Published in final edited form as:

Addict Biol. 2018 March ; 23(2): 781–795. doi:10.1111/adb.12523.

REGIONAL CEREBRAL BLOOD FLOW IN OPIATE DEPENDENCE RELATES TO SUBSTANCE USE AND NEUROPSYCHOLOGICAL PERFORMANCE

Donna E. Murray^{a,b,*}, Timothy C. Durazzo^{c,d}, Thomas P. Schmidt^{a,b}, Troy A. Murray^a, Christoph Abé^e, Joseph Gudyish^f, and Dieter J. Meyerhoff^{a,b}

^aCenter for Imaging of Neurodegenerative Diseases (CIND), San Francisco VA Medical Center, San Francisco, CA

^bDepartment of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, CA

^cDepartment of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA

^dMental Illness Research Mental Illness Research and Education Clinical Centers; Sierra-Pacific War Related Illness and Injury Study Center, VA Palo Alto Health Care System, Palo Alto CA

^eDepartment of Clinical Neuroscience, Osher Center, Karolinska Institutet, Nobelsväg 9, 17177 Stockholm, Sweden

^fPhilip R. Lee Institute for Health Policy Studies, University of California San Francisco, San Francisco, CA

Abstract

Neuroimaging of opiate-dependent individuals indicates both altered brain structure and function. Magnetic resonance-based arterial spin labeling has been used to measure non-invasively cerebral blood flow (i.e., perfusion) in alcohol, tobacco, and stimulant dependence; only one arterial spin labeling paper in opiate-dependent individuals demonstrated frontal and parietal perfusion deficits. Additional research on regional brain perfusion in opiate dependence and its relationship to cognition and self-regulation (impulsivity, risk taking, decision-making) may inform treatment approaches for opiate-dependent individuals. Continuous arterial spin labeling magnetic resonance imaging at 4 Tesla and neuropsychological measures assessed absolute brain perfusion levels,

* Please send correspondence to: Donna E. Murray, Ph.D., Center for Imaging of Neurodegenerative Diseases (114M), San Francisco VA Medical Center, 4150 Clement Street (114M), San Francisco, CA 94121, USA, Office: 415-221-4810 x2-2553, Fax: 415-668-2864, donna.murray@ucsf.edu.

AUTHORS CONTRIBUTION

DJM had central oversight and responsibility for this research. He designed the study and wrote the protocol. JG and clinical team facilitated access to the sODI individuals in the smoking cessation study. DEM, TCD, and CA acquired the imaging data while TCD also supervised cognitive assessments by TPS. TPS also obtained demographic and behavioral data and processed some of the perfusion data. TAM processed most of the perfusion and anatomical data, supervised by DEM. TCD and DJM jointly supervised statistical analyses. DEM was responsible for data preparation, statistical analyses, literature review, and developed and wrote the manuscript. All authors contributed to the writing of the manuscript and approved its final version.

Financial Disclosures

All authors report no biomedical financial interests or potential conflicts of interest.

cognition, and self-regulation in 18 cigarette smoking opiate-dependent individuals (sODI) stable on buprenorphine maintenance therapy. The sODI were compared to 20 abstinent smoking alcohol-dependent individuals (sALC; a substance-dependent control group), 35 smoking controls (sCON), and 29 non-smoking controls (nsCON). sODI had lower perfusion in several cortical and subcortical regions including regions within the brain reward/executive oversight system (BREOS) compared to sALC and nsCON. Perfusion was increased in anterior cingulate cortex and globus pallidus of sODI. Compared to all other groups, sODI had greater age-related declines in perfusion in most BREOS and some other regions. In sODI, lower regional perfusion related to greater substance use, higher impulsivity, and weaker visuospatial skills. Overall, sODI showed cortical and subcortical hypo- and hyperperfusion. Relating to neuropsychological performance and substance use quantities, the frontal perfusion alterations are clinically relevant and constitute potential targets for pharmacological and cognitive-based therapeutic interventions to improve treatment outcome in opiate dependence.

Keywords

magnetic resonance arterial spin labeling; neuropsychological performance; opiate

INTRODUCTION

Opioid use disorders are a worldwide problem with enormous negative consequences to the individual and society in general (e.g., medical costs, loss of wages) (OCNNCC, 2014; SAMHSA, 2015). Neuroimaging of opioid use disorders indicates altered brain structure (Li et al., 2014; Lin et al., 2012; Liu et al., 2009; Lyoo et al., 2006; Qiu et al., 2013; Wang et al., 2012; Yuan et al., 2009) and function (Forman et al., 2004; Yuan et al., 2010). Effects on perfusion (i.e., cerebral blood flow) were mainly studied with nuclear medicine techniques, such as single-photon emission computed tomography imaging, revealing reduced perfusion primarily in anterior brain regions of opiate-dependent individuals (Botelho et al., 2006; Pezawas et al., 2002) but also in parietal, temporal, and occipital cortices (Botelho et al., 2006; Danos et al., 1998; Rose et al., 1996). Non-invasive magnetic resonance imaging arterial spin labeling has been used to quantitate perfusion in alcohol, tobacco, and stimulant use disorders (Clark et al., 2007; Durazzo et al., 2015; Gazdzinski et al., 2006; Gottschalk and Kosten, 2002; Mon et al., 2009; Sullivan et al., 2013; Wang et al., 2007), showing generally lower perfusion primarily in frontal cortex. Only one study in opiate-dependent individuals used arterial spin labeling and reported lower perfusion in frontal and parietal regions related to depression symptoms (Suh et al., 2009).

Cigarette smoking is prevalent among those with opiate use (Guydish et al., 2016) and substance use disorders (Durazzo and Meyerhoff, 2007; Pomerleau et al., 1997; Romberger and Grant, 2004). Comorbid smoking and alcohol dependence were both independently associated with lower perfusion in frontal and parietal regions (Kuruoglu et al., 1996; Melgaard et al., 1990; Nicolas et al., 1993); perfusion reductions are clinically relevant as they are associated with greater smoking severity (Gazdzinski et al., 2006; Mon et al., 2009) and relapse to drinking within the first year after treatment (Durazzo et al., 2010). Further, smoking polysubstance users had lower cortical and subcortical perfusion than smoking

alcohol-dependent individuals (Murray et al., 2015), highlighting perfusion differences between two smoking substance use disorder populations. Also, opiate-dependent individuals have higher impulsivity (Paydary et al., 2016; Qiu et al., 2013; Tolomeo et al., 2016; Xie et al., 2011; Yucel et al., 2007) and worse cognition, especially executive functions (Brand et al., 2008; Pluck et al., 2012), although such research did not consider smoking status. Additional research in opiate-dependence is warranted to explore the relationships of regional perfusion to cognition and measures of self-regulation such as impulsivity, decision making, and risk taking, under the consideration of smoking status. Such information could help improve treatment approaches by tailoring treatments specifically to opiate-dependent individuals.

Early perfusion studies in substance dependence were limited by measurements obtained over large cortical gray matter regions and by not considering smoking status (smoker, non-smoker) in the analyses. Here, we parcellated arterial spin labeling perfusion images into cortical and subcortical subregions and also analyzed the potential effects of smoking on regional perfusion. We focused on regions which are associated with the development and maintenance of addictive disorders (Haber and Knutson, 2010; Makris et al., 2008), largely localized to specific regions in frontal and mesial temporal lobes, limbic system, and striatum. In this report, these regions are collectively referred to as the brain reward/executive oversight system (BREOS; (Durazzo et al., 2012; Durazzo et al., 2014; Murray, 2015)), also termed the extended brain reward system (Cardenas et al., 2011; Durazzo et al., 2010; Durazzo et al., 2011; Kuceyeski et al., 2013). Substance use disorders are associated with long-lasting plastic changes in neuronal and glial tissue of BREOS regions subserving “top-down” inhibitory control/executive functions (Volkow et al., 2012). Compromised integrity of BREOS components is linked to impaired regulation of striatum and limbic regions involved in the evaluation of reward, drive, and emotional expression (George and Koob, 2010). Further, BREOS regions contain nodes that are part of the central executive network, salience network, and reward network used in functional connectivity studies. Previous neuroimaging studies revealed multiple neurobiological abnormalities in BREOS regions in those with alcohol and substance use disorders (Heitzeg et al., 2015; Meyerhoff, 2014) and associated with reward processing and motivation (George and Koob, 2010) as well as deficits in executive functions, working memory, processing speed, and visuospatial skills (Gazzaley, 2007). Here, we compared chronically smoking opiate-dependent individuals (sODI) on buprenorphine maintenance therapy to smoking controls (sCON) and to smoking alcohol-dependent individuals (sALC), to place our findings in the context of a commonly studied treatment-seeking substance-dependent group (Gazdzinski et al., 2006; Mon et al., 2009; Sullivan et al., 2013). To help interpret potential smoking-related deficits in sODI, we also included a group of non-smoking controls (nsCON) for comparison.

Specifically we hypothesized that: (1) sODI have lower perfusion in BREOS and parietal regions than either CON group, (2) sODI have greater regional perfusion alterations than sALC or sCON after controlling for smoking severity, (3) sODI have greater age-related declines in regional perfusion than other groups, and (4) lower perfusion levels are associated with greater smoking severity and poorer neuropsychological performance.

MATERIALS AND METHODS

Participant characterization

All participants were fluent in English, provided written informed consent according to the Declaration of Helsinki and underwent procedures approved by the University of California, San Francisco and the San Francisco Veterans Affairs Medical Center. Eighteen sODI, stable on buprenorphine maintenance therapy for at least 3 months, met DSM-IV criteria for opiate dependence; they were allowed to meet DSM-IV criteria for current abuse or dependence on cocaine, amphetamines, and/or cannabis, but dependence on alcohol or benzodiazepine was exclusionary. sODI were part of a local buprenorphine treatment program and all studies were performed before smoking cessation. Twenty sALC, recruited from substance abuse treatment programs of the Veterans Affairs Medical Center and Kaiser Permanente, met DSM-IV criteria for alcohol dependence and were abstinent from alcohol for 14 ± 10 days (range 1–31) during the study. Thirty-five sCON and 29 nsCON were recruited from the community. All participants were studied with structural magnetic resonance imaging, arterial spin labeling perfusion, and neuropsychological testing; they were allowed to smoke *ad libitum* before assessment and during breaks. Table 1 lists demographics, tobacco and alcohol use variables, as well as neuropsychological measures for the four groups.

Detailed exclusion criteria for sALC and CON were reported earlier (Durazzo et al., 2007); participants in the current study were not included in the Durazzo et al. (2007) cohort. For all groups, participants were excluded for neurological disorders, psychiatric disorders, and vascular risk factors known to affect neurobiology or cognition as well as for magnetic resonance imaging contraindications. In sODI and sALC, hepatitis C, type-2 diabetes, hypertension, unipolar mood disorder, or generalized anxiety disorders were not exclusionary due to their high prevalence in addiction populations (Hasin et al., 2007; Mertens et al., 2005; Parekh and Klag, 2001; Stinson et al., 2005). Six sODI and 2 sALC had hepatitis C (by self-report and medical chart review), while 2 sODI, 5 sALC, and 2 nsCON had medically-controlled hypertension.

Psychiatric, medical, and substance consumption assessment

sODI and sALC completed the Structured Clinical Interview for DSM-IV Axis I disorders Patient Edition, v2.0 (SCID-I/P; (First et al., 1998)) and modules assessing panic and posttraumatic stress disorder; CON completed the screening module. See (Durazzo et al., 2007) for the details of our standard assessment protocol, which was used for the current sALC and CON groups; the cohort from our 2007 publication was not included in the current groups. None of the sALC had a Clinical Institute Withdrawal Assessment of Alcohol scale score of ≥ 8 , which is indicative of clinically significant alcohol withdrawal symptoms; sALC were not in active withdrawal from alcohol. For all four groups, alcohol consumption was estimated with the lifetime drinking history interview (Skinner and Sheu, 1982; Sobell et al., 1988), nicotine dependence was assessed with the Fagerstrom Tolerance Test for Nicotine Dependence (Fagerstrom et al., 1991), and lifetime substance use history (other than alcohol) was assessed with a structured questionnaire (Pennington et al., 2015). Participants also completed the Beck Depression Inventory (Beck, 1978) and the State-Trait Anxiety Inventory (Spielberger et al., 1983).

The sODI lifetime and recent substance use histories are given in Table 2. All sODI were on supervised buprenorphine maintenance therapy for at least 3 months before study with an average dose of 15 ± 9 mg/day. Most sODI used stimulants and marijuana over lifetime, but few used these drugs within the last 30 days: 1 used opiates for 20 days, 1 used cocaine for 1 day, 1 used amphetamines daily, and about one-third of the sample used marijuana recently (3 used for 1 or 2 days, and 3 used for 30 days). The majority of sODI were alcohol drinkers (Table 1) but none met criteria for an alcohol use disorder as it was exclusionary for buprenorphine treatment; only 3 consumed alcohol on > 10 days within the last month prior to study. The sALC group was active cigarette smokers abstinent from alcohol for about 2 weeks and few used other drugs within the last 30 days (3 used marijuana; 2 used cocaine). Thus, both sODI and sALC groups were cigarette-smoking treatment seekers, abstinent from their main drug of abuse for several weeks, and had low levels of other recent substance use.

Neuropsychological performance and laboratory assessment

A standard neurocognitive battery was administered, Z-scores were calculated based on corresponding normative data, and cognitive domains were formed from specific neurocognitive tasks (Durazzo et al., 2007). The cognitive domain scores in sALC, sCON, and nsCON were calculated according to the neurocognitive battery of tests administered to the sODI group (details in (Murray, 2016)). Participants from all groups also completed self-regulation measures: the Barratt Impulsivity Scale (BIS-11; (Patton et al., 1995)) to assess self-reported impulsivity, the Balloon Analogue Risk Task (Lejuez et al., 2002) to assess risk taking, and the Iowa Gambling Task (Bechara et al., 1994) to assess decision making. Laboratory tests within approximately 2 days of the scan evaluated the nutritional and hepatocellular status in all patient groups. See Table 1 for average cognitive domain and self-regulation measures for all groups.

Magnetic resonance data acquisition and processing

Magnetic resonance imaging was performed on a 4 T Bruker MedSpec system with a Siemens Trio console (Siemens, Erlangen, Germany) and an 8-channel transmit-receive headcoil. Scans were acquired between 2007 and 2013; the majority of scans were acquired contemporaneously among groups with most scans acquired between years 2011–2013. The 3D sagittal T1-weighted sequence ($1 \times 1 \times 1$ mm³) used a magnetization prepared rapid gradient echo acquisition and the 2D axial T2-weighted sequence ($0.9 \times 0.9 \times 3$ mm³) used a turbo-spin echo. Perfusion-weighted magnetic resonance imaging used a continuous arterial spin labeling single-shot echo-planar imaging sequence (Nezamzadeh et al., 2010; Tosun et al., 2012), producing 16 oblique-axial 5-mm-thick slices oriented along the orbital-meatal line (in-plane resolution= 5×3.8 mm², 1.22 mm slice gap, TR/TE=5200/9 ms repetition/echo time, 1.2 second labeling duration, 1590 ms post-labeling delay, 90° flip angle, 6/8 partial Fourier encoding and 2894 Hz/pixel bandwidth). The bandwidth was optimized for echo-planar imaging to minimize geometrical distortions due to magnetic susceptibility effects. We acquired forty control and 40 labeling scans, interleaved and averaged to boost the signal-to-noise ratio. Participants were instructed to remain awake with eyes closed during the 7 minute whole-brain perfusion sequence.

The main processing steps for each brain image volume outlined below are part of our in-house perfusion pipeline, including multiple manual quality control checks, as outlined in figures 1 and 2 in Tosun et al. (2012). Briefly, an expectation maximization segmentation algorithm with correction for intensity inhomogeneity was applied to T1 images extracting the brain tissue from the skull, and classified into fractions of white matter, gray matter, and cerebrospinal fluid. Each individual skull-stripped and bias field corrected image was motion-corrected and affine registered to a reference image, an unbiased average brain generated from young-middle aged healthy adults not included in the current dataset, using an unbiased atlas formation technique and then a nonlinear inverse-consistent fluid-flow deformation spatially normalized each affine registered individual brain to the reference brain (Lorenzen et al., 2005). For each participant, the labeled and control images were rigidly (6 degrees-of-freedom) realigned to the first perfusion image acquired to correct for head positioning differences during scanning. The mean labeled and mean control images were computed; the resulting mean control image was subtracted from the mean labeled image, yielding raw perfusion-weighted image.

Then, the raw perfusion-weighted image was intensity normalized by the overall mean perfusion image (i.e., average of mean labeled and mean control images) and intensity scaled to obtain a measure equivalent to regional cerebral blood flow, then the regional cerebral blood flow image was corrected for the tissue partial volume effects. To accomplish this, both mean control perfusion image and regional cerebral blood flow volumes were first mapped onto the T2 structural image space using a multi-resolution affine registration algorithm based on normalized mutual information. We used a fluid-flow warping based distortion correction algorithm and the resulting nonlinear deformation vector field was applied to the affine registered regional cerebral blood flow image. The T2 image was rigidly aligned to the T1 image. The T2 to T1 rigid alignment transformation was applied to the nonlinear geometric distortion-corrected regional cerebral blood flow image. Regional cerebral blood flow images in T1 image space were corrected for partial-volume variations at each voxel, which is expressed in institutional rather than in absolute units of ml/100mg/min, then mapped onto the reference brain image space by applying the participant's structural spatial normalization, then intensity calibrated. The resultant regional cerebral blood flow maps were filtered using a Gaussian smoothing kernel of 8 mm full-width-half-maximum in the reference brain image space. Regional cerebral blood flow images were aligned with FreeSurfer v5.1 parcellated labels (Fischl et al., 2002; Fischl et al., 2004) to yield participant-specific perfusion averages within pre-defined FreeSurfer regions, also part of our in-house pipelines. The inferior 2–3 slices from all perfusion datasets were removed before computation because of image distortions. FreeSurfer regions with at least 50% gray matter tissue were included in analyses. See Table 3 for regions forming the main regions of interest (ROIs): BREOS, parietal, non-BREOS/non-parietal, and subcortical. Left and right hemisphere perfusion values were averaged for bilateral regions after confirming the absence of significant laterality in almost all bilateral regions. From the current study, 2% of ALC and 47% of CON were included in a previous perfusion report of polysubstance use (Murray et al., 2015) and 92% of CON (Durazzo et al., 2015) were used in a previous study comparing regional perfusion in chronic cigarette smokers to nonsmokers.

Statistical analyses

Main effects of group were tested by comparing the four groups (sODI, sALC, sCON, nsCON) on regional perfusion measures with the generalized linear model (GENLIN) using maximum likelihood parameter estimation in SPSS v23. Age x group interactions was tested in the four-group model. Groups differed in the level of self-reported depression and anxiety symptomatology, so that these variables were used as covariates in the generalized linear model, correlations, and linear regressions. Significant main effects for group were followed up with pairwise group comparisons. Follow-up analyses investigated potential smoking severity effects in the three smoking groups. Total cigarettes/day and cigarette pack-years were separately employed as covariates because of group differences (Table 1). Partial correlational analyses used Pearson product moment with age as covariate, and linear regression examined the associations of perfusion with self-regulation measures and cognition (individual tests were adjusted for age via appropriate norms).

For each *a priori* hypothesis (main effect and interactions), $p < 0.05$ was considered statistically significant. In group comparisons of perfusion levels *without* a specific *a priori* hypothesis, we conservatively adjusted alpha levels for *all* pairwise comparisons (corresponding to each generalized linear model for multiplicity), including correlations and linear regressions (unless *a priori*), with a modified Bonferroni procedure (Sankoh et al., 1997). This approach adjusts on the basis of the average intercorrelation of perfusion values across regions (or substance use and neuropsychological variables for correlations) in each analysis for all groups and the number of t-tests performed. The average intercorrelation for BREOS regions was $r = 0.76$ and the alpha level adjusted for 8 tests was $p = 0.030$. The corresponding values for parietal regions were $r = 0.82$, 6 tests, and $p = 0.036$; for non-BREOS/non-parietal regions $r = 0.68$, 10 tests, and $p = 0.024$; for subcortical regions $r = 0.58$, 5 tests, and $p = 0.025$. The average intercorrelation for cognitive domains was $r = 0.61$ and the alpha level adjusted for 6 tests was $p = 0.025$. The corresponding values for BIS was $r = 0.71$, 4 tests, and $p = 0.033$; for drugs $r = 0.22$, 5 tests, and $p = 0.014$; for smoking severity $r = 0.57$, 4 tests, and $p = 0.028$; for alcohol severity $r = 0.38$, 3 tests, and $p = 0.025$. Effect sizes for mean regional perfusion level differences between groups were calculated as Cohen's d (Cohen, 1988).

RESULTS

Participant characteristics and neuropsychological function

As seen in Table 1, the groups were matched on age. While the smoking groups (sODI, sCON, sALC) were not statistically different on years of smoking over lifetime or FTND score, sALC smoked more cigarettes/day and had greater pack-years than sCON (both $p < 0.031$). Further, the time between last cigarette and the scan differed between the three smoking groups (sODI vs sALC, sODI vs sCON, sCON vs sALC) and was used as a covariate. Not unexpectedly, lifetime drinking severity measures differed between groups. As shown in Table 1, sODI had poorer executive functioning than sCON, as well as poorer cognitive efficiency, processing speed, visuospatial skills, working memory, and global cognition than nsCON; sODI also had poorer working memory than both sCON and nsCON. Cognitive function was comparable between sODI and sALC. sODI had higher

self-reported impulsivity than nsCON, but sODI were equivalent to the other smoking groups on all self-regulation measures. The four groups were not statistically different on measures of risk taking and decision-making (Table 1). In addition, those with medically-controlled hypertension were not statistically different on any perfusion measure compared to those without hypertension. Furthermore, within each of the four groups, regional perfusion in those on a medication that could affect perfusion (antidepressant, anxiety, pain, or thyroid medication) was not statistically different compared to the corresponding perfusion values in those not on medications; therefore, running the main GENLIN without those on medications did not alter the main results conveyed here.

Regional perfusion by group

In the 4-group-model, significant main effects for group were observed in BREOS regions (insula, lateral and medial orbitofrontal cortex), the inferior parietal region, in non-BREOS/non-parietal regions (frontal pole, hippocampus, superior temporal), and subcortical regions (globus pallidus, putamen, thalamus). A specific pattern emerged in sODI (Figure 1): sODI demonstrated *higher* perfusion in globus pallidus compared with the other groups, higher rostral and caudal ACC perfusion than sCON, as well as *lower* perfusion than both sALC and nsCON in insula, lateral orbitofrontal cortex, hippocampus, and putamen. In addition, sODI had lower perfusion than nsCON in frontal pole, superior temporal cortex, and caudate (also see Table 3).

Importantly, sODI demonstrated significantly greater age-related declines in perfusion than all other groups studied. sODI demonstrated significantly greater age-related declines in perfusion than both nsCON and sCON in multiple BREOS regions (caudal and rostral middle frontal, medial orbitofrontal cortex, superior frontal, all $p < 0.02$) (see Figure 2 for age-related superior frontal perfusion changes across all four groups), parietal regions (isthmus cingulate, precuneus, posterior cingulate cortex, all $p < 0.037$), and non-BREOS/non-parietal regions (paracentral and precentral, both $p < 0.02$). Also, sODI had greater age-related declines in subcortical nuclei perfusion (accumbens area, caudate, putamen) than sCON (all $p < 0.022$) and greater age-related perfusion decline in the isthmus cingulate and thalamus than sALC (both $p < 0.01$). In addition, perfusion in 27 of the 29 subregions investigated did not differ by sex in the sODI group.

In follow-up pairwise group comparisons, sODI had lower perfusion than sALC in the insula, lateral orbitofrontal cortex, hippocampus, and putamen (all $p < 0.016$). sODI demonstrated lower perfusion than nsCON in insula, lateral orbitofrontal cortex, frontal pole, hippocampus, superior temporal cortex, caudate, putamen, thalamus (all $p < 0.02$) and medial orbitofrontal cortex ($p = 0.026$). Most comparisons of regional perfusion between sODI and sCON were not significantly different. sCON had lower perfusion than nsCON in the medial and lateral orbitofrontal cortex, inferior parietal and superior temporal cortices, frontal pole, hippocampus, caudate, thalamus (all $p < 0.013$), isthmus cingulate and caudate (both $p < 0.024$). Including smoking measures or time between scan and last cigarette as covariates did not alter the pattern of perfusion differences in the 3-group model (sODI, sCON, sALC); in linear regressions, smoking variables were not significant predictors in the model.

Association of perfusion with substance use measures

In sODI, higher amphetamine use in the past 30 days correlated significantly and negatively with insula and putamen perfusion (both $r < -0.52$, $p < 0.01$). Greater smoking severity was not associated with lower perfusion in sODI or sALC.

Although statistically significant before multiple comparison correction, the following correlations were only of moderate strength and need to be considered exploratory. In sODI, buprenorphine dosage correlated negatively with precuneus perfusion ($r = -0.38$, $p = 0.027$). In the past 30 days, heroin/opiate use in sODI correlated negatively with caudal ACC, insula, isthmus cingulate, posterior cingulate cortex, and precuneus perfusion (all $r < -0.41$, $p < 0.02$), while years and amount of opiate use correlated negatively with precuneus, inferior parietal cortex, and frontal pole perfusion (all $r < -0.36$, $p < 0.032$). Only in sCON was greater smoking severity negatively related with perfusion, as seen in lateral OFC, hippocampus, thalamus (all $r < -0.40$, $p < 0.03$), superior frontal, postcentral, and precentral cortices (all $r < -0.36$, $p < 0.04$).

Association of perfusion with neuropsychological performance

In sODI, lower lateral orbitofrontal cortex perfusion was associated with worse visuospatial skills ($r = 0.50$, $p = 0.025$). In sALC, sCON, and nsCON, higher regional perfusion did not correlate with better cognition. However, several negative correlations between perfusion and cognition in nsCON were apparent.

In sODI, lower perfusion in the caudate ($r = -0.73$, $p = 0.001$; see Figure 3) correlated with higher attention-impulsivity and lower pars orbitalis perfusion correlated with higher motor-impulsivity ($r = -0.61$, $p = 0.001$). Further, in sODI lower perfusion in dorsolateral prefrontal cortex components (caudal middle and superior frontal cortex; both $r < -0.63$, $p < 0.001$) and caudate ($r = -0.68$, $p = 0.001$) was associated with higher nonplanning-impulsivity. In contrast to sODI, there were no such significant *negative* correlations between perfusion and impulsivity scores in sCON or nsCON, but a significant *positive* correlation emerged in nsCON. In nsCON ($n = 18$), perfusion in the medial orbitofrontal cortex correlated positively with nonplanning-impulsivity ($r = 0.54$, $p = 0.02$). The sALC group had too few participants with BIS-11 scores for meaningful assessment of correlations with regional perfusion. The regional perfusion levels did not relate significantly to the Balloon Analogue Risk Task and Iowa Gambling Task in any group.

Again, the following moderate-strength correlations should be considered exploratory and hypothesis generating and significant after multiple comparison correction. In sODI, lower perfusion in caudal ACC ($r = -0.45$, $p = 0.015$) correlated with higher attention-impulsivity. Further in sODI, lower perfusion in the rostral and caudal ACC, posterior cingulate cortex, inferior parietal, paracentral, pars opercularis, pars triangularis, postcentral cortex (all $r < -0.49$, $p < 0.015$) was associated with higher nonplanning-impulsivity. In sCON ($n = 30$), lower perfusion in superior frontal, precuneus, paracentral, pars opercularis, and caudate was associated with poorer visuospatial skills (all $r > 0.42$, $p < 0.009$). Also in sCON, perfusion in the caudal ACC, inferior and superior parietal, precuneus, cuneus, precentral, and globus pallidus correlated positively with nonplanning-impulsivity (all $r > 0.42$, $p < 0.017$).

DISCUSSION

This study compared regional brain perfusion levels, cognition, and self-regulation measures between four groups: sODI on buprenorphine maintenance therapy, treatment seeking sALC, sCON and nsCON. In many cortical regions and putamen and relative to nsCON, sODI had perfusion reductions similar to those detected in sCON, but unlike relatively normal perfusion levels observed in recently detoxified sALC. sODI also had regions of increased perfusion compared to the other groups (ACC and globus pallidus), potentially as a compensatory response to low perfusion in highly connected cortices. Also, with increasing age, cortical perfusion in multiple brain regions including BREOS showed steeper declines in sODI than in the other two substance using groups and nsCON. Lower perfusion in sODI related to a history of use (both amphetamines and heroin, but not tobacco), to lower visuospatial skills, and to higher self-reported impulsivity. Collectively, our data demonstrate abnormal perfusion with neuropsychological correlates in sODI, which both may constitute new biomarkers of treatment response and specific targets for behavioral and pharmacological treatment of the majority of opioid addicts on buprenorphine therapy.

Previously, it had been unknown if perfusion in sODI declines with age, which, if present, would reinforce the value of early identification and treatment intervention of opiate dependence. Our results show that sODI had the steepest age-related perfusion declines of all four groups in many regions, including most BREOS regions. In our middle-aged sODI, significantly lower mean perfusion in the same regions as greater age-related perfusion declines than other substance using groups does not bode well for regional cerebral blood flow and their behavioral correlates in sODI of older age. This highlights the necessity for tailoring effective treatment to sODI, addressing perfusion and neuropsychological deficits as early as possible in life.

As predicted, sODI had lower perfusion than recently detoxified sALC in frontal and subcortical regions, despite similar smoking severities. These sODI also had greater metabolite concentration deficits than a 3-week-abstinent alcohol-dependent group with equivalent smoking severities as the current sALC group, notably in the ACC and the dorsolateral prefrontal cortex (Murray, 2016). We showed previously that sCON had lower perfusion than nsCON (Durazzo et al., 2015); because opioid dependence had been related to perfusion deficits, we hypothesized that individuals with chronic exposure to both opioids and tobacco would have lower perfusion than sCON. However, the differences between these groups were restricted to higher perfusion in the ACC and globus pallidus of sODI. Not surprisingly, sODI had lower regional perfusion than nsCON in many regions, consistent with previous reports that did not consider smoking status (Botelho et al., 2006; Danos et al., 1998; Pezawas et al., 2002; Rose et al., 1996). Thus, the combination of opiate dependence and chronic smoking in sODI affected perfusion levels differently in select regions of the BREOS and subcortex. Perfusion differences between sODI and sALC were not accounted for by differences in smoking levels, leaving it unclear if the combined effects of substance abuse and smoking on perfusion are specific to a certain substance.

sODI had higher perfusion in the ACC and globus pallidus. We interpret this as a compensatory response to the lower perfusion in many other brain regions of sODI. Higher

perfusion in frontal and/or globus pallidus with single photon emission computed tomography (PET) or perfusion MRI methods has been shown in cocaine and ecstasy users (Gottschalk and Kosten, 2002; Reneman et al., 2001; Volkow et al., 1988) and in those with obsessive compulsive disease (Hugo et al., 1999). Also, higher ACC perfusion in our sODI is consistent with a PET study that reported higher ACC glucose metabolism in opiate-dependent individuals compared to controls that was not related to maintenance therapy (Galynker et al., 2000) (but presumably related to opiate use). PET findings are relevant as cerebral perfusion is tightly coupled with glucose metabolism (Chen et al., 2011).

Basal ganglia and striatum have been identified as important targets for therapeutic and pharmacological interventions in substance addictions including opiate dependence, while pharmacotherapy effectiveness can be increased when combined with behavioral interventions (Konova et al., 2013). To date, however, subcortical perfusion alterations have not been reported in heroin or opioid dependence; one study in co-occurring cocaine and heroin dependence reported perfusion deficits in the globus pallidus (Levin et al., 1995), whereas another study of abstinent ecstasy users showed higher globus pallidus perfusion (Reneman et al., 2001). We found both hyper- and hypoperfusion in adjacent subcortical structures: higher globus pallidus perfusion and lower caudate and putamen perfusion only in sODI compared to sCON. In light of the overactive drive/reward processing in addiction in subcortical structures, we suspect that hypoperfusion in caudate and putamen in sODI may play a role in the higher impulsivity and poorer cognition observed in this population; this is supported by negative correlations of caudate perfusion with attention-impulsivity and with nonplanning-impulsivity. As the globus pallidus is involved in motor learning and has been described to channel various types of information from the striatum via thalamus to frontal regions (Draganski et al., 2008; Haber, 2003); higher globus pallidus perfusion in sODI may be related to inefficiently conveying such information from hypoperfused striatal regions to (select) hypoperfused frontal regions (i.e., compensatory hyperperfusion in globus pallidus to offset hypoperfusion in connected regions). Imbalances in regional perfusion may be addressed pharmacologically in sODI, while cognitive-based therapeutic interventions may address their neuropsychological correlates.

Alternatively, it is possible that buprenorphine increased globus pallidus and ACC perfusion in sODI. All sODI were on buprenorphine maintenance therapy, which had previously been shown to improve parietal and occipital perfusion in comorbid cocaine- and heroin-dependent individuals in a dose-dependent manner (Levin et al., 1995). Moreover, lower precuneus perfusion was related to buprenorphine therapy in our sODI; it is possible that higher buprenorphine therapy dose had an effect on precuneus perfusion since, in heroin users, greater urge to use opiates (lower buprenorphine dosage) related to lower precuneus perfusion (Sell et al., 2000). Therefore, lower perfusion in many regions and higher perfusion in the ACC and globus pallidus along with altered self-regulation and cognition may be valuable biomarkers for treatment response in sODI.

Among sODI, lower perfusion, mainly in frontal but also in the insula and putamen regions, was associated with both the quantity and duration of illicit substance use (amphetamines and heroin) but not with cigarette smoking measures. We hypothesized that the combination of smoking and opiate dependence (as in the sODI group) would be associated with lower

perfusion than seen in other smoking groups, because frontal perfusion is reduced in alcohol, tobacco, and stimulant dependence; however, smoking severity measures were not related to perfusion in sODI, suggesting that illicit drug use may have had a stronger effect on perfusion levels than smoking in this sample of sODI. That said, it is also clear that cigarette smoking did have a negative effect on brain perfusion in sCON versus nsCON, unlike sODI and sALC, which is supported by prior research (Durazzo et al., 2015). Perfusion in parietal regions did not differ between smoking groups, which suggests that combined smoking and drug use (opiate or alcohol) affected parietal perfusion to similar degrees in sODI and sALC. Since smoking reduced perfusion in controls and given that our detoxified sALC did not show lower perfusion than nsCON (albeit 1-week-abstinent sALC had lower perfusion than nsALC (Gazdzinski et al., 2006)), it is unclear if low perfusion in sODI (relative to a drug-free control group) is related to smoking or opioid use or perhaps both. Future studies which include a non-smoking opiate-dependent group could address this question.

Our opiate-dependent individuals had impaired self-regulation compared with nsCON, consistent with previous research, which, however, had not accounted for smoking status. In sODI only, we found relationships between lower frontal (including dorsolateral prefrontal cortex) and caudate perfusion and higher values on all three impulsivity subscales; these associations and the higher than normal impulsivity in sODI are clinically relevant because impulsivity influences treatment response (Fineberg et al., 2010). Similarly, meaningful associations between visuospatial skills and perfusion were observed only among sODI and sCON. Taken together, altered perfusion relates to clinically-relevant behavioral measures of self-regulation and cognition, demonstrating their clinical utility. Conversely, the direction of significant relationships between perfusion and impulsivity in the nonsmoking control group was unexpected and difficult to interpret.

This study had limitations: our sODI group was relatively small, too few females were enrolled to assess sex effects rigorously, caffeine intake prior to the scan which can potentially affect perfusion measures was not assessed, and substance use measures were based on self-report. Also, sODI had a more extensive substance use history than sALC. Methodological limitations include that the perfusion sequence was optimized only for the cortex, that blood flow velocities (Gdovinova, 2001; Terborg et al., 2002) or capillary transit times, both important for healthy tissue perfusion (Østergaard et al., 2013), were not measured, and that only one post-labeling delay was used, which did not address potential arterial transit time differences between tissue types, and may not have been equally sensitive to perfusion in all tissues and individual participants.

Conclusions

Our results demonstrate altered regional gray matter perfusion and self-regulation deficits were more pronounced in sODI than in the sALC or sCON groups. In sODI, the relationships of regional perfusion levels with altered neuropsychological performance suggest the necessity of addressing self-regulation and cognition, clinically-relevant modifiable behaviors, during treatment. Since greater age-related regional perfusion declines were clearly evident in sODI compared to the other groups in many brain regions, early identification and treatment are especially important in this particular substance using group.

Deficits in perfusion and self-regulation may constitute new biomarkers of treatment response. Therefore, future treatments for sODI could address perfusion deficits pharmacologically and explore cognitive-based therapeutic interventions to improve treatment outcome, preferably under proper consideration of the neurobiological and neuropsychological correlates of cigarette smoking and maintenance therapy.

Acknowledgments

We extend our appreciation to all who volunteered for this study. For patient recruitment we thank Drs. Sharon Hall, Gary Humfleet, Kevin Delucchi, and colleagues of San Francisco Department of Public Health, Mary Rebecca Young, Bill Clift, Kathleen Altieri, Ricky Chen, and Drs. Peter Banys, Steven Batki, and Ellen Herbst of the Veterans Administration Substance Abuse Day Hospital, and Dr. David Pating, Karen Moise, and colleagues from Kaiser Permanente Chemical Dependency Recovery Program in San Francisco.

Role of funding

This work was supported by grants R01 AA10788 (DJM), P50 DA009253 (JG), and DA24136 (TCD) from National Institutes of Health and by SFVA Medical Center resources. Research was administered by Northern California Institute for Research and Education. Apart from funding and resources, the center did not contribute to this research or to the manuscript preparation.

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* Significant pairwise group differences

Figure 1.

Absolute perfusion [institutional units] by group and select regions. Shown are group means and corresponding standard deviations

* Significant pairwise group differences

Figure 2. Superior frontal gray matter perfusion as a function of participant age across the four study groups.

Figure 3.
Caudate perfusion as a function of the attention-impulsivity subscale in sODI (semi-partial correlation adjusted for age and Beck Depression Inventory).

Table 1

Demographics, tobacco and alcohol use variables, neuropsychological measures (cognition, self-regulation), and mood measures for all study groups (mean $\pm$ standard deviation)

Variable	sODI	sALC	sCON	nsCON	p(sODI-sCON)	p(sODI-nsCON)	p(sALC-sCON)
Total n [male, female]	18 [10, 8]	20 [16, 4]	35 [31, 4]	29 [24, 5]			
<u>Demographics</u>							
Age [years]	41.6 $\pm$ 12.6	45.9 $\pm$ 9.5	47.4 $\pm$ 10.2	47.2 $\pm$ 11.2	NS	NS	NS
BMI, Body Mass Index	26.8 $\pm$ 5.4	26 $\pm$ 6.9	27 $\pm$ 4.5	24.4 $\pm$ 2.8	NS	NS	NS
Education [years]	14.3 $\pm$ 1.5	13.8 $\pm$ 1.4	14.7 $\pm$ 2.2	17.1 $\pm$ 2	NS	NS	NS
<u>Cigarette and alcohol use, depression and anxiety</u>							
Total Cigarettes per day	19 $\pm$ 9	13 $\pm$ 8	18 $\pm$ 6	-	NS	-	0.020
Years Smoking	23 $\pm$ 12	25 $\pm$ 11	27 $\pm$ 11	-	NS	-	NS
FTND	5 $\pm$ 2	4 $\pm$ 2	5 $\pm$ 2	-	NS	-	NS
Cigarette-Pack Years	21 $\pm$ 14	16 $\pm$ 14	26 $\pm$ 15	-	NS	-	0.030
Last cigarette before scan [hours]	2.3 $\pm$ 4.9	1.8 $\pm$ 2.8	0.6 $\pm$ 0.4	-	0.003	-	0.030
Lifetime avg. alcohol [drinks/mo]	58 $\pm$ 55	229 $\pm$ 151	26 $\pm$ 14	17 $\pm$ 13	0.020	<0.001	<0.001
1-year avg. alcohol [drinks/mo]	55 $\pm$ 108	299 $\pm$ 159	23 $\pm$ 20	156 $\pm$ 15	NS	NS	<0.001
Years drinking any alcohol	24 $\pm$ 13	29 $\pm$ 9	28 $\pm$ 13	29 $\pm$ 13	NS	NS	NS
Beck Depression Inventory	10.9 $\pm$ 8.1	13.4 $\pm$ 8.3	5.5 $\pm$ 4.3	2.9 $\pm$ 2.9	0.010	<0.001	<0.001
State-Trait Anxiety Inventory: State	32.8 $\pm$ 10.0	36.6 $\pm$ 11.1	28.3 $\pm$ 6.0	25.0 $\pm$ 5.4	NS	0.004	0.010
State-Trait Anxiety Inventory: Trait	38.1 $\pm$ 12.2	43.7 $\pm$ 10.3	33.7 $\pm$ 8.2	32.9 $\pm$ 7.5	NS	NS	<0.001
<u>Cognitive domains (Z-scores)</u>							
Cognitive Efficiency	-0.1 $\pm$ 0.4	0.0 $\pm$ 0.5	-0.2 $\pm$ 0.4	0.6 $\pm$ 0.4	NS	<0.001	NS
Executive Functioning	-0.1 $\pm$ 0.6	-0.2 $\pm$ 0.6	-0.6 $\pm$ 0.6	0.0 $\pm$ 0.5	0.010	NS	NS
Processing Speed	-0.2 $\pm$ 0.5	-0.2 $\pm$ 0.5	-0.3 $\pm$ 0.4	0.5 $\pm$ 0.5	NS	<0.001	NS
Visuospatial Skills	0.0 $\pm$ 1.0	0.5 $\pm$ 0.9	0.4 $\pm$ 1.0	1.3 $\pm$ 0.8	NS	<0.001	NS
Working Memory	-0.1 $\pm$ 0.4	0.1 $\pm$ 0.5	0.4 $\pm$ 0.7	0.9 $\pm$ 0.6	0.010	<0.001	NS
Global Cognition	0.0 $\pm$ 0.5	0.0 $\pm$ 0.5	-0.1 $\pm$ 0.5	0.7 $\pm$ 0.4	NS	<0.001	NS
<u>Self-regulation</u>							
Balloon Analogue Risk Task	30.4 $\pm$ 10.1	29.3 $\pm$ 13.0	29.7 $\pm$ 13.3	30.1 $\pm$ 11.5	NS	NS	NS
BIS-11 Attention-Impulsivity	16.3 $\pm$ 3.7	15.1 $\pm$ 3.2	15.2 $\pm$ 4.3	13.7 $\pm$ 3.8	NS	0.040	NS

Variable	sODI	sALC	sCON	nsCON	p(sODI-sCON)	p(sODI-nsCON)	p(sALC-sCON)
BIS-11 Motor-Impulsivity	23.2 ± 3.9	22.4 ± 4.5	23.9 ± 4	20.3 ± 3.9	NS	0.030	NS
BIS-11 NonPlanning-Impulsivity	24.8 ± 4.9	24.6 ± 5.1	24.0 ± 5.4	20.3 ± 4.9	NS	0.010	NS
BIS-11 Total Impulsivity	64.3 ± 9.3	62.3 ± 10.8	63.2 ± 11.7	54.3 ± 11.2	NS	0.010	NS
Iowa Gambling Task [net total]	19.3 ± 36.8	16.3 ± 40.1	11.2 ± 28.1	34.7 ± 30.2	NS	NS	NS

There were no significant differences between sODI and sALC on any measure listed.

Table 2sODI lifetime substance use histories and recent substance use (mean $\pm$ standard deviation and range)

Substance	%	Duration in yrs	Lifetime g/mo	Previous yr g/mo
Opiates	100	1 $\pm$ 7 (2 – 22)	17 $\pm$ 14 (0.04 – 43)	5 $\pm$ 12 (0.9 – 44; n=6)
Tobacco	100	23 $\pm$ 12 (7 – 45)	558 $\pm$ 262 (300 – 1200) [#]	not available
Alcohol *	90	23 $\pm$ 12 (6 – 44)	58 $\pm$ 55 (1 – 179)	55 $\pm$ 108 (1 – 330)
Marijuana	72	8 $\pm$ 10 (3 – 40)	179 $\pm$ 25 (8 – 90)	9 $\pm$ 25 (2 – 90)
Cocaine	61	3 $\pm$ 5 (1 – 20)	27 $\pm$ 55 (2 – 240)	3 $\pm$ 8 (1 – 32; n=5)
Methadone	56	2 $\pm$ 3 (1 – 10)	not available	not available
Amphetamines	56	2 $\pm$ 3 (1 – 10)	5 $\pm$ 10 (1.2 – 38)	3.8 (n=1)

* Quantities in alcoholic drinks per month; 1 drink defined as containing 13.6 g of ethanol

[#] Number of cigarettes/month

Table 3

Absolute arterial spin labeling perfusion by group and region [institutional units] (mean $\pm$ standard deviation), effect sizes, model and group statistics

Perfusion ROIs		Mean ± SD				Effect Sizes			Group Significance	
		<u>sODI</u>	<u>sALC</u>	<u>sCON</u>	<u>nsCON</u>	<u>sODI vs sALC</u>	<u>sODI vs sCON</u>	<u>sODI vs nsCON</u>	<u>sCON vs nsCON</u>	
BREOS										
Caudal ACC		7248 ± 2017	6380 ± 1988	6040 ± 1994	6373 ± 1990	0.43	0.60 *	0.44	-0.17	NS
Rostral ACC		6810 ± 1889	6183 ± 1889	5695 ± 1889	6303 ± 1889	0.33	0.59 *	0.27	-0.32	NS
Insula		5228 ± 1745	6627 ± 1676	5582 ± 1679	6473 ± 1679	-0.83 *	-0.21	-0.73 *	-0.53	χ²(3)=10.15, p=0.017
Caudal Middle Frontal		7160 ± 1856	6873 ± 1713	6375 ± 1734	6999 ± 1720	0.16	0.44	0.09	-0.36	NS
Rostral Middle Frontal		6876 ± 1733	6365 ± 1630	5791 ± 1645	6177 ± 1634	0.30	0.64	0.42	-0.24	NS
Lateral Orbitofrontal cortex		3841 ± 1741	6301 ± 1669	4474 ± 1682	6140 ± 1673	-1.44 *	-0.37	-1.35 *	-0.99 *	χ²(3)= 33.43, p<0.001
Medial Orbitofrontal cortex		5265 ± 1633	6375 ± 1547	4655 ± 1562	6373 ± 1553	-0.69	0.38	-0.70 *	-1.10 *	χ²(3) = 24.31, p<0.01
Superior Frontal		6207 ± 1480	6053 ± 1366	5598 ± 1384	6170 ± 1371	0.11	0.43	0.03	-0.41	NS
Parietal										
Isthmus Cingulate		6796 ± 2445	7769 ± 2240	6782 ± 2323	8160 ± 2306	-0.42	0.01	-0.57	-0.60 *	NS
Posterior cingulate cortex		7445 ± 2556	7974 ± 2409	7001 ± 2437	7919 ± 2418	-0.21	0.18	-0.19	-0.38	NS
Inferior Parietal		7337 ± 2099	6691 ± 2166	6364 ± 2019	8040 ± 2129	0.30	0.47	-0.33	-0.81 *	χ²(3)=9.97, p=0.019
Superior Parietal		6362 ± 1799	5509 ± 1876	5872 ± 1748	6613 ± 1838	0.46	0.28	-0.14	-0.41	NS
Precuneus		6844 ± 1951	7088 ± 1947	6596 ± 1830	6833 ± 1915	-0.13	0.13	0.01	-0.13	NS
SupraMarginal		7089 ± 1857	6494 ± 1860	6309 ± 1751	6982 ± 1823	0.32	0.43	0.06	-0.38	NS
Non-BREOS/Non-parietal										
Cuneus		7512 ± 2290	6548 ± 2231	6384 ± 2237	7307 ± 2235	0.43	0.50	0.09	-0.41	NS
Frontal Pole		5713 ± 1660	5925 ± 1679	5555 ± 1569	7224 ± 1661	-0.13	0.10	-0.91 *	-1.03 *	χ²(3)=15.20, p=0.002
Hippocampus		2824 ± 2064	4855 ± 2032	3477 ± 2033	5978 ± 2035	-0.99 *	-0.32	-1.54 *	-1.23 *	χ²(3)=28.32, p<0.001
Paracentral		6010 ± 1865	6557 ± 1757	6029 ± 1777	6290 ± 1764	-0.30	-0.01	-0.15	-0.15	NS
Pars Opercularis		6625 ± 2091	6608 ± 2081	5942 ± 1976	6732 ± 2063	0.01	0.34	-0.05	-0.39	NS
Pars Orbitalis		5455 ± 1870	6133 ± 1788	5243 ± 1804	6257 ± 1792	-0.37	0.12	-0.44	-0.56	NS
Pars Triangularis		6407 ± 1803	6070 ± 1812	5872 ± 1702	6124 ± 1778	0.19	0.30	0.16	-0.14	NS
Postcentral		7039 ± 1712	6742 ± 1680	6193 ± 1687	6745 ± 1682	0.18	0.50	0.17	-0.33	NS

Perfusion ROIs	Mean ± SD				Effect Sizes				Group Significance
	sODI	sALC	sCON	nsCON	sODI vs sALC	sODI vs sCON	sODI vs nsCON	sCON vs nsCON	
Precentral	6533 ± 1670	6644 ± 1580	6106 ± 1598	6501 ± 1586	0.07	0.26	0.02	-0.25	NS
Superior Temporal	5266 ± 1962	6113 ± 2060	5224 ± 1921	7281 ± 2023	-0.42	0.02	-1.01 *	-1.04 *	x²(3)=17.70, p=0.001
Subcortical									
Accumbens Area	4776 ± 1759	5657 ± 1661	4546 ± 1681	5221 ± 1667	-0.52	0.13	-0.26	-0.40	NS
Caudate	3900 ± 1723	4114 ± 1723	4306 ± 1543	5246 ± 1623	-0.12	-0.25	-0.80 *	-0.59 *	NS
Globus Pallidus	1120 ± 377	748 ± 345	659 ± 347	788 ± 344	1.03 *	1.27 *	0.92 *	-0.37	x²(3)=16.25, p=0.001
Putamen	4366 ± 1733	5735 ± 1624	4842 ± 1639	5763 ± 1630	-0.82 *	-0.28	-0.83 *	-0.56	x²(3)=10.75, p=0.013
Thalamus	3690 ± 1417	3786 ± 1337	3895 ± 1346	4766 ± 1339	-0.07	-0.15	-0.78 *	-0.65 *	x²(3)=9.95, p=0.019

Reported values are values from a 4-group model with age and depression or anxiety as covariates as described in the text. The perfusion ROI values are the average of the left and right hemisphere. ACC: anterior cingulate cortex; NS: Not significant; Significant model effects in bold.

* Significant pairwise group differences after multiple comparison correction with a modified Bonferroni approach (see text)