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Cortical thickness abnormalities in cocaine addiction – a reflection of both drug use and a pre-existing disposition to drug abuse?

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Summary

The structural effects of cocaine on neural systems mediating cognition and motivation are not well known. By comparing thickness of neocortical and paralimbic brain regions between cocaine dependent and matched control subjects, we found that four of 18 *a priori* regions involved with executive regulation of reward and attention were significantly thinner in addicts. Correlations were significant between thinner prefrontal cortex and reduced keypresses during judgment and decision-making of relative preference in addicts, suggesting one basis for restricted behavioral repertoires in drug dependence. Reduced effortful attention performance in addicts also correlated with thinner paralimbic cortices. Some thickness differences in addicts were correlated with cocaine use independent of nicotine and alcohol, but addicts also showed diminished thickness heterogeneity and altered hemispheric thickness asymmetry. These observations suggest brain structure abnormalities in addicts are related in part to drug use, and in part to predisposition toward addiction.

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Introduction

Animal studies of cocaine's action have implicated brain structures involved with reward/aversion function such as the ventral tegmental area, nucleus accumbens (NAc), amygdala and prefrontal cortex (PFC) (Everitt and Robbins, 2005; Hyman et al., 2006; Kalivas and Volkow, 2005; Koob, 2006). Results of human studies are consistent with the animal literature showing functional activation of subcortical and cortical reward/aversion regions during drug exposure (Breiter et al., 1997; Stein and Fuller, 1992). Human studies have further demonstrated significant alterations in cognitive control in addiction related to functional alterations in the PFC (Bechara, 2005; Goldstein et al., 2007; Volkow and Fowler, 2000). It is unknown, however, whether these observations might parallel findings of structural alterations to the PFC (Fein et al., 2002; Franklin et al., 2002; Matochik et al., 2003; Sim et al., 2007) and amygdala (Makris et al., 2004), despite broad claims that cocaine, potentially in conjunction with alcohol or other drugs, can be neurotoxic (Du et al., 2006; Glauser and Queen, 2007). The absence of quantitative evidence supporting this thesis, beyond the known potential for inducing stroke and seizures, is striking in contrast to what has been reported regarding another psychostimulant, methamphetamine, in animals and humans (Deng et al., 2007; Kuczenski et al., 2007; Thompson et al., 2004).

The present study addressed this issue using T1-weighted MRI of 20 cocaine dependent patients (COC) and 20 matched controls (CON) to study the variation in cortical thickness (Makris et al., 2006b, 2007; Fischl and Dale, 2000; Shaw et al., 2007) of neocortical and paralimbic regions subserving executive control and regulation of reward (to be referred to as "reward regulation" or RWR) and attention function (ATTN). Thickness is a topographical measure that is an indicator of the integrity of cytoarchitecture in the cortex (Makris et al., 2007), and of all the topographical measures that can be made, cortical thickness is the most invariant brain size parameter across mammalian evolution (Prothero and Sundsten, 1984; Mountcastle, 1998). Neocortical enlargement depends primarily on growth of surface area (Rockel et al., 1980; Jones, 1990; Mountcastle, 1998). Cortical surface and brain volume bear a nearly linear relation, and cortical thickness changes minimally for volumes above 3 cm^3 (Hofman, 1989; Mountcastle, 1998). Alterations in thickness might thus be an important observation in functional brain illness. The connection of such measures to well-defined behavioral indices that are known to be affected in cocaine addiction, would be a further index of the importance of these findings to addiction. Cortical thickness was therefore assessed in COC and CON subjects using a double blind semi-automated segmentation/parcellation method integrated with a set of automated steps for topographical measures (Caviness et al., 1996; Worth et al., 1997; Makris et al., 2006b, 2007; Fischl and Dale, 2000).

If differences were seen between COC and CON subjects, we then examined hypotheses of etiology secondary to drug exposure or to potential predisposition. Absent associations of any thickness differences with drug exposure, findings of an alteration in normative asymmetry would argue for a potential genetic etiology (e.g., Piedra et al., 1998; Hyatt and Yost, 1998; Supp et al., 1997; see Methods Appendix, Symmetry Analysis). Similarly, alterations in the pattern of thickness measures across the cortical mantle would contrast with the preservation of thickness measures across mammalian evolution (Prothero and Sundsten, 1984; Mountcastle, 1998). Lastly, to interpret the relevance of any cortical thickness, laterality or pattern differences found in COC subjects with regard to their diagnosis, we examined possible behavioral implications of these findings.

Behavioral assessments involved (1) a keypress task measuring relative preference for a validated picture set (i.e., beautiful versus average faces; Aharon et al., 2001), which build upon operant procedures used in animal addiction research (Everitt and Robbins, 2005;

Hyman et al., 2006; Kalivas and Volkow, 2005; Koob, 2006), and (2) a continuous performance task (CPT) for three categories of attention function, including an effortful attention condition, which involves high information processing demands (Goldstein et al., 2005; Seidman et al., 1998b, 2007; Thermenos et al., 2004) and recruits brain regions traditionally classified with reward processing (Breiter et al., 2006; Breiter and Rosen, 1999; Everitt and Robbins, 2005; McClure et al., 2004; Rolls et al., 2007).

With these behavioral, clinical, and topographical/morphometric measures, our hypotheses were that COC subjects, in contrast to CON subjects, would show quantitative decreases in cortical thickness and volume in cerebral regions dedicated to the control of relative preference and effortful attention, and these topographical alterations would (i) correlate with behavioral indices, and (ii) provide etiological hypotheses for subsequent animal and/or family/twin studies.

Results

Data were analyzed using a hierarchical process that first tested hypotheses with large volumes of tissue and sequentially followed positive results down to more elementary structural units. We grouped the orbitofrontal cortex (FOC), anterior cingulate gyrus (CGa) and paracingulate cortex (PAC), insular cortices (INS) and dorsolateral prefrontal cortex (DLPFC), as RWR regions controlling subcortical and cortical systems that process reward/aversion information (see Appendix 2, Data Analyses for rationale). Systems mediating the alerting, orienting, and executive control of ATTN were also grouped, including the CGa and posterior cingulate gyrus (CGp), inferior parietal lobule (IPL, comprising regions in the angular gyrus (AG), supramarginal gyrus (anterior and posterior, SGa, SGp), and parietal operculum (PO)) and DLPFC (see Appendix 2, Data Analyses for rationale). Given lateralization of ATTN function in humans, we specifically limited a priori regions for ATTN to the right hemisphere (Heilman and Van Den Abell, 1980; Makris et al., 2007; Mesulam, 1990; Seidman et al., 1998b). Across these groupings we then assessed cortical thickness measurements in COC and CON subjects and related these findings to behavioral measurements.

Cortical Volume and Thickness

Overall cerebral exterior was similar ($t(38) = 1.67$, $p = 0.38$) between CON (mean ± SD; 1139.4 ± 147.8cc) and COC subjects (1067.5 ± 123.9cc). Total cortical volume was significantly less ($t(38) = 2.21$, $p = 0.047$) in COC subjects (532.3 ± 67.3cc) relative to CON subjects (584.9 ± 82.2cc). Significant cortical thickness effects were observed using a multivariate general linear mixed model (Table 1), and subsequent pair-wise comparisons revealed significantly thinner cortex in COC subjects for the total RWR system, and separately, for the right hemisphere RWR. A similar trend was also seen for the total ATTN system.

Sub-regions composed of sets of elementary parcellation units or regions of interest (PUs) (Caviness et al., 1996) comprising RWR (FOC, CGa, PAC, INS, DLPFC) and ATTN (CGa, CGp, IPL, DLPFC) were then assessed for cortical thickness. Mean thickness across anatomically linked PUs was significantly thinner in COC subjects for right RWR subregions by multivariate GLM (Table 2). Pairwise contrasts were significant and showed a trend for the right DLPFC and right INS, respectively.

Clusters within right RWR showed significant effects by a multivariate general linear mixed model (Table 3). Pairwise contrasts were significant for the dorsolateral superior frontal gyrus (F1l; BA 9 and 8) and the middle frontal gyrus (F2; BA 46, 9 and 8) of the DLPFC, along with the anterior and posterior insular lobules (Table 3; Figure 1). Given the

conservative bias of hierarchical analyses to potentially miss true positives, PUs containing clusters that met the *a priori* size and significance thresholds, but were not necessarily *a priori* regions of interest, were also included in Table 3. After correcting for multiple comparisons, the right inferior precentral gyrus (PRG) contained a cluster that was significantly thinner, whereas the dorsolateral aspect of the left occipital lobe (OLs) and angular gyrus (AG) contained clusters that were significantly thicker in the COC subjects.

Given that education may be a proxy for drug abuse, but has not been definitively correlated with cortical thickness (Im et al., 2006), analyses were run both with and without covarying for years of education; both sets of analyses yielded similar results.

Analysis of Symmetry and Thickness Heterogeneity—As alterations in normative asymmetries in cortical thickness argue for a genetic etiology of behavior, differences in hemispheric symmetry between groups and distribution of cortical thickness were assessed for potential premorbid influences on addiction.

Significant asymmetry effects were observed in the RWR subregion of the DLFPC [2.8% rightward for controls (i.e., right thickness > left thickness), 0.8% leftward for addicts; $t(38) = 2.2$, $p = 0.03$]. There were no other significant symmetry alterations observed in average thickness of the systems (i.e., RWR or ATTN), sub-regions (or sets of elementary PUs), or clusters of vertices within the *a priori* elementary PUs. Additionally, qualitative comparison of standard deviation maps reveals greater thickness heterogeneity in CON relative to COC subjects (Figures 2a, b). Quantitative assessment by bivariate fit of thickness across vertices indicates greater cortical smoothness or less heterogeneity in the average PU thickness for COC subjects (Figures 2c, d).

Behavioral Effects

Relative preference measures were collected using a dual keypress procedure with beautiful and average faces (see Methods for details). In the attention task (CPT), subjects sought to identify cue-target pairs amidst a string of letters, presented visually one letter per second. Three experimental conditions were utilized where subjects identified cue-target pairs (hits and misses) amidst a string of letters: (i) vigilance/selective attention (qA condition), (ii) sustained attention (q3Ad condition), and (iii) effortful divided attention (q3Ai condition) (Seidman et al., 1998b, 2007; Goldstein et al., 2005; Thermenos et al., 2004).

In the relative preference task, COC subjects produced significantly lower keypress responses (i.e., reduced or restricted preference measures), normalized for subject motor capabilities, for all four categories of stimuli (Figure 3, Table 4). COC subjects also produced significantly lower hits and more misses for sustained attention and effortful divided attention (Table 4).

Correlational Analysis

To test whether structural differences in RWR and associated PU's were potentially related to drug consumption, or had behavioral implications in line with known alterations in attention for stimulant addicts, we examined associations between (a) cortical thickness and drug use, and (b) cortical thickness and behavior. When significant correlations were found with behavior, we further tested the differential contribution of the two systems (RWR and ATTN) by evaluating correlation against sets of PUs that were and were not overlapping between them. It has previously been reported that PUs within RWR but not ATTN (i.e., INS and FOC), demonstrate significant changes in BOLD signal with fMRI during effortful attention (Seidman et al., 1998b; Goldstein et al., 2005), potentially due to both increased allocation of attention resources and motivation/reward processes (Maunsell, 2004).

Measures of Substance Use—Measures of cocaine use were tested *a priori*, whereas measures of alcohol and nicotine use were assessed *post hoc*. Correlations were significant for right RWR ($r(18) = -0.54$, $p = 0.014$) and right CGa ($r(18) = -0.50$, $p = 0.026$) with years of cocaine use. Post hoc correlations with alcohol use did not meet hierarchical constraints for RWR or any sub-region. With a ceiling effect, significant correlations were observed for days of nicotine use and right DLPFC thickness ($r(18) = -0.52$, $p = 0.016$) and mean PU thickness for F1l ($r(18) = -0.63$, $p = -0.024$).

To sort out polysubstance abuse effects on the *a priori* cocaine correlations, we performed partial correlations for years of cocaine and right RWR plus right CGa, covarying for the effects of alcohol and nicotine use, and found significant partial correlation results (all $p < 0.05$; see Appendix 1 for specifics). No significant interaction ($p >> 0.05$) between days of nicotine use and years of cocaine use was observed, nor was a separate post-hoc correlation between age of drug use onset and thickness indices significant ($p >> 0$ .05).

Measures of Relative Preference—Significant correlations were observed between the normalized keypress response (see above), for a number of face conditions and the cortical thickness (a) of one sub-region, right DLPFC, and (b) of cluster thickness in right F2, and right F1l. Separately, significant observations were observed between a number of face conditions and right INS cluster thickness. See Table 5 for synopsis of results.

Measures of Effortful Attention—In a hierarchical analysis, significant correlations were only observed between error measures (i.e., misses) for the effortful divided attention condition (q3Ai), and cortical thickness measures in COC but not CON subjects**,** producing differences in slopes. Significant correlations were observed for right RWR cortical thickness (Figure 4a). Significant effects were then noted for regions not overlapping with ATTN (i.e., RWR_minus_ATTN) but not regions overlapping with ATTN (i.e., RWR_intersect_ATTN; Figures 4b, c). These effects were due to correlations between misses during effortful attention: and (1) orbitofrontal cortex (FOC) PU thickness and (2) posterior insula (pINS) cluster thickness (Figure 4d).

Discussion

Synopsis

COC relative to CON subjects showed reduced total cortical volume, and reduced thickness for the RWR system, including paralimbic cortices such as the INS, and neocortical regions such as the DLPFC. Significant correlation results suggest that some cortical thickness alterations in COC subjects may be partly related to drug use. In contrast, symmetry and variance differences in cortical topography in COC subjects may reflect a predisposition for addiction, a hypothesis that requires future testing.

The functional implications of these cortical topography differences include a set of altered relationships in COC subjects between cortical thickness and (i) relative preference indices plus (ii) effortful attention indices. Specifically, DLPFC thickness and F2, F1l, and anterior INS thickness significantly correlated with altered keypress responses to the four categories of facial stimuli, indicating abnormal cognitive control of preference during judgment and decision-making. The reduction in keypress response to all stimuli in COC subjects is analogous to the restriction in behavioral repertoire that is a defining feature of addiction. Cortical regions correlating with keypress responses did not overlap with regions correlating with performance at an effortful attention task. The effortful attention correlations were consistent with fMRI studies demonstrating activation of the same regions during tasks with high information processing demands (Seidman et al., 1998b, 2007).

Structural Abnormalities in Cocaine Addiction

Prior research comparing brain anatomy between COC and CON subjects has used voxel-based morphometry (VBM) and quantitative multi-spectral tissue characterization techniques, which produce gray matter "density" or "concentration" measures, or volume differences between two groups, respectively. These are *relative* measures, and not *absolute* volume or thickness measures, as reported herein with regard to large cortical volumetric effects (50+ cc volume decrease) and regional thickness changes in COC subjects. The topographical differences found in the cingulate cortex support the reports of "concentration" differences in this region by Franklin and colleagues (2002) and Matochik and colleagues (2003), and the report of insula differences by Franklin and colleagues (2002). In the current study, positive correlations with years of cocaine use were also focused on RWR, and the cingulate cortex. We did not find thickness differences in the FOC consistent with reports by VBM (Fein et al., 2002; Franklin et al., 2002; Matochik et al., 2003; Sim et al., 2007), although FOC cortical thickness did correlate with reduced effortful attention performance for the COC subjects in our study, consistent with Fein et al. (2002). Correlations reported herein, between performance in effortful attention and right RWR, FOC, and pINS thickness, are consistent with fMRI studies demonstrating FOC and pINS recruitment during effortful attention tasks with high information processing demands (Seidman et al., 1998b, 2007).

Current insights in the neurobiology of cocaine dependence emphasize the role of RWR and ATTN dysfunction in this disorder (Goldstein et al., 2007; Tomasi et al., 2007; Volkow and Fowler, 2000). A common thread across the two aforementioned neural networks is the right DLPFC, which was thinner in COC subjects in this study, and is known to project to and to receive connections from paralimbic cortices such as the CGa, FOC, and INS (Cohen et al., 2000; Kringelbach, 2005; Mesulam and Mufson 1985; Mesulam, 2000; Petrides and Pandya, 2002; Seo et al., 2007; Tanaka et al., 2004) and subcortical regions (Alheid and Heimer, 1988; Breiter et al., 1997, 2006; McClure et al., 2004) traditionally implicated with reward/aversion function. In current models of judgment and decision-making that consider issues of homeostasis (e.g., Breiter et al., 2006; Paulus, 2007; Verdejo-Garcia et al., 2006), the DLPFC plays an important role in choice and choice implications over time through the biasing of somatic states that endorse some behavioral options and reject others (Verdejo-Garcia et al., 2006). Interconnections between the DLPFC and INS further constitute an important frontal-limbic interaction needed for normative functioning of the reward system (Mayberg, 2002; Mesulam, 2000). Our data are consistent with these models in that observed reductions in choice behavior with a keypress procedure for COC subjects (Figure 3) correlated, across all categories of experimental stimuli, with their reductions in DLPFC thickness, DLPFC sub-unit (i.e., F2 and F1l) thickness, and INS thickness. These statistically significant associations suggest that one factor contributing to the diminished behavioral repertoire observed with drug dependence may be attributed to a regional reduction of cortical thickness.

Functional Implications of Structural Abnormalities

The regions in COC subjects associated with altered attention function, or years of cocaine use, are paralimbic regions reciprocally connected to the DLPFC, such as the INS, FOC, and CGa (see Figure 5a-c), which have been implicated in reward processing by other studies. The DLPFC itself has topographically proximate regions associated with ATTN functions (posterior section, BA 8 and rostral 6), and with reward regulation for planning and execution of behavior (anterior section, BA 46, 9), underscoring the likelihood of their functional affiliation (Maunsell, 2004). The frontolimbic interactions mediated by the DLPFC-aINSlbl/FOC system appear to be crucial for modulating emotional and motivational significance of incoming stimuli, thus influencing cognitive processing and

decision-making on the basis of real-time emotional and motivational states (Mesulam and Mufson, 1985; Pandya and Yeterian, 1985; Petrides and Pandya, 2002). The CGa is an important regulator of other cortical and subcortical brain regions as well, and appears to be a key structure for the integration of cognitive and emotional aspects of behavior with drives (Paus, 2001), along with monitoring of conflict and modulation of cognitive control, and modulation of attention allocation in real time (Carter et al., 2000; Cohen et al., 2000; Fan et al., 2005). A failure in the interaction between DLPFC-aINSlbl/FOC and DLPFC-PAC/CGa may account for altered behaviors in cocaine dependence such as antisocial and violent behavior as well as progressive loss of judgment concerning “safe” drug use habits (Bechara, 2005). In the somatic marker model, the FOC, INS, and CGa are fundamental components of distributed systems that trigger emotional (somatic) states from secondary inducers (i.e., thoughts about an action), and provide a substrate for feeling emotional states and biasing decisions (Verdejo-Garcia et al., 2006).

Etiologic Hypotheses

This study found correlations between cocaine years of use and (i) RWR cortical thickness, plus (ii) CGa PU thickness, but no correlation with age of cocaine use onset and these thickness measures. This correlation suggests a primary or secondary effect of drug use, but not an increased susceptibility due to earlier onset of drug use. A separate correlation between days of nicotine use and DLPFC plus PU (F1l) thickness was also observed, although this post-hoc finding exhibited a ceiling effect, and did not alter partial correlation results for cocaine with the RWR and CGa. Cocaine partial correlations were also not affected by alcohol use. None of these drug use parameters correlated with each other, pointing to the importance of follow-up longitudinal or family studies to confirm or clarify these findings.

The current study provides evidence that cocaine and polysubstance use has a detrimental effect on brain volume and topography, but not a uniform global effect as might otherwise be expected from Ca2+ toxicity (Du et al., 2006) or from transient cerebral ischemia, stroke, and hemorrhage (Glauser and Queen, 2007). It also provides evidence connecting these structural alterations with a functional effect of cocaine/polysubstance use in the form of worsened attentional function and reduced judgment and decision-making regarding relative preference. Further work is warranted to assess (a) anatomical specificity, and (b) susceptibility across the larger cocaine and polysubstance using population to different patterns of psychostimulant-related alterations to the cortical mantle.

A second etiology is supported by the observation of differences in the symmetry of DLPFC thickness between COC and CON subjects. Alterations to normative asymmetries generally have a genetic basis (e.g., Piedra et al., 1998; Hyatt and Yost, 1998; Supp et al., 1997; see Methods Appendix, Symmetry Analysis), as in many forms of situs inversus (Supp et al., 1997). In human and animal studies, cerebral asymmetry has been significantly correlated with handedness, which in turn has a strong genetic basis (Geschwind et al., 2002; Roubertoux et al., 2003). COC subjects also have a consistent decrease in the standard deviation of cortical thickness across the cortex, and less heterogeneity than controls, which does not correlate with years of drug use. A similar relationship between increased heterogeneity/variability and health has been noted for heart rate variability (HRV) studies (e.g., Krstacic et al., 2007), where medical issues ranging from sepsis to hyperthyroidism to traumatic brain injury to sleep disordered breathing can reduce HRV indices (Tateishi et al., 2007; Chen et al., 2007; Riordan et al., 2007). Despite reduced heterogeneity in cortical thickness, our COC subjects reported a broad range of cocaine use/exposure, with an average use duration of 12 years + 9.8 years (Table 6). In contrast to our data, subjects with a broad range of illness duration, such as with Alzheimer’s disease, will demonstrate an increase in structural variance measures (Burton et al., 2006). Variable lesion sizes with

stroke will also lead to an increase in brain structural variance measures (Caviness et al., 2002). Our findings of changes in thickness asymmetry in DLPFC and reduced heterogeneity in thickness measures despite a large temporal range in drug exposure, argue for a predisposing (i.e., genetic) component to the differences in cortical topography observed between addicts and controls.

Limitations

Given the inherent limitations of any technique of brain segmentation that is used for extracting thickness measures, we included a comparison of an automated and a semi-automated segmentation method as part of this study to underscore the rigor of the methods underlying our results (Appendix 1, Figures A1-A28). The fully automated method (i.e., FreeSurfer) was less time consuming, lower cost, but less accurate for our *a priori* regions than a semi-automated method (i.e., Cardviews). Purely automated approaches are occasionally prone to systematic errors that may obscure subtle neuroanatomic effects; this issue has become an important topic of recent discussion (e.g., Wiegand et al., 2004; Devlin and Poldrack, 2007).

Limitations for group analysis are due in part to registration errors inherent to intersubject mapping and the transformation procedure, as well as the potentially ill-posed nature of intersubject correspondence in topography. Another potential limitation is sample size. Whereas 40 subjects is not a particularly large sample population, the case-control matching used in this study is expected to reduce spurious sources of between group variance. Lastly, the degree of comorbid use (nicotine 90%, alcohol 80%) in COC subjects was consistent with other reports (Simpson et al., 1999; Tang et al., 2007); nevertheless, it raises questions as to their role in the brain differences observed herein.

Conclusion

This study found salient cortical volumetric reduction and cortical thickness decreases in COC subjects for cortical regions regulating reward/aversion function, and regions involved with effortful attention. The correlation of cocaine and nicotine use measures with alterations in regional thickness supports an etiological hypothesis centered on drug effects, whereas the reversal of symmetry findings in DLPFC and the diminished cortical thickness heterogeneity found in COC subjects suggests an alternate predisposition hypothesis. These hypotheses can be directly tested by a combination of animal experiments and family/twin studies (e.g., with nicotine addiction). Relative preference behavior was also uniformly reduced in addicts, and correlated with thinner cortices for regions involved with the organization of behavior; this association may partly underlie the restriction in behavioral repertoire or range in behavioral preferences observed with drug dependence. Keypress and attention findings from this study, and their relation with cortical topography, can be directly tested in animal models of chronic drug self-administration.

Since cortical thickness is the most invariant brain size parameter across the model of mammalian evolution (Prothero and Sundsten, 1984; Mountcastle, 1998), some of the findings reported herein may have causal relevance. A fundamental component of addiction may involve neuroadaptations and/or developmental predispositions involving brain regions necessary for cognitive control of somatic states (Verdejo-Garcia et al., 2006), and judgment and decision-making regarding complex rewards and attention toward goal-objects. Addiction thus may represent a complex syndromic phenotype (Aylsworth, 1998), with multiple effects necessary for compulsive drug use.

Methods

Subjects

Subjects were participants in the Phenotype Genotype Project (PGP) in Addiction and Mood Disorders, recruited by direct advertisement and clinical referrals. They signed consent following the approval of the Massachusetts General Hospital Institutional Review Board. Cohorts were matched, after excluding subjects with residual motion artifacts from motion correction of structural MRI data, on a one-by-one basis across groups with respect to age, handedness, gender, race and educational history. See Appendices for details.

In each group of 20 matched cocaine dependent (COC) and healthy control (CON) subjects, 11 subjects were women (all scanned during their mid-follicular menstrual phase per hormonal testing), 16 subjects were right-handed (Oldfield, 1971), and 13 subjects were Caucasians, 5 subjects were African Americans, and 1 subject was Asian (Benson & Marano, 1998). Compared with CON subjects, COC subjects were not significantly different on age, sex distribution, handedness or race (Table 6, appendices), and within group there were no gender-based age or education differences. However, COC subjects had on average 1.9 fewer years of education ($t(38) = 3.5$, $p = 0.001$), and thus analyses were run both with and without co-varying for years of education, producing the same findings.

Behavioral Measures of Relative Preference and Effortful Attention

Relative Preference The task quantified units of keypress that subjects traded for viewing time of a set of normalized face pictures, comprising model and non-model faces of both genders. This task defined a subject's relative preferences for these stimuli ((Aharon et al., 2001; i.e., their utility for the set of faces (Breiter et al., 2006)), as has been done with angry and other facial expressions (Strauss et al., 2005). Keypress procedures were implemented using MatLab software on a PC computer.

The dependent measures of interest, were the amount of work in units of key press that subjects exerted to (a) approach (positive keypress), (b) avoid (negative keypress), (c) approach and avoid if they overshot or undershot a target view time, or (d) do nothing about to the different categories of stimuli. The key press procedure quantified (i) decision-making regarding the valence of preference and (ii) judgment regarding the amount of value that each picture had relative to the default position of 6 seconds of viewing time (see Appendix I). Keypress behavior was normalized for potential differences in motor coordination or resiliency across groups, using a measure of maximum keypress capacity/speed.

Attention—Three measures of attention were collected during a separate functional MRI sequence, during which subjects performed a continuous performance task (CPT) using visual rather than auditory stimuli (Seidman et al., 1998b, 2007; Goldstein et al., 2005; Thermenos et al., 2004). In the baseline vigilance or selective attention task, subjects were required to respond to "A" immediately following a "Q" (qA). In the lowest-load working memory condition (a sustained attention condition, "q3Ad"), subjects were required to respond to an "A" following a "Q" after three intervening letters (e.g. QxyzA), with no nested sequences. A third task added interference and divided attention load by nesting a subset of QxyzA sequences within each other (e.g., QxQyAzA). Stimuli were presented in blocks, with the three block conditions completely counterbalanced forward and backward one block. Subjects responded to targets with a button press and did not respond to non-targets. Correct responses ("hits") and misses (i.e., errors of commission) at target detection were used in statistical analyses.

Magnetic Resonance Imaging

Whole brain MR images were collected on a Siemens Avanto 1.5 T scanner at the MGH Martinos Center (Charlestown, MA). Three sagittal 3D Magnetization Prepared Rapid Gradient Echo (MP-RAGE) T1-weighted sequences were collected: TR = 2730 ms, TE = 3.31 ms, T1 = 1,000 ms, flip angle = 7°, bandwidth = 195 Hz/pixel, FOV = 256 × 256 mm2, sampling matrix = 256 × 192 pixels, 128 contiguous 1.33 mm slices, averages = 3.

Image Preprocessing and MRI-based Segmentation

Images were re-sampled into a standard coordinate system (Filipek et al., 1994; Makris et al., 2004). A new set of coronal images, not rescaled, were reconstructed at the slice thickness of the original acquisition.

Segmentation was performed with double blinding to group category and study hypotheses for all individuals performing data analysis at the MGH Center for Morphometric Analysis (CMA). Neuroanatomic segmentation was performed on coronal images (Figure 6A) using a semi-automated morphometric technique (Caviness et al., 1996; Filipek et al., 1994; Makris et al., 2004; Makris et al., 2006b; Worth et al., 1997). The cerebrum was segmented into its principal gray matter and white matter structures and total cerebral white matter. Specifically, the cortical ribbon was defined by two outlines, one external outline between the subarachnoid CSF and the cerebral cortex, and the other between the cerebral cortex and the underlying cerebral white matter (Makris et al., 2006b; Worth et al., 1997) as illustrated in Figure 6B. The total number of voxels in each brain region determined its volume.

In contrast to semi-automated and manual routines, one source of error in fully automated cortical thickness measurements (e.g., Fischl and Dale 2000), stems from the placement of the cerebral exterior within the layers of the cortical mantle as opposed to the level of the meningeal pia (Figure 7b; Figures A1- A26, Appendix 2). Another source of error results from the placement of the gray-white border within the cortical layers as opposed to the floor of the sixth layer. Thus using fully automated techniques for cortical segmentation results in an inconsistent estimation of the cortical ribbon (Figures A1- A26, Appendix 2), producing statistically significant differences in derived properties such as thickness (Figures A27-A28, Appendix 2), and undershooting validated estimates of volume (Filipek et al., 1994; Caviness et al., 1996; Seidman et al., 1999; Goldstein et al., 1999; Seidman et al., 2002). The semi-automated approach implemented in the TCP method (see next section) approximates the pial level and the floor of the sixth cortical layer (Figure 7a), which is only partially accomplished by the fully automated segmentation. Thus the implementation of semi-automated or manual routines is currently necessary to represent an anatomically appropriate cortical ribbon, which is a relevant prerequisite for the determination of locations of cortical thinning and the connectional networks in which affected regions belong (Wiegand et al., 2004; Devlin & Poldrack, 2007; Amunts et al., 2007; Passingham, 2007).

The Topological Cortical Parcellation (TCP) System

The TCP system computes measurements of cortical surface topography such as cortical thickness (Makris et al., 2006b, 2007). The overall approach is to segment and/or parcellate the cerebral cortex using Cardviews and then use FreeSurfer to compute cortical thickness differences (Makris et al., 2006b, 2007). The derived measurements can be regionally specific and integrated with systems of cortical parcellation that subdivide the neocortex into gyral-based parcellation units (PUs) (Rademacher et al., 1992; Caviness et al., 1996). See Figure 6 for details.

Data Analyses

The primary analyses tested *a priori* hypotheses derived from published data on the network subserving executive control and regulation of reward functions (RWR) (Alheid and Heimer, 1988; Breiter et al., 1997, 2006; Breiter and Rosen, 1999; Bush et al., 2002; Cohen et al., 2000; Gemba et al., 1997; Kringelbach, 2005; McClure et al., 2004; Mesulam and Mufson, 1985; Rolls et al., 2007; Schoenbaum et al., 1998; Seo et al., 2007; Tanaka et al., 2004; see Results and Methods Appendices for full set of references) and attention (ATTN) (Fan et al., 2005; Heilman and Van Den Abell, 1980; Makris et al., 2007; Mesulam, 2000; Posner and Peterson, 1990; Seidman et al., 1998b, 2007; Thermenos et al., 2004; see Results and Methods Appendices for full set of references) in humans. We implemented a hierarchical set of analyses to probe the thickness effects in the RWR and ATTN systems across three levels of organization. We first evaluated mean thickness in all regions of the two systems, and tested hemispheric contributions if relevant. These systems were further broken down to gyral-based sub-regions comprised of sets of elementary parcellation units (PUs). Lastly, we evaluated clusters of surface vertices at the systems level and within each PU.

For *a priori analyses* of the targeted systems and sub-regions, we focused on group differences within thirty-one [thirteen homotypic regions in the two hemispheres and five additional regions in the right hemisphere (AG, SGa, SGp PO, and CGp)] fine-grained regions of interest (ROIs) or parcellation units (PUs). Sub-region subdivisions or PUs are illustrated in Figure 5. The following PUs were considered for *a priori* analyses in sub-regions of the right and left hemispheres: orbitofrontal cortex (FOC; i.e., anterior (aFOC), posterior (pFOC), medial (mFOC) and lateral FOC (lFOC)); anterior cingulate cortex (CGa; i.e., subgenual CGa, pregenual CGa, and amCGa (anterior-middle CGa)); paracingulate gyrus (PAC; i.e., pregenual PAC and dorsal PAC); insula (INS; i.e., anterior (aINSlbl) and posterior insular lobules (pINSlbl)); and dorsolateral prefrontal cortex (DLPFC; i.e., lateral superior frontal gyrus (F1l) and middle frontal gyrus (F2)) (Caviness et al., 1996, Makris et al., 2006a). The AG (angular gyrus), two subdivisions of the supramarginal gyrus (SG), i.e., SGa (anterior SG) and SGp (posterior SG), the parietal operculum (PO), and posterior cingulate gyrus (CGp) were considered only in the right hemisphere. We considered the inferior parietal lobule (IPL) to comprise AG, SGa, SGp and PO PUs.

Systems—At a systems level, the RWR system included the following sub-regions: FOC (BA 11, 12, 13, 14, 25, 47), CGa (BA 24), PAC (BA 32), INS, and DLPFC (F1l; BA 9 and 8; and F2; BA 46, 9 and 8) bilaterally. The ATTN system included these sub-regions: CGa (BA 24), CGp (BA 23, 26, 29, 30, 31), IPL [AG (BA 39), SG (BA 40), PO (BA 40)], and the DLPFC in the right hemisphere (Heilman and Van Den Abell, 1980).

Gyral-based sub-regions comprised of sets of elementary PUs—At the level of the individual gyrus, we investigated each of the PUs within sub-regions of the RWR (FOC, CGa, PAC, INS, DLPFC) and ATTN systems (CGa, CGp, IPL, DLPFC).

Clusters of thickness differences—Within the REO and attention systems, clusters were identified if they comprised at least 58 contiguous vertices, with each vertex showing group differences at $p < 0.05$. If clusters were in PUs outside of *a priori* regions of interest, they were evaluated as *exploratory analyses*. A cluster of 58 vertices corresponded to a surface area of $31.77mm^2$ and a volume of $135mm^3$, corresponding to cluster sizes used in fMRI analyses (Aharon et al., 2001, Breiter et al., 1997).

Symmetry Analysis—Cortical symmetry was computed using a standard formula (Makris et al., 2004) (see Appendix 2).

Statistical Analysis of Cortical Thickness/Volume and Correlations—At each level of the hierarchy (systems, sub-regions or sets of PUs, and clusters), tests on the average thickness in *a priori* regions of interest were performed with a multivariate general linear mixed model (GLM) for correlated data (Makris et al., 2006a, 2007). The multivariate GLM included the average thickness of the entire neocortex as a covariate. If the multivariate GLM showed a general effect, post-hoc pairwise comparisons were then performed for the measures used in the GLM. Post-hoc pairwise comparisons were evaluated against a correction for the number of post-hoc comparisons performed at each level of analysis. Exploratory analyses of clusters within PUs outside *a priori* systems were corrected for the total number of clusters where at least 58 vertices were observed.

Systems (i.e., RWR) or subregions showing significant group effects were examined with Pearson and Spearman correlations to explore relationships with drug-seeking behavior. We used both parametric and nonparametric correlations to increase our confidence that any findings were not just an effect of non-normal distributions; in results, only Spearman results are reported. If a system (i.e., RWR) or sub-region (DLPFC) demonstrated a significant correlation corrected for the number of comparisons performed regarding cocaine use ($p < 0.05/3 = 0.017$), we then examined if this effect were present for a PU within a sub-region or cluster of vertices with $p < 0.05$. To be reported, a correlation with a drug use measure had to be present for RWR (or sub-region) and a constituent PU/cluster. Correlations were also assessed against alcohol and nicotine use on a *post hoc* basis. If significant correlations were observed for multiple drugs of abuse besides cocaine, we further performed partial correlations to explore relative contributions of these substances.

Similar procedures, with modification, were implemented for assessing correlations between regions showing significant group effects and behavioral measures (see Appendices).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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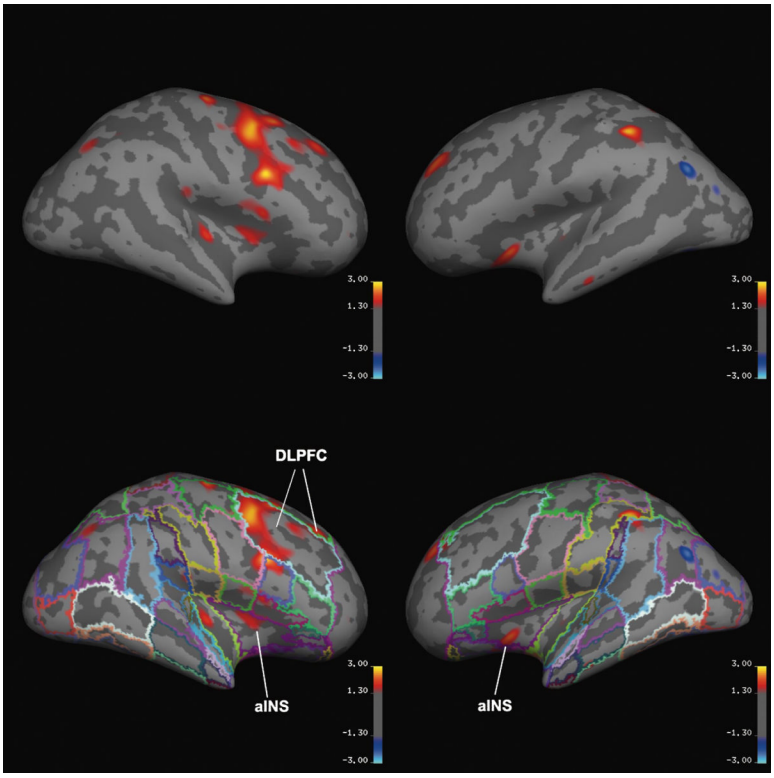

Figure 1.
Inflated cerebral mantle with (below) and without (above) superimposed parcellation from the MNI 305 average brain. Pseudo-color statistical map overlays (red, $p < .05$ and yellow, $p < .001$) illustrate where the cortex of the COC subjects is thinner than in CON subjects. DLPFC, dorsolateral prefrontal cortex; aINS, anterior insula.

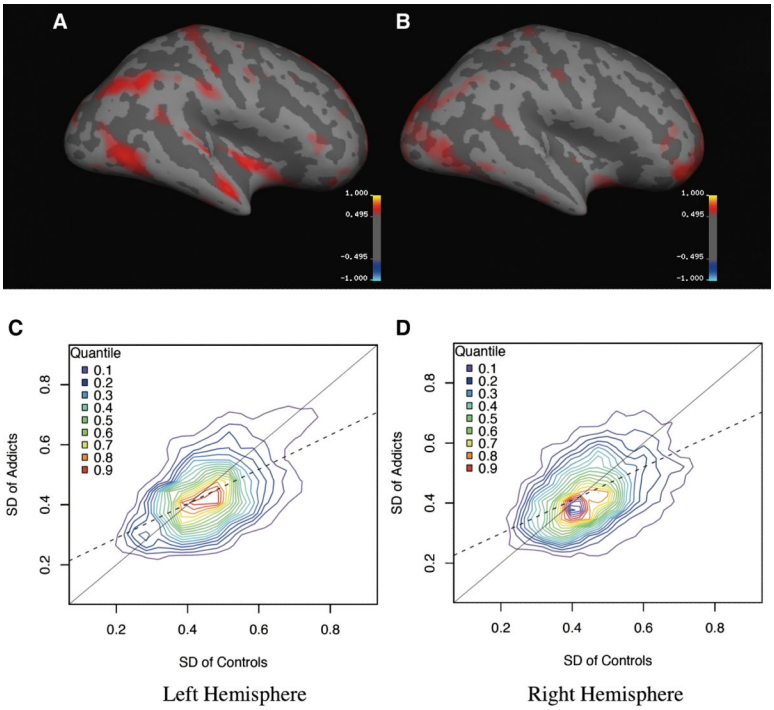

Figure 2.

Standard deviation maps across the inflated cortex (Fig 2a, b) showing greater thickness heterogeneity in CON versus COC subjects. Quantitative assessment of the cortical thickness heterogeneity, using a bivariate fit of thickness across vertices (Fig 2c, d), shows the quantile density contours are centered on the CON section of the plot for both hemispheres.

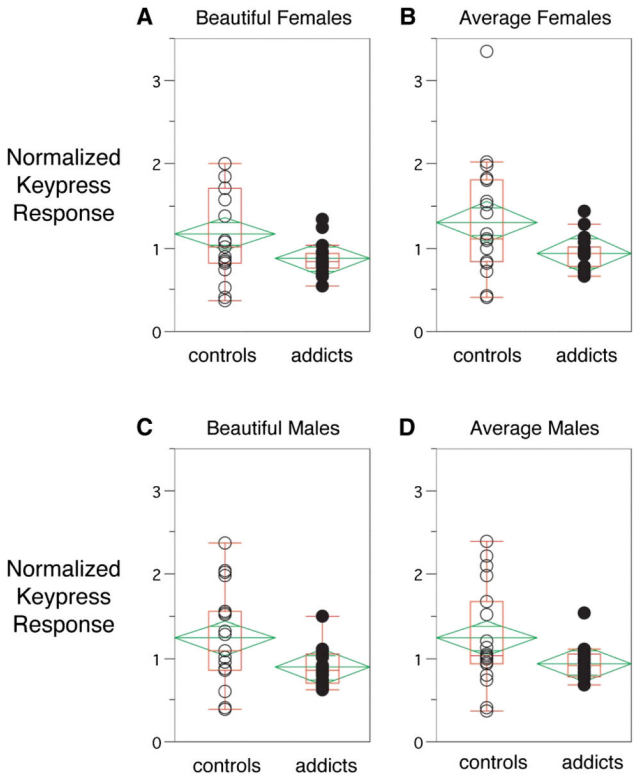

Figure 3.
Box-plots of normalized keypress responses in COC and CON subjects to the BF faces (3A), AF faces (3B), BM faces (3C), and AM faces (3D). The dispersion measure is presented as a diamond, and the horizontal line through the data represents the whole-group mean.

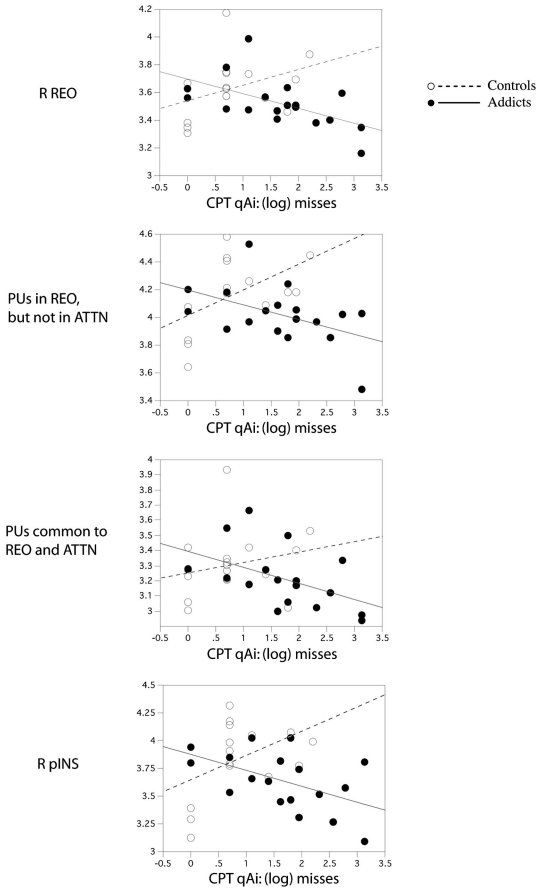

Figure 4.

Correlation plots [CON (dashed lines) and COC (solid lines) subjects] between misses for the effortful divided attention condition (q3Ai task) and average cortical thickness in (i) right RWR, (ii) sets of PUs in RWR but not ATTN, (iii) sets of PUs in RWR and ATTN, and (iv) right posterior INS.

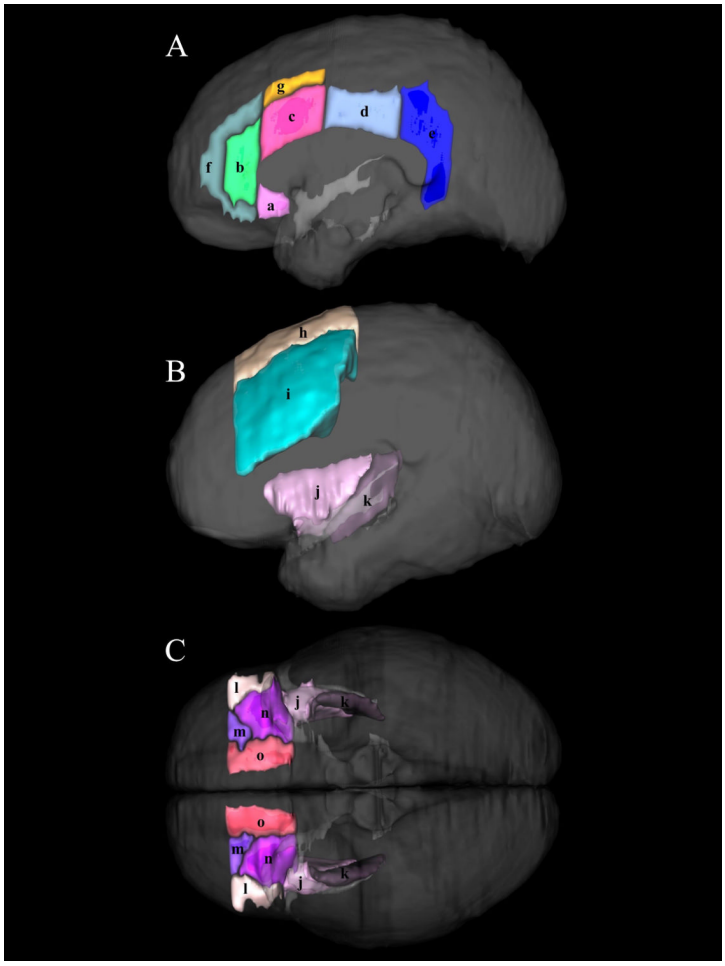

Figure 5.

Anatomical PUs in cingulate gyrus (CG; a-e), paracingulate gyrus (PAC; f, g), dorsolateral prefrontal cortex (DLPFC; h, i), insula (INS; j, k), and orbitofrontal cortex (FOC; l-o). (a) subgenual CGa, (b) pregenual CGa, (c) anterior-middle CGa, (d) posterior-middle CGa, (e) posterior cingulate gyrus, (f) pregenual PAC, (g) dorsal PAC, (h) lateral superior frontal gyrus, (i) middle frontal gyrus, (j) anterior insular lobule, (k) posterior insular lobule. (l) lateral FOC, (m) anterior FOC, (n) posterior FOC, (o) medial FOC. (a - c, f - o) were included in RWR.

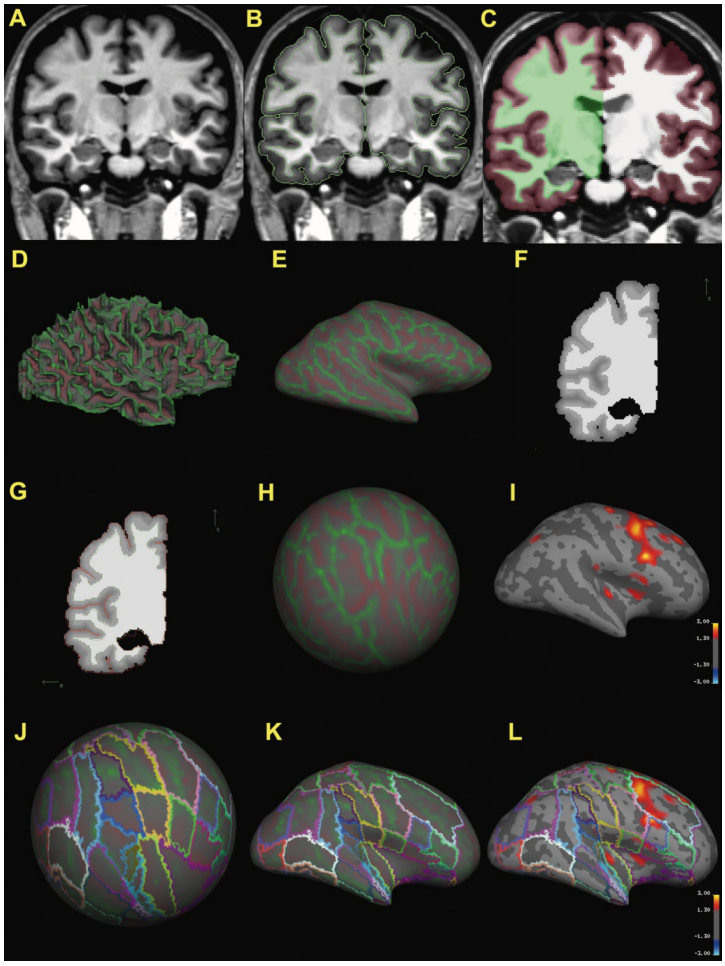

Figure 6.

Topological cortical parcellation (TCP) system. 6A shows an intensity normalized T1-weighted MR coronal image. Segmentation (6B) is executed in *Cardviews* by a semi-automated procedure. Outline files created by *Cardviews* segmentation and parcellation are converted to a *FreeSurfer* volume segmentation (6C). The surface is tessellated, smoothed (6D) and inflated (6E) from the converted *FreeSurfer* volume. An intensity gradient is created throughout the cortex as a function of the distance from the white matter surface (6F). The exterior surface is generated to be consistent with the manual segmentation (6G). The white matter surface of each subject is transferred to spherical coordinates and registered to the average MNI 305 brain (6H). Inter-subject averaging and mapping of cortical thickness differences between groups of subjects; pseudo-color statistical maps where red represents $p < .05$ and yellow $p < .001$ (6I). The registration subject, (MNI 305) (Caviness et al., 1996; Evans et al., 1993; Makris et al., 2007), was segmented, parcellated and overlaid on the spherical surface (6J) and inflated surface (6K). Cortical thickness statistical results are overlain with the parcellation scheme to localize results (6L).

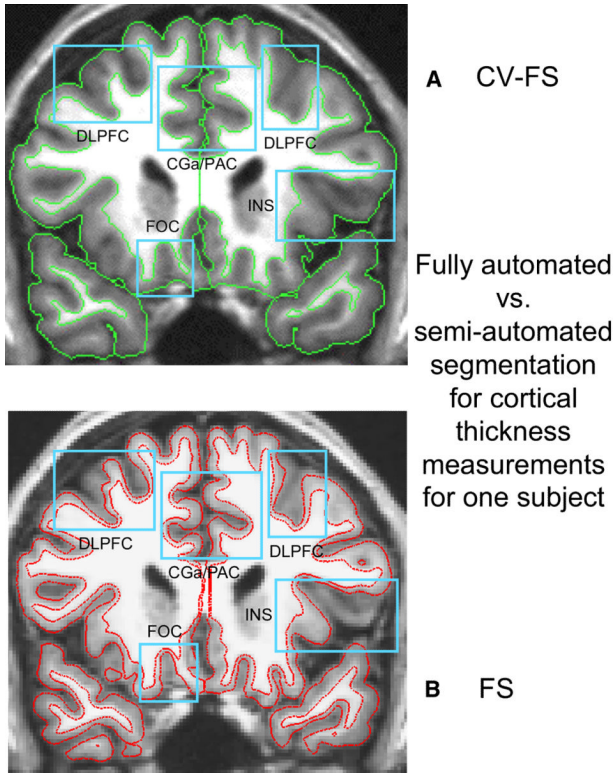

Figure 7.

Segmentations from the FreeSurfer automated system (b) and the semi-automated Cardviews (TCP) system (a). Slices are from the same individual in their native anatomic space. Brain exterior and gray matter – white matter boundaries are shown in green for Cardviews, and in red for the FreeSurfer. Blue boxes are placed where errors are apparent for *a priori anatomic* regions (e.g., FOC, CGa/PAC, INS, DLPFC). Specifically, where (a) the white matter-gray matter boundary and/or (b) the cortical exterior is observed to extend into the cortical ribbon and exclude a block of tissue from the cortical ribbon. CGa/PAC – anterior cingulate gyrus/paracingulate cortex; DLPFC, dorsolateral prefrontal cortex; FOC, orbitofrontal cortex; INS, insula.

Table 1

Average cortical thickness at the systems level (i.e., RWR, and ATTN), followed by an analysis at the hemispheric level for significant effects seen at the systems level. All regions are weighted by the number of vertices in each PU. General linear mixed model covarying for average cortical thickness (of the entire neocortex) for the total RWR and right ATTN systems: $F(2, 40) = 4.9$, $p = 0.013$. General linear mixed model covarying for average cortical thickness for the Right RWR and Left RWR $F(2, 40) = 4.0$, $p = 0.026$. Pairwise post-hoc statistics are listed in the table, where * = significance at alpha (0.05) corrected for 2 comparisons = 0.025. Abbreviations: RWR: reward regulation system.

		Means		Std Devs.			
Region	**# vertices in the network**	**Controls**	**Addicts**	**Controls**	**Addicts**	**T value**	**P-value**
T RWR	26999	3.71	3.59	0.23	0.19	2.8	0.009 *
R RWR	13622	3.69	3.55	0.23	0.19	2.8	0.008 *
L RWR	13377	3.73	3.64	0.25	0.21	0.6	0.60
R Attention	13927	3.36	3.25	0.23	0.18	1.5	0.15

Table 2

Analysis of the average cortical thickness at the sub-region level in parcellation units (PUs) of the RWR network. The general linear mixed model for RWR sub-regions, covarying for average cortical thickness of the entire neocortex, shows $F(5, 40) = 4.9$, $p < 0.001$.

		Means		Std Devs.			
Region	**# vertices in the PU**	**Controls**	**Addicts**	**Controls**	**Addicts**	**T-value**	**P-value**
Right DLPFC	5551	3.65	3.41	0.31	0.21	3.0	0.005 *
Right CGa	2478	2.69	2.80	0.50	0.79	−0.9	0.4
Right FOC	1702	4.22	4.08	0.28	0.28	1.2	0.2
Right INS	2553	4.14	3.96	0.28	0.21	2.5	0.017
Right PAC	1338	4.21	4.08	0.34	0.30	0.8	0.4

* indicates a significant difference at alpha (0.05) corrected for 5 comparisons = 0.01. Abbreviations: DLPFC: dorsolateral prefrontal cortex; CGa: anterior cingulate gyrus; FOC: orbitofrontal cortex; INS: insula; PAC: paracingulate gyrus.

Table 3

Mean cortical thickness for clusters within individual parcellation units (PUs). Test statistics show the group effect after controlling for average thickness of the entire neocortex. The RWR network is comprised of five regions (DLPFC, CGa, FOC, INS, PAC), sub-divided by the parcellation schema. There are 26 distinct parcellation units for post-hoc analyses outside of RWR. The overall multivariate general linear mixed model for RWR units, covarying for average cortical thickness, shows $F(5, 40) = 6.3$, $p < 0.001$.

				Means		Std Devs.		Cluster statistic	
Region	**# vertices in the cluster**	**# vertices in the PU**	**%PU**	**Controls**	**Addicts**	**Controls**	**Addicts**	**T value**	**P-value**
Right RWR									
F1l	754	2189	34.4	3.75	3.43	0.38	0.26	3.1	0.004 *
F2	1810	3362	53.8	3.42	3.12	0.28	0.21	4.0	<0.001 *
subgenual_CGa_BA24_32	0	334	.	.	.	.	.	.	.
pregenual_CGa_BA24	0	882	.	.	.	.	.	.	.
amCGa_BA24	0	1262	.	.	.	.	.	.	.
aFOC	0	268	.	.	.	.	.	.	.
pFOC	15	646	2.3	4.64	4.32	0.52	0.42	.	.
mFOC	4	494	0.8	4.59	4.27	0.52	0.42	.	.
lFOC	0	294	.	.	.	.	.	.	.
aINS	245	1365	17.9	4.31	4.04	0.34	0.26	2.7	0.009 *
pINS	264	1188	22.2	3.57	3.24	0.46	0.30	2.8	0.008 *
PAC_BA32_dorsal	0	358	.	.	.	.	.	.	.
pregenual_PAC_BA32	249	980	25.4	4.52	4.14	0.48	0.44	2.5	0.02
Other Right Hemisphere Regions									
AG	133	1562	8.5	3.70	3.36	0.51	0.33	2.35	0.0244
COa	124	585	21.2	3.79	3.56	0.32	0.27	2.33	0.0253
F1m	94	993	9.5	4.46	4.16	0.45	0.36	2.17	0.0366
F3o	203	629	32.3	3.47	3.22	0.24	0.24	3.27	0.0023
FMC	112	431	26.0	4.58	4.18	0.52	0.50	2.29	0.0277
FO	184	699	26.3	3.91	3.70	0.25	0.24	2.49	0.0172
FP	113	4281	2.6	4.34	4.01	0.43	0.40	2.32	0.0262
LG	142	1677	8.5	2.59	2.85	0.27	0.32	−2.81	0.0078
PO	64	513	12.5	3.34	3.10	0.34	0.30	2.06	0.0469
PRG_inf	278	1854	15.0	3.33	3.07	0.25	0.22	3.45	0.0014 **
PRG_mid	284	1425	19.9	2.85	2.56	0.37	0.23	2.79	0.0083
Other Left Hemiphere Regions									
AG	137	1264	10.8	3.66	3.97	0.39	0.27	−3.34	0.0019 **
aINS	180	1366	13.2	4.87	4.48	0.39	0.42	2.82	0.0076
BFsbcmp	157	944	16.6	1.59	2.19	0.48	0.72	−3.18	0.0030
F1l	119	2118	5.6	4.11	3.86	0.32	0.20	3.15	0.0032
F1m	101	1132	8.9	4.25	4.02	0.31	0.23	2.67	0.0111
F2	92	3652	2.5	3.94	3.66	0.42	0.28	2.32	0.0260

				Means		Std Devs.		Cluster statistic	
Region	**# vertices in the cluster**	**# vertices in the PU**	**%PU**	**Controls**	**Addicts**	**Controls**	**Addicts**	**T value**	**P-value**
FP	206	4829	4.3	4.03	3.71	0.45	0.26	2.98	0.0050
OLs	62	1773	3.5	3.80	4.08	0.37	0.35	−3.43	0.0015 **
PCN	78	2233	3.5	3.27	3.54	0.37	0.34	−2.86	0.0070
pFOC	62	506	12.3	4.68	4.31	0.37	0.57	2.21	0.0337
POG_inf	156	2139	7.3	3.45	3.23	0.21	0.25	2.92	0.0059
POG_med	149	874	17.0	3.82	3.45	0.47	0.43	2.47	0.0183
SGp	100	2074	4.8	3.75	3.47	0.42	0.29	2.22	0.0323
SPL	65	1436	4.5	3.63	3.31	0.51	0.39	2.10	0.0429
TOF	75	926	8.1	3.30	3.57	0.25	0.46	−2.76	0.0089

* indicates a significant difference at alpha (0.05) corrected for 5 comparisons = 0.01, and

** indicates a significant difference at alpha (0.05) corrected for 26 comparisons = 0.0019. Abbreviations: RWR: reward regulation system; BA: Brodmann's area; F1l: superior fronal gyrus lateral division; F2: middle frontal gyrus; CGa: anterior cingulate gyrus; amCGa: anterior cingulate gyrus, anterior middle division; aFOC, pFOC, mFOC, lFOC: anterior, posterior, medial, lateral fronto-orbital cortex; aINS: anterior insula; pINS: posterior insula; PAC: paracingulate gyrus; AG: angular gyrus; COa: anterior central opercular cortex; F1m: medial superior frontal gyrus; F3o: inferior frontal gyrus, pars opercularis; FMC: frontal medial cortex; FO: frontal operculum cortex; FP: frontal pole; LG: lingual gyrus; PO: parietal operculum cortex; PRG_inf: precentral gyrus inferior division; PRG_mid: precentral gyrus middle division; BFsbcmp: basal forebrain subcomponent; OLs: superior lateral occipital cortex; PCN: precuneus cortex; POG_inf: postcentral gyrus, inferior division; POG_med: postcentral gyrus, medial division; SGp: posterior supramarginal gyrus; SPL: superior parietal lobule; TOF: temporal occipital fusiform cortex.

Table 4

Top: normalized keypress responses in COC and CON subjects to the BF, AF, BM, and AM faces. Bottom: the three task components of the CPT are signified by qA (vigilance condition), a3Ad (a sustained attention condition), and q3Ai (an effortful and divided attention condition). Correct hits are listed as a ratio of hits to possible targets, and thus will range from 0 to 1. Misses are presented as an absolute number. Degrees of freedom are 35 for the normalized keypress response and 34 for performance on the CPT task.

	Means		Std Devs.			Statistic
Test	**Controls**	**Addicts**	**Controls**	**Addicts**	**T-value**	**P-value**
Normalized keypress response						
beautiful females	1.17	0.87	0.54	0.19	2.2	0.03
average females	1.31	0.94	0.69	0.20	2.2	0.04
beautiful males	1.24	0.89	0.57	0.23	2.4	0.02
average males	1.24	0.94	0.58	0.20	2.1	0.048
Performance on CPT task						
hits: qA	0.91	0.90	0.18	0.13	0.2	0.9
hits: q3Ad	0.89	0.72	0.12	0.24	2.6	0.01
hits: q3Ai	0.77	0.61	0.18	0.20	2.4	0.02
misses: qA	2.53	4.26	4.68	5.60	−1.0	0.3
misses: q3Ad	2.06	5.26	2.56	5.96	−2.1	0.048
misses: q3Ai	2.76	7.21	2.41	6.91	−2.5	0.02

Table 5a

Correlations between the relative preference measures (normalized keypress response) for all face conditions and the cortical thickness (a) of one subregion, right DLPFC, and (b) of cluster thickness in right F2, right F1l, and INS.

	Controls			Addicts			Slope comparison	
Normalized keypress response	**n**	**r**	**p**	**n**	**r**	**p**	**T-value**	**P-value**
DLPFC								
beautiful females	19	0.06	0.8	19	−0.54	0.02	−1.9	0.07
average females	19	−0.02	0.9	19	−0.53	0.02	−1.9	0.06
beautiful males	19	0.02	0.9	19	−0.60	0.01	−2.1	0.04
average males	19	0.00	0.9	19	−0.62	0.01	−2.3	0.03
F2								
beautiful females	19	0.01	0.9	19	−0.66	0.002	−2.2	0.03
average females	19	−0.03	0.9	19	−0.68	0.001	−2.7	0.01
beautiful males	19	−0.03	0.9	19	−0.71	0.001	−2.5	0.02
average males	19	−0.09	0.7	19	−0.71	0.001	−2.6	0.01
F1l								
beautiful females	19	0.09	0.7	19	−0.51	0.02	−1.9	0.07
average females	19	−0.04	0.9	19	−0.49	0.03	−1.7	0.10
beautiful males	19	0.05	0.8	19	−0.53	0.02	−1.9	0.06
average males	19	0.02	0.9	19	−0.55	0.02	−2.0	0.05
INS								
beautiful females	19	0.14	0.6	19	−0.48	0.04	−2.0	0.06
average females	19	−0.15	0.5	19	−0.47	0.04	−1.4	0.16
beautiful males	19	0.09	0.7	19	−0.47	0.04	−1.9	0.07
average males	19	0.03	0.9	19	−0.56	0.01	−2.2	0.03

Table 5b

Correlations between the effortful divided attention measures (misses) and cortical thickness measures.

	Controls			Addicts			Slope comparison	
Region	**n**	**r**	**p**	**n**	**r**	**p**	**T-value**	**P-value**
right RWR	16	0.37	0.16	18	−0.56	0.01	2.6	0.016
RWR minus ATTN	16	0.52	0.04	18	−0.48	0.05	3.1	0.004
RWR intersect ATTN	16	0.22	0.42	18	−0.50	0.03	1.8	0.075
right FOC (PU)	16	0.71	0.002	18	−0.41	0.09	4.1	0.0003
right pINS (cluster)	16	0.53	0.04	18	−0.57	0.01	3.3	0.002