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Cerebellar Vermis Involvement in Cocaine-Related Behaviors

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Although the cerebellum is increasingly being viewed as a brain area involved in cognition, it typically is excluded from circuitry considered to mediate stimulant-associated behaviors since it is low in dopamine. Yet, the primate cerebellar vermis (lobules II–III and VIII–IX) has been reported to contain axonal dopamine transporter immunoreactivity (DAT-IR). We hypothesized that DAT-IR-containing vermis areas would be activated in cocaine abusers by cocaine-related cues and, in healthy humans, would accumulate DAT-selective ligands. We used BOLD fMRI to determine whether cocaine-related cues activated DAT-IR-enriched vermis regions in cocaine abusers and positron emission tomography imaging of healthy humans to determine whether the DAT-selective ligand [^{11}C]altropane accumulated in those vermis regions. Cocaine-related cues selectively induced BOLD activation in lobules II–III and VIII–IX in cocaine users, and, at early time points after ligand administration, we found appreciable [^{11}C]altropane accumulation in lobules VIII–IX, possibly indicating DAT presence in this region. These data suggest that parts of cerebellar vermis mediate cocaine's persisting and acute effects. In light of prior findings illustrating vermis connections to midbrain dopamine cell body regions, established roles for the vermis as a locus of sensorimotor integration and motor planning, and findings of increased vermis activation in substance abusers during reward-related and other cognitive tasks, we propose that the vermis be considered one of the structures involved in cocaine- and other incentive-related behaviors.

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INTRODUCTION

A common circuitry has been proposed to regulate drug-seeking behaviors evoked by stimulant drugs, their cues, and stress (Kalivas and McFarland, 2003). The circuitry includes a 'limbic subcircuit' (ventral tegmental area, amygdala/extended amygdala, mediodorsal thalamus, and lateral tegmental nucleus) that channels information into a 'motor subcircuit' (dorsal prefrontal cortex/anterior cingulate and nucleus accumbens core) referred to as a 'final common pathway' linking cognitive processing to behavioral output (Kalivas and McFarland, 2003). Most, but not all structures comprising these circuits exhibit relatively high concentrations of dopamine and dopamine transporters (DAT), the latter of which is blocked by cocaine and other stimulants, leading to the rapid synaptic dopamine increases thought to contribute to the acute behavioral effects of cocaine and other abused drugs.

Yet, a number of brain structures with relatively low dopamine and DAT levels appear to mediate effects of cocaine and other stimulants. One such region is the frontal cortex, which is intimately connected with the circuitry described above but is low in dopamine and DAT. By virtue of its involvement in salience attribution and in regulating inhibition of inappropriate behavioral responses, the frontal cortex appears to act as a higher order locus of control over stimulant and other drug-seeking behaviors (for review, see Goldstein and Volkow, 2002). Another brain area, the cerebellum, has been proposed to play a role in reinforcement (Martin-Solch *et al*, 2001). The cerebellum, like the frontal cortex, has relatively low concentrations of dopamine and dopamine receptors, and whole cerebellar DAT binding is very low (Kaufman *et al*, 1991; Fischman *et al*, 2001). Thus, it typically is excluded from consideration as a region mediating drug-associated behaviors. However, as has been noted by Cotterill (2001), 'Muscular contraction is the nervous system's only externally directed product, and the signaling routes which pass through the various brain components must ultimately converge on the motor areas'

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(Cotterill, 2001). Indeed, recent data suggest that the cerebellum plays fundamental roles in a number of cognitive processes required for executing goal-directed and suppressing disadvantageous behaviors, including sensory functions (Paradiso *et al*, 1999), attention (Allen *et al*, 1997; Bischoff-Grethe *et al*, 2002), conditioned response learning (Logan and Grafton, 1995), and executive functions (Smith and Jonides, 1997; Ernst *et al*, 2003; Hülsmann *et al*, 2003) including response inhibition (Mostofsky *et al*, 2003). Thus, the cerebellum is critically interposed to link internal processing of exteroceptive and interoceptive stimuli to action.

A cerebellar role in stimulant-associated behaviors is suggested by several functional imaging studies. Cerebellar activation in response to presentation of cues for cocaine initially was reported by Grant *et al* (1996) who noted a correlation between cerebellar activation and degree of cocaine craving. Subsequent studies noted cerebellar activity during cocaine craving (Kilts *et al*, 2001; Bonson *et al*, 2002), during recall or imagery of cocaine-use experiences (Wang *et al*, 1999; Kilts *et al*, 2001), and during stimulant expectancy (Volkow *et al*, 2003). Acute administration of or cues for other stimulants or psychoactive drugs also has been associated with increased cerebellar activity (Volkow *et al*, 1996, 1988; London *et al*, 1990; Ghatan *et al*, 1998; Sell *et al*, 1999; Domino *et al*, 2000). Two studies reported cerebellar midline (vermis) activation by alcohol odor cues and by stimulant expectancy (Schneider *et al*, 2001; Volkow *et al*, 2003). Such findings are intriguing in light of reports localizing DAT immunoreactivity (DAT-IR) and mRNA in primate cerebellar vermis (Melchitzky and Lewis, 2000; Hurley *et al*, 2003). Moreover, in rodents, the vermis is a context-dependent self-stimulation site (Ball *et al*, 1974) and vermis lesions alter cortical dopamine turnover (Snider and Snider, 1977). Together, these findings suggest that the cerebellum and the vermis in particular may exert some regulatory control over forebrain dopamine neurotransmission.

To date, a role for the vermis in mediating effects of abused drugs has not been evaluated or articulated in detail. Accordingly, we used blood oxygen level-dependent functional MRI (BOLD fMRI) to assess whether presentation of cocaine-related audiovisual cues evokes vermis activation in cocaine abusers. We retrospectively analyzed fMRI data acquired as part of our previously published study noting cocaine cue-associated anterior cingulate and left dorsolateral prefrontal cortex activation (Maas *et al*, 1998). That study reported no significant BOLD effect in cerebellum (Maas *et al*, 1998). However, it was published prior to the vermis DAT-IR findings of Melchitzky and Lewis (2000) and cerebellum was analyzed as a whole structure, an approach that would have missed small activation areas due to partial volume effects. In our reanalysis, we hypothesized that we would observe selective cocaine cue-associated BOLD activation in vermis regions (lobules II–III and VIII–IX) reportedly containing axonal DAT-IR (Melchitzky and Lewis, 2000).

In addition, though DAT-IR and mRNA have been localized in vermis (Melchitzky and Lewis, 2000; Hurley *et al*, 2003), no study to date has directly characterized vermis DAT density or distribution. While we (Kaufman *et al*, 1991; Fischman *et al*, 2001) and others documented low whole cerebellar DAT-binding levels *in vitro* and *in vivo*, as noted above, global DAT-binding measurements might have missed DAT-enriched zones. Thus, we conducted an *in vitro* autoradiographic study in human post-mortem cerebellar vermis tissue sections and an *in vivo* positron emission tomography (PET) study of healthy human cerebellum, using the DAT-selective cocaine congeners [^{3}H]2β-carbomethoxy-3β-(4-fluorophenyl) tropane ([^{3}H]CFT) (Kaufman *et al*, 1991) and [^{11}C]2β-carbomethoxy-3β-(4-fluorophenyl)-*N*-(1-iodoprop-1-en-3-yl) nortropane ([^{11}C]altropane) (Fischman *et al*, 2001), respectively, to examine vermis ligand accumulation. We hypothesized that [^{3}H]CFT and [^{11}C]altropane would accumulate selectively in vermis lobules II–III and VIII–IX.

MATERIALS AND METHODS

BOLD fMRI

We studied 10 crack cocaine abusers (six men) with $\geqslant$6-month histories of at least biweekly crack abuse (mean (SD) age = 36 $\pm$ 7 years old), and eight comparison subjects (three men, 31 $\pm$ 6 years old). Crack cocaine was the preferred drug of abuse by cocaine subjects but history of other drug use was not grounds for exclusion. Comparison subjects reported no history of drug abuse of any form. Subjects were screened with the Structured Clinical Interview for DSM-IV Axis I Disorders. Subjects with histories of psychotic disorder or current Axis I mood disorder were excluded. All subjects were otherwise healthy and had no history of neurological disorder. All subjects tested negative for recent drug (Triage Test, Biosite Diagnostics Inc.) and alcohol (Alco Sensor III, Intoximeters Inc.) use immediately prior to the fMRI study.

Studies were conducted with approval from the McLean Hospital Institutional Review Board and subjects provided written informed consent. The cocaine cue audiovisual presentation consisted of four contiguous 150-s alternating segments of neutral (butterflies) and cocaine-related scenes and sounds (Childress *et al*, 1999) adapted for presentation to each subject via an MRI-compatible audiovisual system (Maas *et al*, 1998), while supine in the magnet.

All fMRI data were obtained on a 1.5 Tesla General Electric Signa scanner (Milwaukee, WI) retrofit with a whole body resonant gradient set (Advanced NMR Systems Inc., Wilmington, MA). Gradient echo planar images were acquired from 16 oblique-coronal slices, including four to five slices containing cerebellum, with the following parameters: 7-mm thickness, 3-mm skip, TE = 40 ms, TR = 5 s, $\alpha = 90^{\circ}$, in-plane resolution = 3.125 $\times$ 3.125 mm^{2}). Matched anatomical T1-weighted images also were acquired for region of interest (ROI) placement.

To quantify craving levels, a visual analog desire for cocaine scale was administered prior to and after scanning, to determine change scores, as described previously (Maas *et al*, 1998). All fMRI data were motion-corrected before analysis (Maas *et al*, 1997). One image slice, containing the bulk of cerebellar lobule VIII, was selected for vermis ROI placements. Three ROIs (Figure 1a and b) encompassing anterior vermis (AV: lobules II–III), posterior-superior vermis (PSV: lobules V–VI), and posterior-inferior vermis (PIV: lobules VIII–IX) were selected to compare axonal

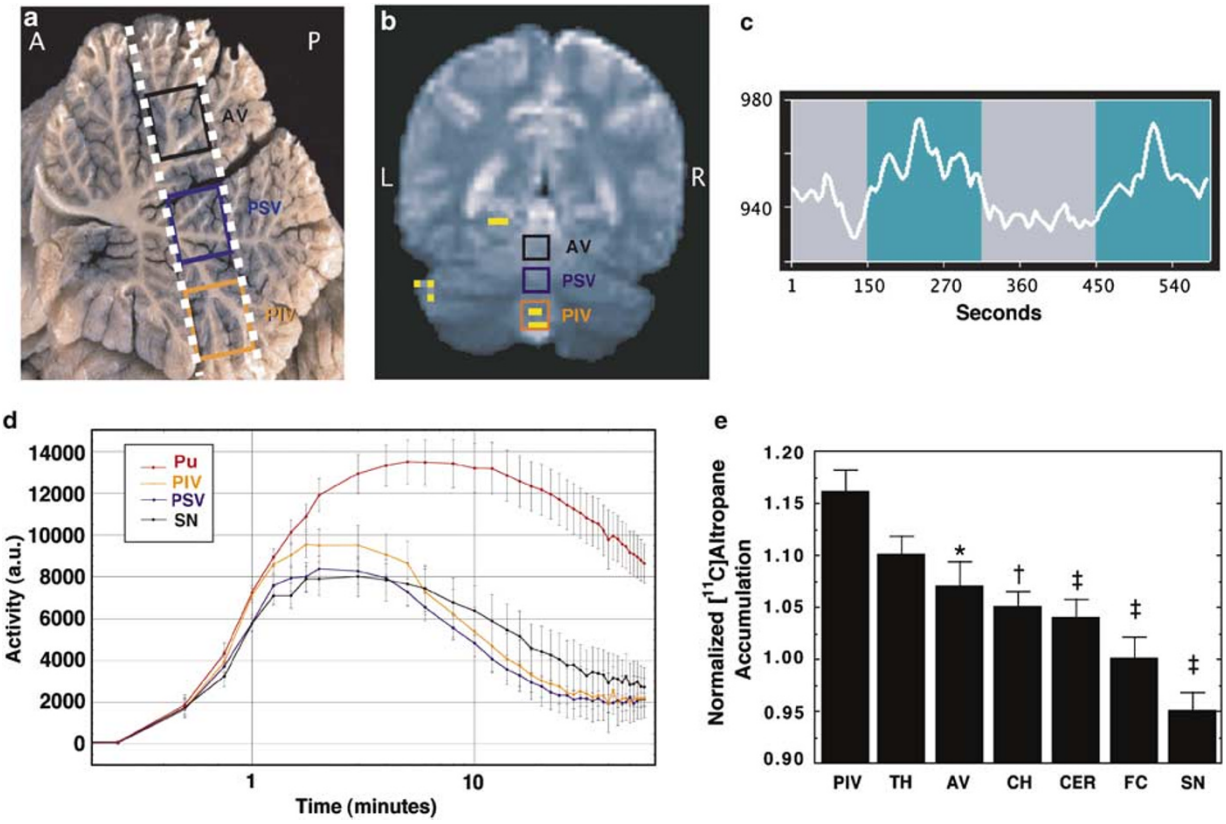

Figure 1 BOLD fMRI activation of and [^{11}C]altropane accumulation in vermis. (a) Midsagittal vermis gross anatomy section overlaid with the approximate position of the coronal oblique fMRI acquisition slice (A, anterior; P, posterior; L, left; R, right). The black, blue, and orange box overlays on panels a and b represent the AV, PSV, and PIV, respectively. (b) BOLD activation map from a single cocaine subject overlaid on an oblique image. Yellow pixels represent activation foci at the $P = 9 \times 10^{-12}$ statistical significance level. (c) PIV activation time course for pixels within the PIV box on panel b; bluish gray and green epochs indicate neutral and cocaine cue periods, respectively. (d) [^{11}C]altropane PET time–activity curves. Shown are mean (SE) activity levels (a.u. – arbitrary units) from 11 healthy subjects in putamen (Pu), posterior-inferior vermis (PIV), posterior-superior vermis (PSV), and substantia nigra (SN). (e) Normalized regional [^{11}C]altropane accumulation during the initial 6 min after ligand infusion. Shown are means (SE) in various brain regions, normalized to PSV accumulation. Posterior-inferior vermis (PIV); thalamus (TH): anterior vermis (AV); cerebellar hemispheres (CH); whole cerebellar slice (axial aspect) (CER); frontal cortex (FC); substantia nigra (SN). *Post hoc* tests with Bonferroni multiple comparisons correction for significant difference from PIV: $^{*}P < 0.05$; $^{\dagger}P < 0.01$; $^{\ddagger}P \leqslant 0.005$. In all panels, regions with bilateral representations were averaged into single data values.

DAT-IR-enriched zones (AV and PIV) to the DAT-IR-poor zone (PSV). These ROIs were identified on matched anatomical MR images and mapped to the midcerebellar fMRI slice by a single rater blind to subject identities. BOLD fMRI activation was estimated as percent change in the mean ROI intensities measured between neutral and cocaine-cue fMRI segments and as spatial activation extent (fraction of regional pixels exceeding an $r = 0.30$ activation threshold, as noted previously (Maas *et al*, 1998)). We established good inter-rater reliability for both activation measures (Maas *et al*, 1998).

[^{11}C]altropane *In Vivo* PET

PET with [^{11}C]altropane was conducted in 11 healthy adults (two women) aged 23.9 ± 0.9 years old, who provided informed consent to participate in this study. Images were acquired using a HR+ (CTI, Knoxville, TN) PET camera. Camera imaging parameters are in-plane and axial resolutions of 4.5-mm FWHM, with 63 contiguous slices of 2.5-mm separation. Images were acquired in 3D mode and reconstructed using an iterative algorithm to an in-plane resolution of 4.5-mm FWHM. Photon attenuation measurements were made with ^{68}Ge rotating pin sources. For each scan, ~ 5 mCi of [^{11}C]altropane was injected intravenously over 30 s. Dynamic image collection started at infusion and images were acquired in 15-s frames (initial 2 min), in 1-min frames (next 4 min), and in 2-min frames (remaining 54 min). All projection data were corrected for detector response nonuniformity, dead time, random coincidences, and scattered radiation.

The initial 11 volumes acquired immediately after injection of the [^{11}C]altropane bolus were summed to create blood flow images on which ROIs were manually traced using an in-house tool written for AVS (Advanced Visual Systems Inc., Waltham, MA). ROIs were positioned bilaterally on frontal cortex, thalamus, substantia nigra, and cerebellar hemispheres. ROIs also were traced within the highest intensity core of the putamen bilaterally on axial slices. For vermis, three ROIs were sampled in the sagittal plane within AV, PSV, and PIV. The complete set of ROIs was replicated on summed volumes (14–31) to represent bound [^{11}C]altropane.

Relative regional [^{11}C]altropane accumulation levels were calculated over the first 6 min after ligand infusion as quotients of summed activity within each ROI, divided by PSV summed activity. The referent PSV reportedly is DAT-IR devoid (Melchitzky and Lewis, 2000). For regions with bilateral representations, ROI values were averaged across hemispheres. Relative activity levels were analyzed with ANOVA to detect a regional difference in [^{11}C]altropane accumulation. The putamen, which contains high DAT levels, was excluded from all statistical analyses, so that it did not bias our global analyses in favor of finding regional differences in [^{11}C]altropane accumulation. *Post hoc* tests were conducted using a Bonferroni correction for multiple comparisons.

[^{3}H]CFT *In Vitro* Receptor Autoradiography

Cerebellar vermis tissue blocks from two healthy women (pathologically confirmed) were obtained from the Harvard Brain Tissue Resource Center at McLean Hospital and stored until sectioning at -80°C. Subject age, post-mortem index, and time interval between death and the autoradiography study were 60 ± 2.8 years, 19.3 ± 7.1 h, and 1.8 ± 0.3 years, respectively. Autoradiography was conducted as described (Kaufman *et al*, 1991). Vermis tissue blocks were sectioned (20 μm thickness) sagittally on a cryostat at -18°C. Tissue sections were thaw-mounted onto Adhesion Superfrost Plus microscope slides (Brain Research Laboratories, Newton, MA) and stored at -80°C. Tissue sections were equilibrated at 0°C 12 h prior to autoradiography studies. Six sections per brain were preincubated for 20 min in Tris buffer (50 mM Tris-HCl containing 100 mM NaCl, pH 7.4 at 4°C), then incubated in triplicate for 2 h in buffer containing tracer (10 nM) concentrations of [^{3}H]CFT ([^{3}H]WIN 35 428, spec. act.: 81.3 Ci/mmol, Dupont-New England Nuclear, Boston, MA) to measure total binding, or with 10 nM [^{3}H]CFT and 30 μM (−)-cocaine hydrochloride to measure nonspecific binding, washed with two 1-min rinses in ice-cold buffer, dipped rapidly in ice-cold distilled water, and dried with chilled desiccated air. Tissue sections and autoradiographic standards ([^{3}H]Microscales, Amersham Biosciences Corp., Piscataway, NJ) were apposed to autoradiographic film (Hyperfilm-[^{3}H], Amersham Biosciences Corp., Piscataway, NJ) for 10 weeks at 4°C. Films were developed at room temperature using Kodak D-19 developer (5 min), rinsed in water for 30 s, fixed in Kodak Rapid Fix for 5 min, and washed for 20 min. Films were dipped in Kodak Photoflo and hung to air dry. Densitometric data were acquired from DAT-IR-enriched lobule VIII and DAT-IR-poor lobule VI, as well as from whole vermis and vermis white matter, using the MCID analysis system (St Catharines, Ont.). Densities are expressed as regional ratios and statistical analyses were conducted using one sample *t*-tests.

RESULTS

BOLD fMRI Studies

Cocaine but not comparison subjects reported increased desire for cocaine following cocaine cue presentation. Mean desire ratings increased by 2.2 (0–10 scale) arbitrary units (SD = 2.7, $t = 2.7$, $P < 0.03$). There was a group difference in vermis BOLD activation ($F_{1,16} = 4.95$, $P = 0.04$) with cocaine subjects exhibiting higher mean percent increases (0.48% magnitude difference) than comparison subjects. Within vermis, BOLD activation magnitudes differed by region ($F_{2,32} = 7.51$, $P = 0.002$); *post hoc* Scheffe tests indicated greater BOLD activations in AV and PIV than in PSV ($P < 0.01$). Mean BOLD activation spatial extent scores also were greater ($F_{1,16} = 7.17$, $P < 0.02$) and regional differences were identified ($F_{2,32} = 6.70$, $P = 0.004$) in cocaine subjects; *post hoc* Scheffe tests indicated greater spatial activation extent in PIV than PSV ($P < 0.005$). We found a marginal association between desire rating change score and BOLD activation increase in PIV ($R = 0.713$, $P < 0.02$), though that finding was strongly influenced by an outlier case, which, when removed, eliminated statistical significance. Although we did not identify sex differences on these measures, our study was not adequately powered to test for an effect of sex, and thus we cannot rule in or out any effects of sex.

Autoradiography and PET Imaging Studies

[^{3}H]CFT-specific binding levels approached background (< 10 pmol/g tissue equivalent) throughout vermis gray matter (data not shown). Although [^{3}H]CFT binding in lobule VIII was higher than white matter levels (108.7 ± 0.4%, $P < 0.005$, one sample *t*-test), it was marginally lower than binding in either lobule VI (DAT-IR-poor) or in whole vermis (95.3 ± 3.7 and 93.0 ± 0.4%, respectively, $P < 0.02$, one sample *t*-test).

In PET imaging studies, high [^{11}C]altropane accumulation levels were detected in putamen, as expected. At early time points following ligand administration, time–activity curves were suggestive of greater peak [^{11}C]altropane accumulation in PIV than in all other areas but putamen (Figure 1d). There was a regional difference in normalized ligand accumulation ($F_{6,76} = 12.2$, $P < 0.001$, excluding putamen). *Post hoc* testing with Bonferroni correction for multiple comparisons indicated that PIV [^{11}C]altropane accumulation was greater than in substantia nigra, frontal cortex, and all other cerebellar regions (Figure 1e). Thalamic [^{11}C]altropane accumulation was equivalent to that in PIV. We were unable to detect appreciable PIV accumulation using binding potential analysis (data not shown), though that method may be less sensitive for detecting transient ligand accumulations in regions containing low specific binding densities.

DISCUSSION

These data document cocaine cue-induced cerebellar vermis BOLD fMRI activation in cocaine users and selective PIV [^{11}C]altropane accumulation in healthy subjects at early time points following ligand administration. Consistent with our *a priori* hypotheses, BOLD activation occurred only in AV and PIV, regions containing axonal DAT-IR (Melchitzky and Lewis, 2000). Group differences (cocaine users *vs* controls) in BOLD activation magnitudes (0.62 and 0.37% in AV and PIV, respectively) were substantially larger than those we reported previously in the same subjects in anterior cingulate (0.29%) and left dorsolateral prefrontal

cortex (0.20%) (Maas *et al*, 1998). This may indicate that cocaine cue exposure induces greater neuronal activation in vermis than in forebrain structures (Kim *et al*, 2004). Alternatively, the larger apparent BOLD signal response in vermis ROIs could have resulted from less partial voluming (and less BOLD activation dilution per volume tissue) for discrete vermis lobules.

Since we observed significant activation in vermis lobules VIII–IX, which also are activated by smooth pursuit oculomotor movements (Tanabe *et al*, 2002), and since such movements were necessary to view the cocaine cue program, smooth pursuit eye motion may have contributed to BOLD responses. However, smooth pursuit eye movements occurred in all subjects but lobules VIII–IX were activated only in cocaine subjects. This suggests that cocaine-related visual stimuli, salient only to cocaine users, induced either new activity or a potentiated form of smooth pursuit activation in lobules VIII–IX in cocaine abusers. Vermis lobules VII and VIII process auditory information (Brodal, 1980) and the combination of salient auditory and visual cocaine-related cues may have contributed to lobule VIII–IX activation. As there were no other overt motor requirements in our paradigm, we interpret these findings to suggest that salient polysensory qualities of the cue paradigm selectively activated portions of the vermis.

It also is conceivable that the vermis BOLD activations we identified in cocaine users represent early sensory processing of visual and auditory stimuli presented in the cocaine cue paradigm. In this regard, neurophysiology studies in cats noted vermis lobule VIII activation in response to auditory–visual stimuli (Snider and Stowell, 1944). PET blood flow studies in healthy humans documented anterior and posterior vermis activations during early sensory recognition of complex auditory and visual stimuli (Penhune *et al*, 1998). These regions were proposed to be part of a supramodal sensory timing apparatus that computes temporal parameters of incoming sensory stimuli to support timed motor responses (Penhune *et al*, 1998). While visual and/or auditory sensory stimuli might induce early vermis activations independent of DAT activity, the localization of significant DAT-IR in this region in primates implies that dopaminergic mechanisms linked with reward could coexist and interact with such early sensory processing circuits. From these findings, we conclude that axonal DAT-IR-enriched vermis lobules are activated by cocaine-related cues. The vermis also is activated during stimulant expectancy (Volkow *et al*, 2003) and in alcoholics during alcohol odor cue-induced craving (Schneider *et al*, 2001), implying that it may generally activate in response to drug-associated stimuli in drug abusing cohorts.

Our PET findings suggest that at early time points after ligand administration [^{11}C]altropane accumulated at higher levels in PIV than in substantia nigra, frontal lobe, and other cerebellar areas. This finding is consistent with the report of DAT-IR enrichment in this area (Melchitzky and Lewis, 2000). PET time–activity curves indicated that PIV [^{11}C]altropane washout was more rapid than in putamen or substantia nigra, suggesting different ligand kinetics in PIV *vs* putamen and substantia nigra. It is unlikely that the excess PIV [^{11}C]altropane accumulation is solely the result of blood flow differences since PET blood flow data from healthy adults indicate mismatches between cerebellar blood flow patterns, which are higher in cerebellar hemispheres than vermis and homogenous within vermis (Ouchi *et al*, 2001; Ito *et al*, 2003) and [^{11}C]altropane accumulation, which was lowest in cerebellar hemispheres and was heterogeneous within vermis. Although it is possible that excess [^{11}C]altropane accumulation in PIV represented labeling of other sites (see below), a parsimonious conclusion is that DAT may be present in the DAT-IR-enriched PIV and that this region may be a proximate site of action of cocaine, methylphenidate, and other drugs that interact with the dopamine transporter.

Our human post-mortem autoradiography studies were unable to detect vermis-specific [^{3}H]CFT binding. Thus, our autoradiography data appear to conflict both with our own PET imaging data and with prior DAT-IR findings (Melchitzky and Lewis, 2000). The lower DAT affinity and selectivity of CFT *vs* altropane (Madras *et al*, 1998), and the lower affinity of radioreceptor ligands (nanomolar range) *vs* immunohistochemical ligands (subnanomolar range), may in part explain why we failed to detect specific [^{3}H]CFT autoradiography binding in vermis, when binding was detected with other DAT-selective ligands. Two additional factors may have contributed to our inability to detect specific [^{3}H]CFT binding with autoradiography: our studies were conducted in the post-mortem state in tissues from elderly subjects. DAT radioligand binding declines post-mortem by up to 35% after 5 or more hours of post-mortem time (Patel *et al*, 1993) and the post-mortem interval for tissues used in this study averaged 19.3 h. In addition, a number of studies have shown that DAT radioligand-binding density declines with age in healthy subjects (see, for example, Kaufman and Madras, 1993; Volkow *et al*, 1994; van Dyck *et al*, 1995). The 3.5-decade age difference between our PET and autoradiography subjects (averaging 25 and 60 years old, respectively) might have resulted in a significant depletion of DAT activity (using an 8% per decade decline in DAT activity, van Dyck *et al*, 1995). Together, post-mortem time and aging effects could result in significant losses of functional DAT, comparable to the differences reported between cryopreserved human caudate nucleus and fresh rat striatum (Eshleman *et al*, 2001). Thus, if [^{11}C]altropane accumulation in the vermis indeed reflects DAT binding, and if vermis and striatal DAT losses are parallel with post-mortem factors and age, then conceivably, detection of specific [^{3}H]CFT binding to vermis DAT would be severely compromised. This could explain our negative autoradiography findings. Recent rodent studies suggest that the age-associated decline in functional DAT results not from loss of DAT protein but from reduced functional DAT expression in the plasma membrane (Salvatore *et al*, 2003). Accordingly, in healthy subjects at any age, DAT may be easier to detect with immunohistochemical than with radioreceptor methods. This also means that a proportion of vermis DAT-IR detected in prior studies may not represent functional DAT protein.

Interestingly, thalamic [^{11}C]altropane accumulation was statistically equivalent to that in PIV (Figure 1e). DAT-IR has been reported in thalamus (Melchitzky and Lewis, 2001) and thalamic [^{11}C]cocaine accumulation was proposed to reflect DAT binding (Telang *et al*, 1999). Moreover, a very recent report described a significant dopaminergic innervation of the primate thalamus including a confirmation of

widespread DAT-IR localization (Sanchez-Gonzalez *et al*, 2005). Thus, thalamic [^{11}C]altropane accumulation may reflect DAT-binding sites. Clearly, additional pharmacological studies are required in PIV and thalamus to more precisely characterize the nature of cocaine congener accumulation in these areas. This is important because cocaine has comparable affinity for dopamine, norepinephrine (NET), and serotonin transporters, and cocaine's effects may be mediated in some regions via interactions with sites other than DAT. For example, frontal lobe dopamine uptake occurs primarily via NET activity (Moron *et al*, 2002). NET is present in cerebellum including vermis (Ding *et al*, 2003). Accordingly, some cerebellar regions containing NET might mediate effects of cocaine and its cues. While the present data do not identify vermis substrates activated by cocaine or its cues, they suggest that the PIV contains elements that may mediate or participate in both effects.

Cerebellar Connectivity to Dopamine Circuitry

Our findings suggesting that parts of the vermis mediate effects of cocaine and its cues are consistent with prior data documenting vermis connections to dopamine cell body regions in the ventral tegmental area (VTA) and substantia nigra (Snider *et al*, 1976). In addition, the VTA projects to cerebellum (Ikai *et al*, 1992) implying the presence of a reciprocal midbrain to cerebellum circuit. A subset of VTA efferents to cerebellum appears to be dopaminergic (Ikai *et al*, 1992) and some of those projections could be a target for DAT-IR labeling and contain DAT-binding sites.

Interestingly, in rodents, a proportion of VTA efferents bifurcates, sending projections both to cerebellum *and* either prelimbic/anterior cingulate or piriform-entorhinal cortex; such projections are segregated from VTA connections to subcortical (including limbic subcircuitry) structures (Ikai *et al*, 1994). Those bifurcating projections, together with cerebellar efferents to VTA (Snider *et al*, 1976), could form a separate circuit connecting cerebellum to frontal and temporal lobes independent of ascending thalamic (Middleton and Strick, 2001) and descending pontine (Schmahmann and Pandya, 1997) relays. Such circuitry could be a basis for forebrain dopamine turnover changes induced by vermis lesions (Snider and Snider, 1977), could account for our finding of vermis activation in cocaine abusers by cocaine-related cues, and could explain why the cerebellum tends to coactivate with frontal lobes during some cognitive tasks (see below).

Reward Circuitry, The Cerebellum, and Incentive-Related Behaviors

The reward circuitry has been proposed to participate as a shared pathway for processing drug and nondrug rewards (Garavan *et al*, 2000) and aversive stimuli (Becerra *et al*, 2001). Vermis activation also occurs in response to nondrug rewards or their anticipation (Rogers *et al*, 1999; Kunig *et al*, 2000; Martin-Solch *et al*, 2001; Knutson *et al*, 2003), painful or aversive stimuli or their anticipation (Paradiso *et al*, 1999; Casey *et al*, 2000; Becerra *et al*, 2001), and interoceptive stimuli triggered by vegetative regulatory functions including thirst (Egan *et al*, 2003), hunger (Tataranni *et al*, 1999), and respiratory stress (Evans *et al*, 2002). Together, those findings are consistent with the suggestion that the cerebellum and the vermis process multimodal sensory inputs to influence cortical excitability and enhance motor sequence learning and execution (Molinari *et al*, 2002).

That multimodal sensory processing function may be a form of or closely related to selective attention, as vermis participates both in attentional processes linked to motor responses (Allen *et al*, 1997) and in response reassignment, which involves context-dependent changes in sensorimotor sets to facilitate motor outputs (Bischoff-Grethe *et al*, 2002). These capacities may be very important in drug dependence (and its treatment) since a 'hyperattentive state' with regard to salient drug-related stimuli may underlie drug craving and relapse (Franken, 2003). Vermis activation in response to cocaine-related cues (present study) and in response to alcohol odor cues (Schneider *et al*, 2001) may indicate that it is involved in 'hyperattentive states.' This could be significant as vermis also is involved in later stages of voluntary movement planning (Hülsmann *et al*, 2003) and thus is positioned to strongly influence behavioral output (Cotterill, 2001).

Of course, the vermis and other cerebellar areas do not function in isolation but rather coordinate task processing duties with other forebrain structures via cerebello-thalamo-cortical (Middleton and Strick, 2001) and cortico-ponto-cerebellar streams (Schmahmann and Pandya, 1997), and perhaps also via VTA circuitry (see above). The fronto-cerebellar interplay seems to be dynamic in nature and normally is dominated by frontal structures (Smith and Jonides, 1997; Gould *et al*, 2003), with cerebellar structures playing a supporting role. However, in addiction disorders, in which the frontal lobes are known to be compromised (Goldstein and Volkow, 2002), cerebellar (and vermis) activity appears to increase to support several tasks involving frontal lobe function including monetary reward response (Martin-Soelch *et al*, 2001), response inhibition (Hester and Garavan, 2004), and working memory (Desmond *et al*, 2003). Vermis activation also occurs during reward tasks in Parkinson's and in attention deficit hyperactivity disorder patients, but not in comparison subjects (Ernst *et al*, 2003; Goerendt *et al*, 2004; Kunig *et al*, 2000). In addition, increased cerebellar (and vermis) activation occur to support working memory function in frontotemporal dementia, Parkinson's Disease, and schizophrenia, (Mentis *et al*, 2003; Meyer-Lindenberg *et al*, 2001; Rombouts *et al*, 2003). Thus, several domains of frontal lobe function pertinent to addiction-related behaviors appear to be supported by cerebellum and vermis. Along with the present findings, these observations suggest that the vermis plays a central role in organizing sensory inputs and planning motor responses to rewarding and other incentive-related stimuli, and that its role in modulating these responses may increase when the frontal lobes are compromised by disease or chronic drug use.

Limitations

These findings must be interpreted in light of several limitations. First, our fMRI data were acquired with older technology and analyzed retrospectively, after learning that

DAT-IR is present in primate vermis (Melchitzky and Lewis, 2000). Thus, fMRI acquisition parameters were not optimized for detecting cerebellar activations, and in particular, for activations localized to specific vermis lobules. For this reason, we believe that the BOLD activation magnitudes we identified may be very conservative estimates of localized vermis responses to cocaine-related cues. Second, the ligand we used for PET-imaging studies, [^{11}C]altropane, exhibits fast washout kinetic properties. Thus, it probably is not optimal for detecting DAT in regions with low DAT densities. Indeed, binding potential analysis was unable to identify DAT binding in PIV. Yet, we found statistically significant normalized [^{11}C]altropane accumulation differences within vermis and cerebellum (when referenced to the DAT-devoid PSV) that cannot be attributed to blood flow differences (Ouchi *et al*, 2001; Ito *et al*, 2003), suggesting the presence of DAT binding in PIV. Third, we were unable to detect specific [^{3}H]CFT binding in vermis lobule VIII suggesting some discrepancy between [^{3}H]CFT and both DAT-IR and [^{11}C]altropane labeling. As noted above, this discrepancy could be related to differential kinetics and pharmacological specificity for these ligands (Madras *et al*, 1998; Fischman *et al*, 2001) as well as from age and post-mortem reductions in functional DAT expression (Patel *et al*, 1993; Salvatore *et al*, 2003). Notwithstanding these limitations, we believe the present findings support the concept that the cerebellar vermis is involved in mediating cocaine-related behaviors. We also believe that these findings warrant further studies to better characterize cerebellar and vermis roles in cocaine- and other incentive-related behaviors and to identify vermis substrates mediating the effects noted presently.

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