results regarding structural brain abnormalities are largely inconsistent [38-40]; but once more data are available, meta-analyses may bring clarity.

A more promising strategy for disentangling the predisposing causes from the stimulant-related effects is a search for vulnerability markers. Endophenotypes have been defined as measurable traits that mediate between the predisposing genes (genotypes) and the clinical symptoms (phenotype) [41]. As brain structure has been shown to be highly heritable [42], the brains of unaffected first-degree relatives offer an opportunity to identify familial vulnerability markers or imaging endophenotypes for psychiatric disorder. We recently used this strategy in 50 sibling pairs, of whom one was dependent on stimulant drugs while the other had no history of chronic drug abuse, and a group of unrelated healthy control volunteers [37]. We found abnormally increased gray matter volume in subcortical regions such as the amygdala, hippocampus and putamen in both members of the sibling pairs, suggesting that these abnormalities predated drug-taking in the dependent individuals (Figure 2b and c). A significant reduction of gray matter in the prefrontal cortex, specifically in the orbitofrontal cortex and anterior insula, was unique to the dependent group, with the changes in orbitofrontal volume directly relating to the duration of cocaine exposure.

We have also studied a group of recreational cocaine users who had no family history of dependence but had been using cocaine on a regular basis without making the transition to dependence. As shown in Figure 2a, this recreational user group did not show any structural endophenotypic markers of increased risk as seen in the sibling pairs, but instead showed increased gray matter volume in the orbitofrontal cortex, anterior cingulate and insula [43], suggesting a substrate of resilience against addiction. These data indicate that inter-individual differences in brain systems underlie a person’s risk for developing stimulant dependence. In other words, the use of the same drug may have different effects depending on the individuals’ neurobiological vulnerability profile. As we did not study the first-degree relatives of the recreational cocaine users, we can only speculate about the nature of their potential resilience. Future studies are warranted to clarify whether vulnerability and resilience represent the extreme ends of a continuum for the risk to develop addiction, or whether these are separate constructs [44,45].

How specific are the structural brain abnormalities for stimulant drug dependence?
Our meta-analysis identified significant structural abnormalities in prefrontal brain regions extending to the insula and pregenual anterior cingulate cortex. A similar neuropathology, specifically in the anterior cingulate in conjunction with the insula, has recently been identified by meta-analyses in other psychiatric disorders, including bipolar disorder [46,47] and schizophrenia [48,49,50]. Substance abuse is common in these psychiatric disorders [51], and it is conceivable that this shared neuropathology of abnormal prefrontal structures, which has been associated with dysfunction in self-regulation and self-awareness [21**, reflects an increase in vulnerability for stimulant drug dependence in these patient populations. By contrast, familial vulnerability for stimulant drug dependence, as seen in the first-degree relatives of stimulant-dependent individuals, seems to be associated with subcortical abnormalities such as the enlargement of the putamen [37] and compulsive traits [52,53], resembling the neuroimaging and cognitive abnormalities associated with obsessive–compulsive disorder [19,54]. Both vulnerability-related changes, that is, the gray matter decrease in the anterior cingulate and insula cortex and the increase of subcortical structures, specifically the putamen, may mediate different kinds of behavioral vulnerabilities, which need to be targeted differentially by specific preventative strategies.

One psychiatric disorder frequently discussed with regard to risk for addiction is attention deficit hyperactivity disorder (ADHD) [55*]. Both disorders, stimulant drug dependence and ADHD, are associated with a highly impulsive phenotype that increases the vulnerability for recreational drug use to develop into drug addiction [56]. Despite the shared impulsive phenotype, the neuropathology of these two disorders is distinctly different: In contrast to stimulant drug dependence, ADHD has been robustly associated with a decrease in basal ganglia volume [36,57,58], which seems to normalize with progressing age and prolonged stimulant medication [36]. Moreover, ADHD has not been associated with compulsive traits, which may explain why methylphenidate, which is pharmacologically similar to cocaine [59], is not compulsively abused by patients with ADHD [60]. Taken together, stimulant drug dependence is associated with a distinctive neuroanatomical profile, which overlaps partly with neuropathological changes that have also been associated with other psychiatric disorders.
Conclusion

Although the number of structural neuroimaging studies in stimulant drug dependence has been growing steadily over the past decade, their impact on clinical practice for the treatment of stimulant-dependent individuals has been limited. We used a voxel-wise meta-analysis approach to identify a number of structural abnormalities in the prefrontal cortex most robustly associated with stimulant drug dependence, including the ventromedial cortex, anterior cingulate gyrus, right inferior frontal...
cortex and insula. Similar brain abnormalities have also frequently been reported in patients with psychotic disorders, suggesting that a behavioral and emotional phenotype characterized by insufficient regulatory control may be an underlying, if not a sufficient, component of addiction vulnerability. Prolonged abuse of stimulant drugs seems to exacerbate this pathology. By contrast, familial vulnerability for addiction has been shown to involve abnormalities in limbic-striatal structures (i.e., putamen, amygdala, and hippocampus) associated with habit learning and compulsivity. Whether these distinct pathologies require separate therapeutic interventions needs to be determined by future studies. Neuroimaging has the potential to provide new insight into complex psychiatric conditions, opening up new avenues for diagnosis and treatments that lie beyond the scope of the classical clinical phenotype.

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Degenhardt LJ: Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet 2012, 379:55-70. This paper gives an excellent overview of the extent of illicit drug use around the world and its consequences. The authors introduce the reader to the numbers and figures published annually in the World Drug Report, synthesizing the data in an accessible and comprehensible form, and finishes with a series of questions which make reader think about this topic, irrespective of their background and familiarity with the topic of addiction.


21. Medford N, Critchley HD: Conjoint activity of anterior insular and anterior cingulate cortex: awareness and response. Brain Struct Funct 2010, 214:539-549. This paper reviews the growing evidence in the literature of the functional relationship between the anterior insula and the anterior cingulate cortex. The authors systematically highlight how the joint action of these two brain structures underlies a variety of cognitive, affective and behavioral aspects of human life.


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This paper comprehensively reviews the extensive evidence for prefrontal cortex function in drug addiction, with a focus on functional neuroimaging studies published over the past decade. The authors critically analyse the evidence with regard to the contemporary models of addiction and discuss the wider clinical implications of these impairments.


In this paper the authors meta-analyse the prospective effect of childhood ADHD on substance misuse later in life. They illustrate that there is a number of mediators influencing the outcome of ADHD, including substance abuse, and that they argue that future studies should focus on mediating variables to better understand how ADHD and substance abuse are linked.


