Abnormal Brain Structure Implicated in Stimulant Drug Addiction

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not TRIF, did not generate IRA B cells (Fig. 3, C and D), indicating a specific MyD88-dependent pathway. The process could depend on direct B1a binding to LPS via TLR4, or on indirect, extrinsic factors such as TLR4-expressing macrophages. To discriminate between these two possibilities, we adoptively transferred B1a B cells from WT mice into *Tlr4*$^{-/-}$ mice (Fig. 3E). B1a WT B cells, but not endogenous *Tlr4*$^{-/-}$ B cells, differentiated to IRA B cells, indicating that direct TLR4 signaling on B1a B cells is sufficient to generate IRA B cells.

To test whether IRA B cells are restricted to TLR4-mediated recognition, we injected TLR ligands Pam3CSK4 (ligand for TLR1/2), Poly(I:C) (TLR3), FLA-ST (TLR5), FSL-1 (TLR2/6), R848 (TLR7/8), and CpG ODN1668 (TLR9). The ligands Pam3CSK4, FSL-1, and R848 yielded IRA B cells (fig. S10A), a finding that we confirmed in vitro (fig. S10B). We also wondered whether GM-CSF can play an autocrine role for B1a–IRA B cell conversion (*23*). B1a cells expressed Csf2Rβ (CD131) (fig. S11A) and, when placed in culture with antibodies against CD131, failed to give rise to IRA B cells (fig. S11, B and C) but remained alive and gave rise to CD43^{+} CD138^{+} cells. Thus, IRA B cells develop via MyD88-dependent pathways and use GM-CSF as an autocrine factor.

The spleen's open circulation (*24*) allows blood leukocytes to enter and exit easily. To reside in the spleen, leukocytes resort to adhesive ligands; MZ B cells, for example, rely on VLA-4 and LFA-1 (*25*). We wondered whether splenic IRA B cells, which express VLA-4 and LFA-1 at high levels, might behave similarly. Injection of neutralizing antibodies to VLA-4 and LFA-1 diminished IRA B cell numbers and revealed that the two integrins are responsible for retention (Fig. 3F).

Are IRA B cells functionally important? To answer this, we focused on the cecal ligation and puncture (CLP) sepsis model (*26*). We generated mixed chimeras by reconstituting lethally irradiated mice with μMT- and GM-CSF–deficient (*Csf2*$^{-/-}$) bone marrow cells. In these mice (called GM/μMT chimeras), the μMT marrow contributed all leukocytes except B cells, whereas the *Csf2*$^{-/-}$ marrow contributed only *Csf2*$^{-/-}$ cells. Consequently, the only population completely lacking the capacity to produce GM-CSF in the reconstituted mice were B cells. We tested the quality of the chimeras and their controls by PCR (fig. S11, A and B) and by flow cytometry (fig. S11, C and D).

In response to severe CLP, 40% of control mice survived and recovered, but every GM/μMT chimera died within 2 days (Fig. 4, A and B). To characterize this phenotype further, we profiled GM/μMT chimeras and controls for several sepsis-relevant indices 20 hours after CLP, before any mortalities. Compared with IRA B cell–containing controls (fig. S11E), the peritoneal cavities of GM/μMT chimeras had more leukocytes, mostly neutrophils (Fig. 4C), and experienced a severe IL-1β, IL-6, and TNFα cytokine storm in the serum (Fig. 4D) and peritoneum (Fig. 4E). This inflammatory signature typically associates with a defect in bacterial clearance. Indeed, neutrophils from the GM/μMT chimeras phagocytosed bacteria poorly (Fig. 4F). Moreover, the GM/μMT chimeras had a modest reduction of serum IgM, but not IgG (Fig. 4G), and developed severe liver and lung pathologies (Fig. 4H). Finally, bacterial titer measurements revealed that GM/μMT chimeras were more infected than controls (Fig. 4, I and J). Although it is possible that other bone marrow cells contribute GM-CSF for the protection against sepsis in this setting, the most likely explanation is that IRA B cells protect against septic shock by controlling the organism's ability to clear bacteria.

GM-CSF is a pleiotropic cytokine that influences the production, maturation, function, and survival of its target cells. GM-CSF's role in sepsis has remained elusive because its indiscriminate ablation is protective (*27*), but its supplementation can be beneficial (*28*). The in vivo identification of GM-CSF–producing B cells illustrates a previously unrecognized locational specificity that dictates the cytokine's function. IRA B cells differ from other subsets because their pathogen recognition pathways and tissue distribution license GM-CSF expression. The function is important in sepsis and gives rise to questions as to how IRA B cells participate in other infectious and inflammatory diseases.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/science.1215173/DC1
Materials and Methods
Figs. S1 to S12
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Abnormal Brain Structure Implicated in Stimulant Drug Addiction

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Addiction to drugs is a major contemporary public health issue, characterized by maladaptive behavior to obtain and consume an increasing amount of drugs at the expense of the individual's health and social and personal life. We discovered abnormalities in fronto-striatal brain systems implicated in self-control in both stimulant-dependent individuals and their biological siblings who have no history of chronic drug abuse; these findings support the idea of an underlying neurocognitive endophenotype for stimulant drug addiction.

Drug dependence is increasingly recognized as a "relapsing brain disorder" (*1*) and, in support of this view, marked structural changes in striatal and prefrontal brain regions have been reported in people dependent on stimulant drugs (*2*). These reports, however, raise

the question of whether these brain abnormalities may have predated drug-taking, rendering individuals vulnerable for the development of dependence.

Individuals at risk for drug dependence typically have deficits in self-control (*3*, *4*), which may reflect a diminished ability to recruit prefrontal networks for regulating behavior (*5*). Stimulant drugs are highly reinforcing, because they directly affect brain systems implicated in motivated behavior, such as the basal ganglia and the limbic system (*6*), and they modulate control systems in the prefrontal cortex (*7*). Malfunction of these circuitries may increase the susceptibility for stimulant-induced neuroadaptive changes and facilitate the development of drug dependence.

As brain structure is, to a large extent, inherited (*8*) and drug dependence runs in families (*9*), a genetic or epigenetic influence on addictive behaviors seems plausible. Yet, we know very little about the mechanisms through which risks for drug dependence might be inherited. Endophenotypes are quantitative traits, mediating between the predisposing genes (genotypes) and the clinical symptoms (phenotypes) in complex disorders (*10*). As heritable traits, endophenotypes can be measured objectively in both patients and their unaffected first-degree relatives. We compared brain structure and the ability to regulate behavior in 50 biological sibling pairs; within each pair, one sibling satisfied the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) criteria for dependence on stimulant drugs and the other had no history of chronic drug or alcohol abuse (*11*). The sib-pairs were also compared with 50 unrelated healthy volunteers matched for age and intelligence quotient (table S1). Tobacco was smoked by members of all groups, but smoking rates were significantly higher in the sib-pairs than in the unrelated volunteers (table S1), which is not surprising for individuals with a greater-than-normal genetic risk of drug dependence.

We used the stop-signal task (*12*), one of the most widely used measures of inhibitory control, which requires individuals to rapidly suppress an ongoing, well-established response whenever an auditory signal is suddenly presented. The stop-signal reaction time (SSRT) estimates the time that an individual needs to withhold an ongoing response and can predict the onset of substance abuse in vulnerable individuals (*4*). The neural circuitry underlying stop-signal task performance has been well-characterized and there is ample evidence for the association of SSRT with both the functional and structural integrity of brain systems known to be compromised in stimulant drug dependence (*13*, *14*). We observed marked impairments in the regulation of behavior in both drug-dependent individuals and their biological siblings who have no history of chronic drug abuse (Fig. 1A). Indeed, the deficits in SSRT were as pronounced in the nondependent siblings as in the stimulant-dependent patients. Moreover, the variance in SSRT within sib-pairs was significantly smaller than in unrelated sib-pairs (permutation test, $P = 0.033$), which suggests that poor inhibitory control is a familial trait in vulnerable individuals and not a result of long-term drug abuse.

To investigate the relation between inhibitory control and brain structure, we calculated from each individual's diffusion tensor images the fractional anisotropy (FA) values that serve as a general index of the integrity of white matter fiber tracts (*15*) and analyzed them using tract-based spatial statistics (TBSS) implemented in FSL software (*11*). We compared the mean FA values between the groups within a tract-based skeleton (*16*) and found evidence for a significant reduction of FA in the sib-pairs compared with healthy unrelated volunteers (indicated in blue in Fig. 1B). Again, the variance of FA within biological sib-pairs was significantly smaller compared with the variance within unrelated sib-pairs (permutation test, $P = 0.004$), which suggested that the observed white matter abnormalities were shared among members of the same family and may have predisposed them to drug-taking. In the stimulant-dependent individuals, reduced FA was associated with the duration of stimulant abuse (fig. S2A), which suggests that white matter changes can also result from drug-taking (although these effects of drug exposure were less anatomically extensive than the effects of familial risk for dependence).

Previous research shows that stop-signal task performance is subserved by a neural network, including the inferior frontal gyrus (IFG), the basal ganglia (caudate-putamen), and the presupplementary motor area (pre-SMA) (*17*, *18*). On the basis of previous studies, we created a region of interest using Hammer's probabilistic atlas (*19*), as indicated in orange in Fig. 1B. Within this region of interest, we regressed each participant's SSRT score on their white matter FA. Reduced FA in fiber tracts adjacent to the right IFG was significantly associated with poorer inhibitory control and accounted for ~6% of the variance in SSRT (Fig. 1C). The variability of the abnormality in the right prefrontal white matter was significantly similar within biological siblings compared with unrelated sib-pairs (permutation test, $P = 0.004$). Together, these results support the idea that self-control deficits are subserved by white matter disorganization in the right prefrontal lobe; this finding provides an objective vulnerability marker for an increased, possibly inherited, risk for developing stimulant drug dependence.

We also compared the gray matter volume maps of healthy volunteers with those of the drug-dependent individuals (Fig. 2A) and of the non–drug abusing siblings (Fig. 2B) using voxel-based morphometry analysis implemented in FSL software (*11*). The brains of the sib-pairs showed distinct abnormalities relative to the healthy control volunteers. Specifically, key structures previously implicated in addiction, such as the medial temporal lobe (*20*) and the basal ganglia (*21*, *22*), were significantly enlarged in the sib-pairs. We also identified a significant reduction of gray matter volume in the posterior postcentral gyrus and adjacent areas, such as the superior temporal gyrus and the posterior insula, in both drug-dependent individuals and their siblings compared with healthy volunteers (Fig. 2C). The

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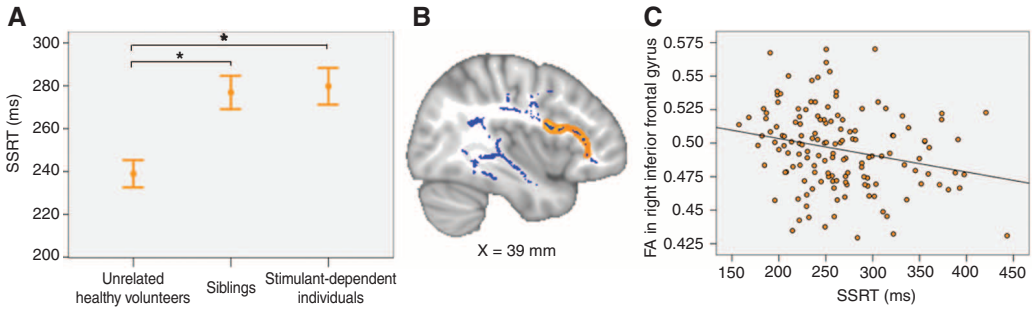
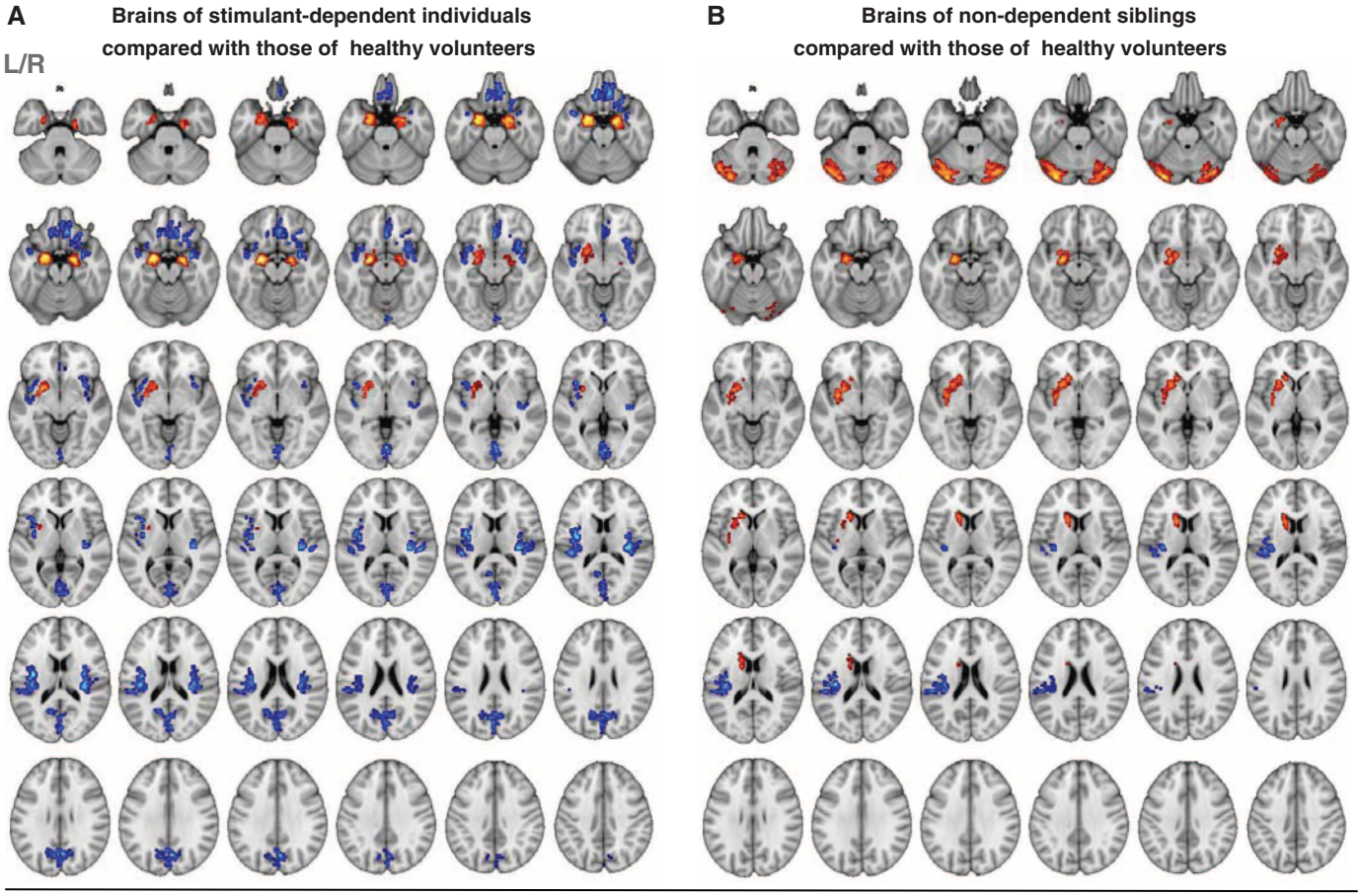


Fig. 1. Deficits of motor inhibitory control and white matter organization in stimulant-dependent individuals and their nondependent siblings. (**A**) SSRT differed significantly between the three groups ($F_{2,141} = 9.9$, $P < 0.001$). SSRT was significantly prolonged in both the stimulant-dependent individuals and their siblings compared with unrelated healthy volunteers (Bonferroni correction, $P \leq 0.005$, for both comparisons). (**B**) The skeleton of group differences in mean FA is colored in blue ($F_{2,141} = 26.3$, $P < 0.001$); on the basis of previous studies, regions of interest were selected within the blue skeleton, which included the IFG and the presupplementary motor area (colored in orange). (**C**) Scatterplot showing that participants with greater mean FA in the right IFG had better inhibitory performance (shorter SSRT) on the stop-signal task (the correlation coefficient, $r = 0.24$; the linear correlation constant, $R^2 = 0.057$, $P < 0.005$).

within-pair variability of the gray matter volume increase in the putamen (permutation test, $P = 0.013$) and of the volume decrease in the posterior insula (permutation test, $P = 0.012$) were both significantly smaller in biological siblings than in randomly paired siblings, which indicated that this abnormality is shared between members of the same family. By contrast, the enlargement of the amygdala in the sib-pairs did not survive the test of familiality (permutation test, $P = 0.144$), which suggested that other, nonfamilial factors may account for this abnormality. Note that higher tobacco exposure in the nondependent siblings is unlikely to explain the pattern of gray matter abnormalities identified as an endophenotype for stimulant dependence, as shown by similar results from a separate analysis restricted to nonsmokers (fig. S1). Moreover, gray matter regions associated with the duration of stimulant drug exposure differed clearly in location from the regions identified as markers of familial risk for stimulant drug dependence (fig. S2B)

The involvement of the putamen is consistent with its implication in fronto-striatal circuits for stop-signal performance and proposed antecedent problems in response control (*23*). However, the additional regions identified as showing changes in the sib-pairs may be related to other psychological processes underlying addiction. Thus, brain abnormalities observed in the sib-pairs in neural systems underlying learning and memory [such as the medial temporal lobe (*24*)], and habit formation [such as the putamen (*25*)] are intriguing, given that some forms of drug addiction are thought to develop through maladaptive acquisition and control of habits (*26*). Enlargement of limbic and striatal structures has been reported previously in patients with obsessive-compulsive disorder (OCD) (*27*), and like addiction, OCD is characterized by dysfunctional habits and "out-of-control" behavior. Our findings may



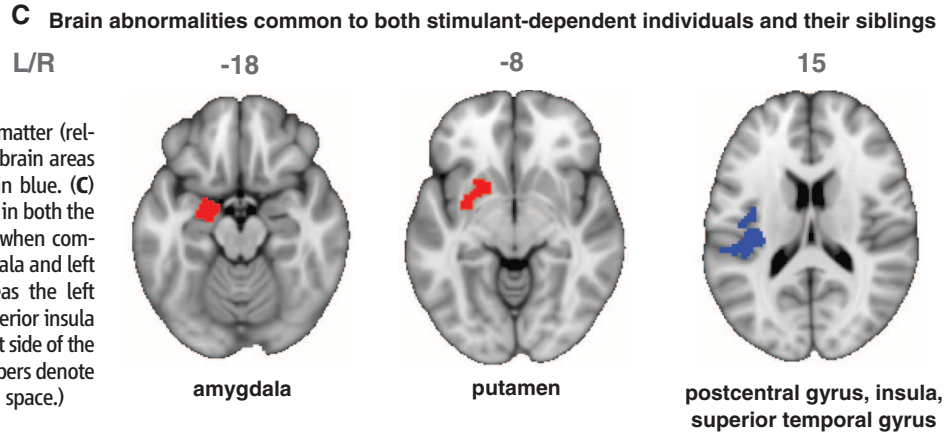


Fig. 2. Similar abnormalities in gray matter brain volume were found in stimulant-dependent individuals (**A**) and in their nondependent siblings (**B**) when separately compared with healthy volunteers. Brain areas of abnormally increased gray matter (relative to healthy volunteers) are colored in red, and brain areas of abnormally decreased gray matter are colored in blue. (**C**) Three clusters of shared abnormality were identified in both the stimulant-dependent individuals and their siblings when compared with unrelated healthy volunteers: left amygdala and left putamen were both significantly enlarged; whereas the left postcentral gyrus, superior temporal gyrus, and posterior insula were significantly reduced in gray matter volume. (Left side of the brain is shown on the left side of each slice; the numbers denote Z coordinates for each slice in standard stereotactic space.)

indicate markers of neural vulnerability for pathological habit formation, which could further facilitate the effects of drugs of abuse by interfering with limbic-striatal functions. Pathological habits in drug addiction typically result in compulsive drug-taking behaviors when prefrontal control fails to regulate behavior (*26*). Our data are also in keeping with preclinical research indicating that impairments in response control are predictive of cocaine reinforcement and dopamine receptor dysfunction in the striatum (*28*). Deficits in inhibitory prefrontal control were evident in both drug-dependent individuals and their siblings who do not abuse drugs, which may reflect an increased risk for out-of-control drug-seeking or drug-taking behaviors, which could pave the way for the development of drug dependence.

The identified profile of familial abnormalities remarkably resembles the developmental changes of brain structure during adolescence, i.e., limbic-striatal structures mature before prefrontal brain systems. This developmental asynchrony has been suggested to create an imbalance between mesolimbic reward and prefrontal control systems, which predisposes adolescents to sensation-seeking and impulsive behavior, rendering them potentially vulnerable to drug-taking (*29*). Our previous data on biological siblings of stimulant-dependent individuals indicated a propensity for increased impulsivity, as measured on the Barratt Impulsivity Scale, contrasting with normal scores on measures of sensation-seeking traits (*30*). The present findings show that even stronger effects in the sib-pairs are observed with an objective measure of impulse control, the SSRT. These findings are also related to changes in brain structure, including the inferior frontal cortex and putamen, which are key nodes in a neural network that mediates response regulation.

Our findings thus indicate that gray matter changes in the dorsal striatum, together with abnormal inferior prefrontal cortical connectivity, underlie an increased risk for developing stimulant drug dependence. However, the almost equivalent impairments in SSRT in both the stimulant-dependent individuals and their unaffected siblings need careful interpretation, as they do not reflect the classic pattern for endophenotypes, i.e., that the first-degree relatives have trait values intermediate between the patients and the unrelated healthy volunteers (*10*). Presumably, the siblings must have some other resilience factors that counteract the familial vulnerability to drug dependence. The identification of these brain and behavioral biomarkers for familial risk of drug dependence demonstrates that an individual's predisposition to become addicted to stimulant drugs may be mediated by brain abnormalities linked to impaired self-control.

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Supporting Online Material

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Materials and Methods
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