Acute Effects of Single-Dose Aripiprazole and Haloperidol on Resting Cerebral Blood Flow (rCBF) in the Human Brain

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Abstract: Antipsychotic drugs act on the dopaminergic system (first-generation antipsychotics, FGA), but some also directly affect serotonergic function (second-generation antipsychotics, SGA) in the brain. Short and long-term effects of these drugs on brain physiology remain poorly understood. Moreover, it remains unclear whether any physiological effect in the brain may be different for FGAs and SGAs. Immediate (+3.30 h) and different effects of single-dose FGA (haloperidol, 3 mg) and a SGA (aripiprazole, 10 mg) on resting cerebral blood flow (rCBF) were explored in the same 20 healthy volunteers using a pulsed continuous arterial spin labeling (pCASL) sequence (1.5T) in a placebo-controlled, repeated measures design. Both antipsychotics increased striatal rCBF but the effect was greater after haloperidol. Both decreased frontal rCBF, and opposite effects of the drugs were observed

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in the temporal cortex (haloperidol decreased, aripiprazole increased rCBF) and in the posterior cingulate (haloperidol increased, aripiprazole decreased rCBF). Further increases were evident in the insula, hippocampus, and anterior cingulate after both antipsychotics, in the motor cortex following haloperidol and in the occipital lobe the claustrum and the cerebellum after aripiprazole. Further decreases were observed in the parietal and occipital cortices after aripiprazole. This study suggests that early and different rCBF changes are evident following a single-dose of FGA and SGA. The effects occur in healthy volunteers, thus may be independent from any underlying pathology, and in the same regions identified as structurally and functionally altered in schizophrenia, suggesting a possible relationship between antipsychotic-induced rCBF changes and brain alterations in schizophrenia. *Hum Brain Mapp* 34:272–282, 2013. © 2012 Wiley Periodicals, Inc.

Key words: arterial spin labeling; resting blood flow; antipsychotics; haloperidol; aripiprazole

INTRODUCTION

Antipsychotic drugs are the pharmacological treatment of choice for schizophrenia. First-generation antipsychotics (FGA; such as haloperidol) have a high selectivity for dopamine receptors, with an antagonistic action at dopamine D2 receptor subtypes and a comparatively lower affinity for other receptors, such as serotonin 5-HT₂, in the brain [Meltzer et al., 1989]. Second-generation antipsychotics (SGA) have a lower propensity to cause extra pyramidal side effects than FGAs [EPS; Meltzer, 2004]. SGAs are characterized by significant pharmacological heterogeneity. Pharmacologically, they have a broader neurochemical action, and a combined affinity for the dopamine D2 and serotonin 5-HT₂ receptor subtypes [Horacek et al., 2006]. Aripiprazole is a SGA, but unlike other drugs in this group, is a partial D2 receptor agonist and, similarly to haloperidol, has a lower affinity for the serotonin 5-HT_{2A} than for the dopamine D2 receptor subtype [Mamo et al., 2007]. As with other SGAs, aripiprazole is also a partial agonist at 5-HT_{1A} receptors [Jordan et al., 2002].

Though our understanding of the pharmacodynamic effects of different antipsychotics has advanced, the precise nature of different antipsychotics short and long-term effects on brain physiology remains unclear. Growing evidence from our and other groups suggests that structural brain changes observed in schizophrenia are partly associated with antipsychotic treatment, with FGAs being associated with increased basal ganglia and decreased frontal and temporal cortical volumes, and SGAs less so [Dazzan et al., 2005; Navari et al., 2009]. The mechanisms underpinning such changes are unknown, and it remains unclear whether they occur independently from the underlying pathophysiology of psychosis. Positron emission tomography (PET) studies in schizophrenia indicate that antipsychotic drugs also alter resting state activity and metabolism of these brain areas (basal ganglia, temporal and frontal cortices) [Miller et al., 2001; Lahti et al., 2003, 2009]. This suggests that resting cerebral blood flow (rCBF) alterations could possibly mediate some structural brain changes observed in schizophrenia. In support of

this, a recent study reported decreased striatal volume and subsequent functional-structural decoupling 1 to 2 hours following a single haloperidol administration in healthy volunteers [Tost et al., 2010].

Exploring antipsychotic-specific rCBF changes in healthy individuals can provide essential insights into the mechanisms underpinning antipsychotic action, while eliminating the confounding effects of illness status. Few studies have used this approach with inconsistent results, in terms of the direction and timing of changes observed. While some have found both FGA and SGA to be associated with striatal metabolic changes 12 hours [Bartlett et al., 1994; Kim et al., 2007], but not 2 hours postadministration [Bartlett et al., 1996; Lane et al., 2004], others have reported an early effect (2 hours) on metabolism with SGA (risperidone) in frontal regions [Lane et al., 2004]. More recently, increased rCBF in the putamen, consistent with the location of D2 receptors, and decreased rCBF in the insula and anterior temporal lobes, have been associated with the D2 receptor antagonist metoclopramide, as early as 60 min after dose administration [Fernandez-Seara et al., 2010]. Only one study has explored the early effects of a single dose of FGA and SGA, in patients, using a between-subjects design [Lahti et al., 2005]. Results showed that both drug groups were associated with increased striatal (greater after FGA than SGA) and decreased frontal rCBF. Also, while SGA increased temporal lobe rCBF, FGA decreased rCBF in this region.

Therefore, existing evidence suggests that antipsychotics are associated with rCBF changes and these may be drug class specific. Unfortunately, until now the immediate and different effects of antipsychotics have been explored predominantly using cross-sectional designs, comparing the effects of different drugs across different individuals, in clinical and healthy populations. A repeated measures design controls for potential cohort differences, reducing the likelihood that differences between drugs are due to intersubject variation. Implementation of this approach has been limited by the need to use a radio-labeled tracer to explore drug effects on rCBF in PET imaging. Recently, a novel, contrast-free approach to determine rCBF in a non-invasive manner has become available: arterial spin

labeling imaging (ASL) [Detre et al. 1992; Williams et al., 1992]. ASL has been recently successfully used to investigate the effects of psychoactive compounds on resting state blood flow [Fernandez-Seara et al., 2011; Kofke et al., 2007; Perthen et al., 2008]. In this study, we used a recent variant of ASL known as pulsed-continuous arterial spin labeling (pCASL) [Dai et al., 2008] in a repeated measures design to: (a) evaluate the effects of antipsychotic administration on rCBF; and (b) determine if a single dose of the FGA haloperidol and the SGA aripiprazole, have immediate (within 4 hours) and different effects on regional and global rCBF.

Based on findings from existing studies, and the known pharmacological action of the compounds used in our study, we hypothesized that (1) striatal rCBF would increase after both haloperidol and aripiprazole, but would be greater following haloperidol than aripiprazole, on account of the D2 antagonist (haloperidol) versus D2 partial agonist (aripiprazole) action of these drugs; (2) at cortical level, frontal rCBF would decrease after both haloperidol and aripiprazole, while temporal rCBF would increase only after aripiprazole.

MATERIALS AND METHODS

Sample

Twenty healthy right-handed English speaking Caucasian males, aged 18 to 33 (mean 23 years SD 4.5), participated. Mean intelligence, measured with the National Adult Reading Test [NART: Nelson, 1982], was 118.3 (SD 6.1) and body mass index was within the normal range (mean 23.6, SD 3.7). Participants were nonsmoking, university students with no recent or current drug or medication use and had no exposure to psychotropic medication, or history of personal or familial psychiatric diagnosis. The study was approved by the Human Research Ethics Committee of the Institute of Psychiatry, London, and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants after the nature of the experimental procedures was explained to them.

Design

We used a fully counterbalanced, randomized within-subject, double blinded cross-over design ensuring neither participant or researcher were aware of the intervention administered on each visit. Participants received a single dose of haloperidol (3 mg), aripiprazole (10 mg), and placebo, in a randomized order on three visits. Compounds were administered in identical capsules. Antipsychotic dose and time of administration (3 h and 30 min) before scanning were intended to achieve a striatal D2 receptor occupancy level comparable across the two compounds and that was within the “window of therapeutic range” (65–80%) during scan acquisition [Fitzgerald et al., 2000;

Grunder et al., 2008; Kapur et al., 2000; Kubo et al., 2005; Yokoi et al., 2002]. Fourteen days minimum separated each visit to allow for drug washout. No alcohol or medications were used for 24 h, or caffeine for 6 h, before scanning.

Blood pressure and clinical side effects, measured using the Barnes Akathisia scale [Barnes, 1989], the Simpson Angus scale [Simpson and Angus, 1970], and the Abnormal Involuntary Movement Scale (AIMS: National Institute of Mental Health), were evaluated 30 min before and post-scan acquisition. Blood samples, to measure plasma drug metabolite levels, were acquired 15 min before each scan and the estimated level of D2 receptor occupancy for the different antipsychotics was predicted using these plasma levels and Emax models. The Emax models (see below), based on putamen and caudate D2 receptor occupancies, using ED₅₀ and Emax for haloperidol [Fitzgerald et al., 2000] and aripiprazole [Grunder et al., 2008] were computed with the following formula:

$$\text{occupancy} = \frac{(E_{\text{max}} * [\text{conc}])}{(ED_{50} + [\text{conc}])}$$

where ED₅₀ (plasma concentration to provide 50% receptor occupancy) was 0.40 ng/ml for haloperidol and 9.5 ng/ml for aripiprazole, and Emax (max attainable receptor occupancy) was 100% for haloperidol and 92% for aripiprazole.

To explore the relationship between plasma level (a proxy for D2 receptor occupancy) and quantitative CBF, the mean plasma drug levels were correlated with the mean CBF values of brain areas where antipsychotic specific CBF changes were identified by the voxel-wise analysis.

Image Acquisition

Participants were scanned with eyes open and images were acquired in a General Electric Signa HDX 1.5 T scanner at the Centre for Neuroimaging Sciences, Institute of Psychiatry. rCBF measurements were made using a pulsed-continuous arterial spin labeling technique (pCASL, Dai et al., 2008]. Arterial blood was labeled using a train of Hanning radio frequency (RF) pulses each 500 μs in duration, with a repetition rate of 1500 μs resulting in a 1000 μs space between pulses. A train of gradient pulses of similar duration and repetition rate (each followed by a refocusing lobe) were employed to achieve flow-driven adiabatic inversion. The maximum gradient amplitude under the Hanning pulses and the average gradient intensity over the RF train duration, were 9 mT/m and 1 mT/m, respectively. These values were chosen to ensure that the adiabatic condition for inversion and the exclusion of the first aliased labeling plane away from the excitation bandwidth of the Hanning pulse, were both met [Dai et al., 2008]. In the control phase, the sign of alternate Hanning pulses was reversed, and the amplitudes of the gradient

pulses were adjusted so that the net RF and gradient amplitudes over the 1.5 s irradiation were both zero. Thus, the magnetization transfer effect is compensated whilst achieving no inversion of arterial spins.

After a postlabeling delay of 1.5 s, the image was acquired with a three-dimensional Fast Spin Echo (FSE) spiral multishot readout. This delay has been found to be appropriate in investigations using healthy participants of a similar age range as the ones included in our study [Howard et al., 2011]. To minimize blurring, the spiral acquisition was very short (4 ms), and the required resolution was achieved with eight interleaves (TE 32 ms/TR = 5,500 ms; ETL = 64). Images were acquired at a $48 \times 64 \times 48$ matrix on a $18 \times 24 \times 18$ cm field of view. Images were reconstructed to a 256^2 matrix, resulting in a nominal spatial resolution of 1×1 mm in plane. Sixty slices of 3 mm thickness were obtained. Three pairs of tagged-untagged images were collected. Selective saturation of the image slab was applied at 4.3 s before acquisition; selective inversion was applied 3 s before acquisition with further nonselective inversions at 1.5 s, 764 ms, 334 ms and 84 ms before imaging. This repeated inversion achieved successful suppression of the background static tissue signal, thus maximizing the sensitivity to blood perfusion.

Following the three arterial spin labeling (ASL) control-label pair averages, images were acquired with the same imaging sequence but with inversion recovery preparation instead of ASL. One sequence with saturation of 4.3 s and then an inversion at 1,650 ms before imaging was used to create a fluid suppressed image. A second sequence with saturation at 4.3 s and then inversion at both 2,408 ms and 511 ms was also acquired to create a fluid and white matter suppressed image. For both these sequences, the receiver gain was automatically lowered by 21 dB relative to the ASL sequence to avoid receiver saturation. These images were used to help quantify blood flow from the ASL as described in the following paragraph.

For quantification of flow, the sensitivity of the image was calibrated to water at each voxel [Alsop and Detre, 1996; Buxton et al., 1998; Williams et al., 1992]. When surface coils are employed, the spatially nonuniform sensitivity complicates this calibration. Often the underlying tissue signal is used as an indicator of water sensitivity, but a water density in each voxel, or partition coefficient, must then be assumed. We observed that the signal intensity in the inversion-prepared fluid-suppressed image was relatively constant for different tissues. This is likely because more complete recovery occurs for shorter T1 tissues, which tend to have lower water density. Using a neighborhood maximum algorithm to avoid regions with partial volume of suppressed fluid, a low-resolution sensitivity map was created. This map was calibrated for water sensitivity by assuming the tissue was white matter with a water concentration of 0.735 gm/ml [Herscovitch and Raichle, 1985] and a T1 of 900 ms, and using the equations for inversion recovery signal attenuation. By assuming gray matter with a water concentration of 0.88 gm/ml and

a T1 of 1,150 there was only a 5% calibration difference. This calibration produced a sensitivity map, C , equal to the fully relaxed MRI signal intensity produced by 1 g of water per ml of brain.

With this coregistered sensitivity map C , we calculated cerebral blood flow (CBF) using the equation

$$CBF = \frac{\rho_b(S_c - S_l)}{2\alpha C \omega_a T_{1a} \exp\left(-\frac{w}{T_{1a}}\right) \left(1 - \exp\left(-\frac{tl}{T_{1a}}\right)\right)}$$

where ρ_b is 1.05 g/ml [the density of brain tissue; Herscovitch and Raichle, 1985], $[\alpha]$ is the labeling efficiency [assumed to be 95% for labeling times 75% for background suppression; Garcia et al., 2005], w is 1.5 s [the postlabeling delay; Alsop and Detre, 1996], tl is 500 ms (the labeling duration), T_{1a} is 1.4 ms [the T1 of arterial blood which was slightly lower than the value of Lu et al., 2004], ω_a 0.85 g/ml (the density of water in blood; Herscovitch and Raichle, 1985), S_l and S_c are the signal intensities in the labeled and control images, respectively.

This equation assumes that the labeled blood remains in the arterioles and capillaries and does not reach the tissue. The CBF quantification process does not alter the qualitative appearance of the images obtained by subtracting the label from the control image.

The whole ASL pulse sequence, including the acquisition of calibration images, was performed in 6:08 min. Two additional structural, high spatial resolution images were acquired for coregistration and normalization, including a T2 weighted fast spin echo and fluid-attenuated inversion-recovery fast spin echo (FLAIR FSE) scan to exclude the presence of any brain pathology.

Image Preprocessing

rCBF images were processed using Statistical Parametric Mapping (SPM, version 5, available at: www.fil.ion.ucl.ac.uk/spm). For each participant, one T2 scan was used in the preprocessing steps of the CASL images acquired under each treatment condition, which ensured that the normalization parameters applied to each scan were identical within individual. To improve the spatial normalization of the rCBF maps to the Montreal Neurological Institute, we employed a three-step procedure: (i) extra-cerebral signal from the T2 scan was removed using the "Brain Extraction Tool" (BET) of the Functional Software Library [FSL: Smith, 2002]. The T2 scan was used here as the threshold based approach of the BET algorithm performs better with standard anatomical images. The skull stripped T2 volume and its corresponding binary mask were then coregistered to the rCBF map; (ii) the coregistered, binary, brain-only mask, was multiplied by the rCBF map to remove extra-cerebral signal from this scan. The skull stripped T2 and rCBF maps were then coregistered back to the space of the original T2 scan (returned to their original frame of reference); (iii) the original T2 scan

Figure 1.

A sample of 25 (from a data set of 60) horizontal slices, from a CBF map from one of the study participants showing image quality in native space obtained with pCASL using a three-dimensional-fast spin echo readout. The maps in this figure have been multiplied by a binary brain mask obtained from the individual T2-weighted anatomical scan of each subject. These images are acquired in 6:08 min and have a nominal resolution of $1 \times 1 \times 3$ mm. Note the absence of the image distortion and signal dropout artefacts commonly observed with gradient recalled readout techniques.

was normalized to the MNI based T2 template provided in SPM, and the transformation matrix was applied to the rCBF map and the T2 scan. This procedure enhanced the quality of the normalization. The data were then smoothed using a 10 mm Gaussian Smoothing kernel (see Fig. 1 for preprocessed rCBF maps).

Statistical Analysis

For analysis of all other descriptive data, the Statistical Package for the Social Sciences (SPSS), version 15 was used. Haloperidol and placebo comparisons were based on 20 subjects. Comparisons with aripiprazole were based on 18 participants as two developed nausea and vomiting. rCBF maps of all subjects, acquired on each scan visit, were entered into a flexible factorial model in SPM and analyzed using a random effects, general linear regression model. This model was first run without covarying for global CBF, then repeated including global CBF as a covariate. Even if global CBF was not significantly different at the group level, this approach explored whether small

interindividual physiological differences limited the identification of antipsychotic-induced regional CBF changes. The effects of antipsychotic on global CBF change was explored using a repeated measures ANOVA in SPSS, having extracted the mean global CBF values using the MarsBar toolbox [Brett, 2010; available at: <http://marsbar.sourceforge.net/> last updated 2010] in SPM5. Within each random effects model in SPM, we performed three paired contrasts (*t*-tests) to identify increased and decreased rCBF between the antipsychotic conditions: haloperidol versus placebo, haloperidol versus aripiprazole, aripiprazole versus placebo. For each comparison, we first conducted an initial voxel-wise whole-brain search, using a threshold of $P < 0.001$ uncorrected for multiple comparisons. To account for any nonisotropic smoothness of the data, nonstationary cluster extent correction was applied [Gaser, 2007], and statistically significant clusters were accepted at $P < 0.05$ (corrected for multiple comparisons [Friston et al., 1994]). Additionally, small volume corrections were applied bilaterally to each contrast using independent, anatomically-defined, a priori regions, created with the anatomical automatic labeling [AAL: Tzourio-Mazoyer et al., 2002] toolbox extension in SPM5. Region of interest (ROI)-level statistics were accepted at $P < 0.05$ corrected for family-wise error (FWE). Based on the PET studies by Lahti et al. [2003, 2005], nine regions of interest were examined: the inferior frontal, middle frontal, anterior cingulate, superior temporal, middle temporal, hippocampus, thalamus, putamen, and caudate. To achieve optimal accuracy, we chose not to use a linear transformation and instead labeled MNI coordinates using a combination of FSL view MNI structural atlas [Mazziotta et al., 2001], the Talairach and Tournoux atlas [Talairach and Tournoux, 1988], and the Brodmann template [Brett et al., 2001; Damasio and Damasio, 1989; Frey et al., 1987; Rorden and Brett, 2001].

RESULTS

Global CBF Changes

No significant differences in global CBF were observed across the three intervention groups ($F_{(2,34)} = 0.122$ n.s.; Fig. 2). The global signal change after each antipsychotic, relative to placebo was less than 1%.

Voxel-Wise and Region of Interest Analysis Covarying for Global CBF

Haloperidol versus placebo

Whole brain analysis revealed that haloperidol induced greater perfusion than placebo in three clusters (Table I); The first cluster centered in the right putamen (see Fig. 3), extended into the left putamen, bilaterally into the caudate and parahippocampal gyrus and also into the left insula and right hippocampus; The second cluster

Figure 2.

Mean and standard error bars showing global CBF values for each intervention. Values represent millilitres of blood per 100 g tissue per minute. PLA, placebo; HAL, haloperidol; ARI, aripiprazole. No significant differences across treatment conditions were detected.

centered in the left precentral gyrus (primary motor cortex), extended into the right precentral gyrus (primary motor cortex), left premotor cortex (supplementary motor area), right postcentral gyrus, and right ventral posterior cingulate; The third cluster centered on the left premotor cortex (supplementary motor cortex), extended into the

left precentral gyrus (primary motor cortex) and left postcentral gyrus (primary somatosensory cortex). ROI analysis revealed that haloperidol also induced greater perfusion than placebo in the left hippocampus, and in the left ventral anterior cingulate.

Whole brain analysis revealed that haloperidol reduced perfusion compared with placebo in a cluster centered on the left inferior temporal gyrus (Fig. 3; Table I). ROI analysis showed reduced perfusion after haloperidol than placebo in the left middle frontal gyrus.

Aripiprazole versus placebo

Whole brain analysis revealed that aripiprazole induced greater perfusion than placebo in four clusters (Table I); The first cluster centered in the left claustrum (see Fig. 4), extending into the left putamen, insula, caudate, superior temporal gyrus, and hippocampus; The second cluster centered in the right putamen, extending into the right claustrum and insula. The third and fourth clusters were centered in the right ventral anterior cingulate (see Fig. 4) and right cerebellum respectively, with the latter cluster extending into the inferior occipital lobe. ROI analysis revealed that aripiprazole induced greater perfusion than placebo in the left superior temporal gyrus.

Whole brain analysis revealed that aripiprazole reduced perfusion, relative to placebo, in five clusters. The first cluster was centered in the right ventral posterior

TABLE I. Significant clusters of rCBF change after each antipsychotic

Contrast/brain area	HEM	MNI coordinates			T scores	No. voxels	P	Mean CBF ($\pm$ SD)			% CBF change
		X	Y	Z				PLA	HAL	ARI	
Haloperidol > placebo											
Putamen	R	30	4	0	8.72	7,295	0.000	366(45)	401(51)	Na	9.6
Precentral gyrus (primary motor)	L	0	-22	66	5.36	1,185	0.000	519(81)	549(90)	Na	5.3
Premotor cortex (supplementary motor)	L	-20	-26	70	4.21	295	0.036	519(82)	554(106)	Na	6.6
Haloperidol < placebo											
Inferior temporal gyrus	L	-58	-56	-14	6.19	1,153	0.000	487(72)	445(50)	Na	8.6
Haloperidol > aripiprazole											
Putamen	R	12	10	-10	5.46	743	0.002	Na	404(53)	375(56)	8.0
Aripiprazole > placebo											
Claustrium	L	-32	-14	4	6.20	2,668	0.000	435(51)	Na	468(64)	7.6
Putamen	R	30	6	0	5.64	754	0.002	421(48)	Na	452(56)	7.3
Anterior cingulate gyrus	R	2	12	32	5.19	533	0.006	560(73)	Na	600(91)	7.2
Cerebellum	R	44	-80	-28	5.11	423	0.010	330(60)	Na	379(69)	14.9
Aripiprazole < placebo											
Posterior cingulate gyrus	R	2	-26	30	5.74	904	0.001	694(102)	Na	652(94)	6.0
Superior frontal gyrus (PFC)	R	16	54	24	5.16	333	0.025	402(67)	Na	367(73)	8.6
Superior parietal lobe	L	-36	-76	48	5.00	334	0.025	603(114)	Na	557(99)	7.7
Inferior occipital gyrus	R	12	-94	-4	4.83	350	0.022	542(120)	Na	499(71)	7.9
Orbitofrontal cortex (PFC)	R	10	64	-12	4.17	285	0.039	370(53)	Na	346(55)	6.4

P (corrected P value): $P < 0.05$.

Results are presented from the GLM covarying for global CBF effects. % CBF changes were calculated using the mean change, relative to placebo.

Hem: hemisphere; MNI: Montreal Neurological Institute anatomical coordinates; SD: standard deviation; PLA: placebo; HAL: haloperidol; ARI: aripiprazole; PFC: prefrontal cortex.

Figure 3.

Haloperidol compared with placebo. Whole brain analysis showing a significant CBF (a) increase bilaterally in the striatal CBF (top-horizontal slices) and in the motor cortex (bottom-sagittal slices) and (b) decrease in the left inferior temporal CBF, after haloperidol. These results were covaried by the individual global CBF value. Images are shown in MNI space.

cingulate and extended into the left precuneus and parieto-occipital sulcus. The second cluster was centered in the right superior frontal gyrus. The third was centered in the left superior parietal lobe, extending into the inferior parietal lobe. The fourth and fifth clusters were centered in the right inferior occipital lobe, extending into the left inferior occipital lobe and in the right orbitofrontal cortex respectively (Fig. 4, Table I). The ROI analysis identified lower perfusion after aripiprazole than placebo in the left middle frontal gyrus (dorsolateral prefrontal cortex).

Haloperidol versus aripiprazole

Whole brain analysis revealed that haloperidol induced greater perfusion than aripiprazole in a cluster centered in the right ventral putamen, and extending into the left putamen, left caudate and left amygdala (Fig. 5, Table I). There were no brain regions in which greater perfusion was evident after aripiprazole compared with haloperidol in the whole brain analysis. However, ROI analysis revealed a greater perfusion in the left superior temporal gyrus following aripiprazole relative to haloperidol.

Voxel-Wise Analysis Without Covarying for Global CBF

Whole brain analysis revealed that haloperidol significantly increased perfusion relative to placebo in two clus-

Figure 4.

Aripiprazole compared with placebo. Whole brain analysis showing a significant relative CBF (a) increase bilaterally in the caudatum and putamen (top-horizontal slices), the right anterior cingulate and right cerebellum (bottom-sagittal slices) and (b) decrease in the left superior parietal lobe, right posterior cingulate and bilaterally in the inferior occipital lobe (top sagittal slices), and in the right superior frontal gyrus and orbitofrontal cortex (bottom sagittal slices), after aripiprazole. These results were covaried by the individual global CBF value. Images are shown in MNI space.

ters. The first was centered on the right putamen, and extended into the right caudate, and the second was centered on the left putamen and extended into the left caudate. No other areas of significant CBF change were evident when the interventions were compared with one another or placebo.

Figure 5.

Haloperidol compared with aripiprazole. Whole brain analysis showing a significant relative CBF increase bilaterally in the striatum after haloperidol. These results were covaried by the individual global CBF value. Images are shown in MNI space.

Plasma Antipsychotic Levels and Predicted Dopamine D2 Receptor Occupancies

At 3 h 20 min postintervention, mean plasma metabolite levels of haloperidol and aripiprazole were $1 \mu\text{g/l}$ ($\pm\text{SD}$: 0.6) and $42 \mu\text{g/l}$ ($\pm\text{SD}$: 11), respectively. The Emax models predicted that mean striatal D2 receptor occupancy was 68% (range 56–86%) and 74% (range 65–78%) after haloperidol and aripiprazole respectively, indicating that the level of receptor occupancy was comparable across the two drugs.

The Relationship Between Plasma Antipsychotic Levels and CBF Changes

There was a significant negative correlation ($r = -0.485$, $P < 0.05$) between haloperidol plasma level and CBF after haloperidol in the premotor cortex (the third cluster in which haloperidol elicited a significant elevation in perfusion relative to placebo), indicating that a higher plasma drug level was associated with lower regional CBF. Mean plasma antipsychotic level was not correlated with any other regional mean CBF values identified as being altered by antipsychotic administration in the voxel-wise analysis.

Blood Pressure and Clinical Side Effects

Haloperidol and aripiprazole induced more extra-pyramidal side effects than placebo ($\chi^2 = 7.37$, $P < 0.05$), immediately before scanning, but these were not evident after the scanning session ($\chi^2 = 2.0$, n.s.). There were no significant differences in tardive dyskinesia ($\chi^2 = 2.0$, n.s.), akathisia (all participants had a negative score), systolic ($F_{(2,32)} = 2.27$, n.s.) or diastolic ($F_{(2,32)} = 0.22$, n.s.) blood pressure.

DISCUSSION

Using a novel, contrast-free approach, we directly compared the effects of a FGA (haloperidol) and a SGA (aripiprazole) on rCBF in the same healthy individuals, and found early and antipsychotic specific changes in striatal, frontal, and temporal regions.

Increased striatal rCBF was evident after both antipsychotics, only 3 h and 30 min after administration. This is the earliest change reported for haloperidol and for any SGA and is consistent with studies reporting later effects at 12 h after administration of haloperidol or aripiprazole [Bartlett et al., 1994; Kim et al., 2007]. Interestingly, such a change was not evident in early investigations of haloperidol and SGAs in healthy volunteers, which report no change in striatal glucose metabolism 2 h after administration (haloperidol or risperidone), using fluorodeoxyglucose PET [FDG-PET; Bartlett et al., 1996; Lane et al., 2004]. The early striatal rCBF increase following haloperidol however, is consistent with findings from the first (early) investigation of a different D2 antagonist on resting blood flow using PET [Mehta et al., 2003], and a recent ASL study

exploring metoclopramide (also a D2 antagonist) in healthy volunteers [Fernández-Seara et al., 2010]. Interestingly, the three positive studies all used a water-labeling method (^{15}O -enriched water PET and ASL), suggesting that the measurement of resting state CBF via this noninvasive technique may provide a sensitive probe of early psychoactive effects.

Despite its unique high affinity and partial agonism at D2 receptors [Mamo et al., 2007], aripiprazole induced striatal changes similar to those reported in patients following other SGAs [Lahti et al., 2005, 2009; Liddle et al., 2000]. This suggests that the functional effects of dopaminergic modulation associated with SGAs in this brain region are comparable, regardless of the heterogeneous receptor affinity profiles and intrinsic activity of this group of drugs.

Alongside this striatal change, we have found a rCBF increase in cortical motor areas following haloperidol administration. This is the first report of early rCBF cortical motor changes in healthy individuals, a previous report having observed the increase after 1 week of haloperidol treatment in patients [Lahti et al., 2009]. This finding is consistent with data on the susceptibility of the cortical-striatal circuitry to functional remodeling in response to dopaminergic modulation [Tost et al., 2010]. Furthermore, the absence of such effects in these brain regions after aripiprazole indicates D2 receptor antagonism and not partial agonism may result in this brain circuitry becoming susceptible to alteration.

We observed a decrease in rCBF in frontal areas after both antipsychotics, although this was more widespread (evident in the middle, orbitofrontal, and superior frontal gyrus) after aripiprazole. These findings support previous reports of metabolism reductions in this brain region following haloperidol in healthy individuals and in patients [Bartlett et al., 1994; Lahti et al., 2005]. Aripiprazole effects are also in line with the only other PET study conducted in healthy volunteers [Kim et al., 2007], and are notably comparable to those associated with other SGAs [Ngan et al., 2002]. Both antipsychotics also altered rCBF in the cingulate, with haloperidol being associated with a rCBF increase in the anterior, and a rCBF decrease in the posterior, cingulate. Aripiprazole unexpectedly increased anterior cingulate rCBF, an effect not observed in the only other aripiprazole study exploring metabolism 12 hours after administration [Kim et al., 2007]. However, another SGA (olanzapine) has also been reported to increase anterior cingulate rCBF 5 h after administration in patients [Lahti et al., 2005]. Olanzapine and aripiprazole share similar affinity for serotonin 5HT-2A receptors [Gardner et al., 2005], suggesting that antagonism at this receptor subtype could underpin the immediate rCBF changes observed in this brain region.

In the temporal lobe, we observed different effects for haloperidol and aripiprazole. Increased rCBF after aripiprazole in the superior temporal gyrus is the earliest change to be reported in this brain region, and is

consistent with effects observed at 12 h [Kim et al., 2007]. Olanzapine has also been associated with increased temporal rCBF in patients [Lahti et al., 2005, 2009], providing further evidence for the possible role of serotonin blockade in these rCBF alterations. Haloperidol was associated with decreased temporal cortex rCBF, whereas previous healthy investigations with PET reported no change [Bartlett et al., 1994, 1996]. Our findings are based on a larger sample size and are in agreement with patient studies reporting that single, short-term, and chronic haloperidol administration are all associated with decreased temporal rCBF [Lahti et al., 2005, 2009].

Our findings of an early effect of both antipsychotics on brain perfusion are consistent with PET occupancy studies, showing that antipsychotics impact at the receptor level within hours of administration [Nordstrom et al., 1992; Tauscher et al., 2002]. This suggests a possible relationship between the ability to block dopamine receptors and the level of resting blood perfusion. The validity of this possible relationship is at least partly supported by independent data which shows that treatment response is associated with both the level of striatal rCBF [Lahti et al., 2009] and of dopamine D2 receptor occupancy [Kapur et al., 2000]. Interestingly, our data also reveal that higher haloperidol plasma levels, a proxy for occupancy, are correlated with lower rCBF in the premotor cortex following haloperidol. Still, a direct link between occupancy alone and perfusion change seems unlikely, since although aripiprazole and haloperidol bind with similar high affinity to D2 receptors, they are nevertheless associated with different striatal rCBF changes in our sample.

Although the precise mechanisms underpinning rCBF changes in response to administration of psychoactive substances are unclear, the underlying assumption of our work is that enhanced neuronal and postsynaptic activity increases energy demand [Sadaghiani et al., 2010], resulting in areas of increased perfusion following antipsychotic administration. In brain areas where dopamine D2 receptors are densely distributed (such as the striatum), antagonism may give rise to increased presynaptic dopamine synthesis and release, due to loss of inhibitory feedback mechanisms. In brain regions innervated by these densely D2 populated areas, such as the frontal and temporal cortices, downstream inhibitory and excitatory processes may also be involved [Fazio et al., 2010; Mattay et al., 2002]. Using ASL, however, we cannot exclude that some of the effects observed have a vascular rather than entirely neuronal origin. This might explain some of the discrepancies between our results and those carried out using FDG-PET.

Finally, our Emax models indicated that drug plasma levels predicted similar striatal D2 receptor occupancy for both compounds and the comparable increase in extra-pyramidal symptoms (EPS) we observed after both drugs is consistent with this [Kapur et al., 2000]. It is also interesting that CBF increased in the striatum after both antipsychotics, supporting the role of this brain region in motor

behavior [Alexander and Crutcher, 1990] and in the motor side effects associated with antipsychotics. Importantly, our predicted occupancies were within the therapeutic range [Kapur et al., 2000], indicating our findings are relevant to the doses used in patients. Furthermore, the rCBF alterations cannot simply be explained by differences in drug occupancy. This is particularly relevant when interpreting the opposite effects of these drugs on rCBF in the temporal cortex.

It is noteworthy that, when global CBF was not included as a covariate, there were fewer rCBF changes observed. However, global CBF itself was not significantly different after each intervention, suggesting that without its inclusion, small interindividual physiological differences may have limited the identification of regional differences at group-level. Therefore, inclusion of global CBF as a covariate helped resolve regional differences by removing small interindividual differences.

One limitation of the study may be the use of a single scan after each intervention in this within-subject design, which did not allow us to explore whether drug effects on rCBF persisted beyond the day of scanning. However, data suggesting that cognitive effects do not persist 24 h after antipsychotic administration [Legangneux et al., 2000], suggests our 14 day washout period was sufficient. Also, intellectual capacity and smoking are different in patients compared with controls [De Leon and Diaz, 2005; Lewis and Levitt, 2002], potentially limiting the generalization of our findings to schizophrenia. For example, the comparability of single dose and chronic treatment effects remains unknown. Nevertheless, rCBF changes, particularly in temporal and corticostriatal circuitry, observed in this study are consistent with those observed in single and chronic dosing studies in patients [Lahti et al., 2005, 2009]. Thus, researching the effects of these compounds on rCBF in healthy individuals offers valuable insights into their effects in patient populations, indicating that CBF alterations evident after repeated dosing are in fact observed within hours of a single drug administration, and are not due to an interaction with the pathogenesis of the disorder.

CONCLUSIONS

This study indicates that there are immediate and different rCBF changes after a single dose of antipsychotics in the striatum and cortical-striatal loop, frontal, and temporal cortices. The sensitivity of these brain regions to immediate antipsychotic effects in our study might suggest that rCBF changes could underpin or reflect the “early-onset” of therapeutic effect proposed by Kapur et al. [2005]. Moreover, changes were observed in regions in which our and other groups have previously observed structural alterations associated with FGA or SGA effects in schizophrenia, suggesting that rCBF alterations may interact with, or partly contribute to, structural changes, although

the underpinning mechanisms remain unclear. Our results also highlight the importance of controlling for antipsychotic generation when interpreting neurocognitive and neuroimaging data in schizophrenia, and further research into the functional implications of these findings would be beneficial. Finally, we have shown that pCASL offers a potential alternative to ^{15}O -enriched water PET for investigating the effects of psychotropic compounds on brain rCBF. Given the value of repeated scanning for investigating treatment response, and the sensitivity of pCASL to immediate brain changes (after only a single dose) in regions known to be targeted by antipsychotic drugs, future use of this tool for exploring the prediction of treatment response in schizophrenia would be highly advantageous.

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