Arterial spin labeling in patients with schizophrenia: a systematic review

Tiago M. Guimarães[1], João Paulo Machado-de-Sousa[1,2], José A. S. Crippa[1,2], Mara R. C. Guimarães[1], Jaime E. C. Hallak[1,2]

[1] *Department of Neuroscience and Behavior, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (FMRP-USP), Ribeirão Preto, SP, Brazil.*
[2] *National Institute for Science and Technology – Translational Medicine (INCT-TM), National Counsel of Technological and Scientific Development (CNPq), Brazil.*

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Abstract

Background: Neuroimaging studies are an invaluable source of information about the physiopathology of schizophrenia. Arterial spin labeling (ASL) is a new magnetic resonance technique (MRI) that is able to effectively evaluate brain function without the use of radiation. **Objective:** To make a systematic review of studies using ASL to compare resting-state regional cerebral blood flow (rCBF) patterns in patients with schizophrenia and healthy controls. **Methods:** Original articles were searched for on PubMed, Scopus, Web of Science and PsycINFO electronic databases. The search terms used were 'arterial', 'spin', 'labeling', and 'schizophrenia'. Only studies comparing resting-state rCBF were included, a qualitative synthesis was then performed. **Results:** Ten articles were included in the review among a total of 22. Decreased rCBF in schizophrenia patients was described in the anterior cingulate, cuneus, fusiform gyrus, frontal lobe, left middle frontal gyrus, inferior frontal gyrus, lingual gyrus, middle occipital gyrus, and parietal lobe. The putamen was the only region with increased rCBF in schizophrenia. **Discussion:** The evidence of the studies reviewed lends support to the concept of hipofrontality in schizophrenia. rCBF alterations were found in regions classically associated with schizophrenia. ASL seems to be valid, and reliable tool to assess schizophrenia.

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Introduction

Schizophrenia is one of the world's 10 leading causes of disability-adjusted life years and, despite current progress in research and treatment, continues to be a major etiologic, diagnostic, and therapeutic challenge[1]. It has been estimated that around 1% of the world population suffers from this chronic and disabling disorder. The onset of schizophrenia usually occurs in late adolescence or early adult life, meaning great losses in educational, social, and economic outcomes for individuals and for society as a whole[2]. Currently available evidence suggests that schizophrenia occurs as the result of a combination of genetic, environmental, and social risk factors[3].

The clinical presentation of schizophrenia is heterogeneous and its manifestations vary among patients and during the course of the disorder[4]. Symptoms can be divided into five dimensions or syndromes: positive (delusions and hallucinations), negative (affective flattening, avolition, anhedonia, social isolation, and alogy), cognitive (executive dysfunction, memory and attention), disorganization (disorganized speech and behavior) and affective (depression, anxiety, dysphoria and mania)[5].

Functional neuroimaging studies have proved to be an invaluable source of information about the physiopathology of schizophrenia. Many of these studies use radiation-based tracers, like positron emission tomography (PET) and single-photon emission computed tomography (SPECT)[6]. In addition, a growing number of studies have been carried out using newer functional magnetic resonance imaging (fMRI) methods that are able to effectively evaluate brain function without the use of radiation. Blood-oxygen level dependency (BOLD) and arterial spin labeling (ASL) are among these methods. BOLD uses the concentration of deoxyhemoglobin as an endogenous tracer to estimate brain metabolism. The concentration of deoxyhemoglobin is dependent upon regional cerebral blood flow (rCBF), local rate of oxygen consumption, and regional cerebral blood volume[7]. ASL, on the other hand, is based on the quantification of the water flow within brain regions, which is considered to provide an indirect measure of metabolism[8].

In ASL, the tracer is a magnetic label (tag) applied to water molecules of flowing blood prior to their reaching the region under assessment. Such labeling consists in an inversion of proton spins of arterial water. After an interval that allows water molecules to be exchanged within tissues, an image, referred to as 'labeled' or 'tagged', is acquired. In this image, blood water is in a different magnetization state from that of static tissue water. Also, a control image of the same slice is acquired in which inflowing blood is not labeled. By calculating the difference between control and tagged images, investigators can create an image that corresponds to the proportional rCBF in a given brain region[8].

Four types of ASL spin preparation methods are used currently: pulsed ASL (PASL), continuous ASL (CASL), pseudo-continuous ASL (pCASL), and velocity-selective ASL (VS-ASL). The difference between these methods lies in the method used to magnetically tag water molecules in inflowing blood (Figure 1)[9].

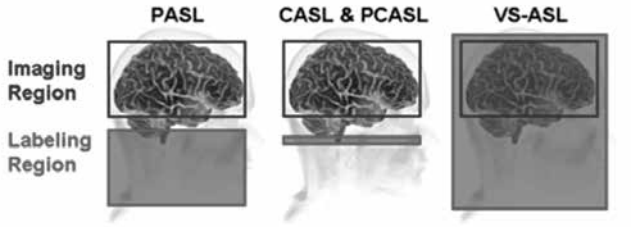

Figure 1. Tagging method for the acquisition of different arterial spin labeling (ASL) sequences. Pulsed ASL (PASL) inverts a great portion of spins (unmoving and moving) proximal to the imaging region. Continuous and pseudo-continuous ASL (CASL and pCASL) labels a narrow plane of spins continuously proximal to the imaging region. Velocity selective ASL (VS-ASL) selectively tags moving spins of a certain velocity to measure perfusion. Figure extracted from Huan *et al.*[45].

Address for correspondence: Tiago M. Guimarães. Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo. Av. Bandeirantes, 3900, 3º andar – 14048-900 – Ribeirão Preto, SP, Brazil. E-mail: t.guimaraes@icloud.com

PASL uses short (5-20 ms) radio-frequency (RF) pulses in a large plane proximal to the imaging region as the method of spin inversion. CASL uses long and continuous RF pulses (1-2 s) along with a constant gradient field to induce an inversion in a narrow plane of spins, usually applied at the base of the brain. pCASL was introduced to eliminate the CASL demand on hardware and reduce RF pulses. This technique uses a train of discrete RF pulses in combination with synchronous gradient fields to mimic CASL. VS-ASL selectively inverts spins based on blood velocity rather than spatial location. In comparison with the other techniques, pCASL has a higher efficiency, easier implementation, and less hardware overload[9].

ASL is a promising method to study brain metabolism non-invasively and without the need for radiotracers and, despite having been in use for some time in schizophrenia patients, no systematic reviews have been published to date on this topic. Our objective, therefore, was to make a systematic review of case-control studies that used ASL to compare resting-state rCBF patterns in patients with schizophrenia and healthy controls.

Methods

We performed a systematic search for case-control studies that compared resting-state rCBF in patients with schizophrenia and healthy controls. No limits of age, language or publication date were set for the searches, but articles describing interventions and assessing rCBF in conditions other than resting-state studies were excluded. Methods of rCBF quantification should be one of the ASL techniques listed above. Diagnostic criteria should be ICD-10, DSM IV/V or other validated method.

The articles to be included in the review were searched for in electronic databases (PubMed, PsycINFO, Web of Science, and Scopus) and through hand search of the reference lists of articles found in the databases. The last search was performed on June 10, 2015 by two of the authors using the search terms 'schizophrenia', 'arterial', 'spin', 'labeling'. No filters were applied in the searches. The process of article search and selection followed the guidelines proposed in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[10].

One reviewer assessed the eligibility of articles for inclusion in the review in an unblinded manner, that is, the title and abstract of all articles found using the search terms were read in order to apply the inclusion criteria, and articles pre-selected in this initial assessment were read in full to refine the selection process and exclude articles that failed to fulfill the inclusion criteria or include new ones from the reference lists of the articles reviewed. Another author used a data extraction table designed to collect data from the articles included, which was then checked by a third author for accuracy. The data extraction table included information on (1) characteristics of trial participants, (2) type of ASL, (3) type of MRI equipment and (4) rCBF outcomes.

The primary outcome of this review was the comparison of relative rCBF between patients and healthy controls, that is, the presence of increased or decreased rCBF in one group relative to the other. For the purpose of this review, the results presented in the articles were considered *convergent* if two or more studies obtained an identical outcome for the same region, and *divergent* if two or more studies obtained different outcomes for the same region. Superimposed regions were not considered. For example, if one study reported increased rCBF in the superior corona radiata and another one described the same result in the corona radiata as a whole, this was not considered a convergent result.

Results

General characteristics of reviewed articles

The process of article search and selection is summarized in Figure 2. As shown, 22 articles were excluded after examination of their titles and abstracts as they clearly did not meet the inclusion criteria of the review. The flow diagram also details the reasons for the exclusion of 5 of the 15 articles selected in the initial step.

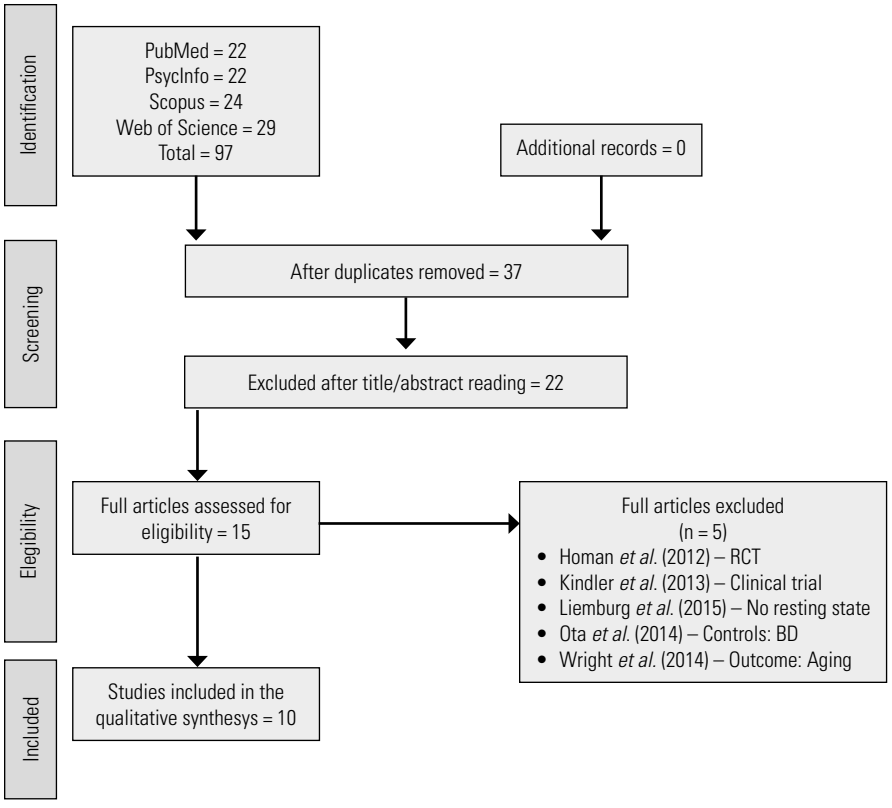

Figure 2. Flow diagram showing the procedure of article search and selection. RCT: randomized controlled trial; BD: bipolar affective disorder.

Among the articles included in the review, 10 were case-control studies published in English. Table 1 shows the main characteristics of the articles included in the review. All the studies used DSM-IV/V or ICD-10 criteria for diagnosis, except for the one by Pinkham *et al.*[11], who used the Diagnostic Interview for Genetic Studies. Homan *et al.*[12] investigated only one region of interest, the left superior temporal gyrus, in patients with medication-resistant auditory verbal hallucinations. All the other studies performed whole-brain analysis.

Outcomes

Convergent results

The main outcomes of the articles reviewed are summarized in Table 2. No qualitative distinctions were found between different ASL techniques. All the articles reported significant differences between schizophrenia patients and healthy controls, except for the one by Horn *et al.*[13], which was the only study to find no differences in rCBF between patients and controls (although the authors found a positive correlation between formal thought disorder and rCBF). It should be mentioned here that the study by Horn *et al.*[13] did not acquire images from superior regions of the brain because of technical limitations.

Divergent results

Divergent rCBF results were found in five regions of the brain. Of note, most of the divergent findings were described in the same study, by Scheef *et al.*[14] (see Table 3 for details).

Table 2. Convergent results in the articles reviewed. Increases or decreases in rCBF are relative to healthy controls

Brain region	↑CBF	↓CBF	Total of patients
ACC		Kindler *et al.* (2013) Scheef *et al.* (2010) Zhu *et al.* (2015)	145
CN		Kindler *et al.* (2013) Pinkham *et al.* (2015) Scheef *et al.* (2010)	77
FF		Kindler *et al.* (2013) Pinkham *et al.* (2015)	66
FL		Kindler *et al.* (2013) Scheef *et al.* (2010)	45
IFG		Pinkham *et al.* (2011) Pinkham *et al.* (2015)	62
LG		Kindler *et al.* (2013) Pinkham *et al.* (2011)	64
L_MFG		Pinkham *et al.* (2011) Zhu *et al.* (2015)	130
MOG		Pinkham *et al.* (2011) Pinkham *et al.* (2015) Zhu *et al.* (2015)	162
PL		Kindler *et al.* (2013) Scheef *et al.* (2010)	45
Put	Pinkham *et al.* (2011) Zhu *et al.* (2015)		130

ACC: anterior cingulate cortex; rCBF: regional cerebral blood flow; CN: cuneus; FF: fusiform gyrus; FL: frontal lobe; IFG: inferior frontal gyrus; LG: lingual gyrus; L_MFG: left middle frontal gyrus; MOG: middle occipital gyrus, PL: parietal lobe; Put: putamen.

Table 1. Characteristics of the articles included in the review

Study	ASL Technique - T	Patients (F/M)	Patients age (mean/SD)	Duration of illness	Age of onset	CLPZ Eq. - mg/day (mean/SD)	PANSS (mean/SD)
Homan *et al.* (2013)	pCASL 3T	11 (8/3)	37.1 (8.8)	na	23.3 (4.4)	714.5 (475.5)	67.1 (18.9)
Horn *et al.* (2009)	PASL 1,5T	13 (5/8)	29.6 (11.2)	2.79 (2.6)	na	556.2 (na)	63.9 (16.7)
Kindler *et al.* (2013)	pCASL 3T	34 (16/18)	41.5 (12.9)	na	na	518.9 (235.7)	75.5 (17.3)
Liu *et al.* (2012)	PASL 3T-	19 (8/11)	na	20.5 (10)	26 (8.9)	622.1 (418)	na
Ota *et al.* (2014)	pCASL 3T	36 (19/17)	37.9 (13)	16.8 (11.3)	na	604.8 (459.2)	61.8 (19.3)
Pinkham *et al.* (2011)	PASL 3T	30 (12/18)	35.7(10)	na	na	373.7 (333.4)	na
Pinkham *et al.* (2015)	pCASL 3T	16 (8/8) 16 (5/11)	38.5 (7.7) 38.8 (13.2)	na	na	332.2 (371.2) 350.5 (546.7)	32 (5.3) 25.1 (5.5)
Scheef *et al.* (2010)	CASL 3T	11 (3/8)	32 (5)	na	na	un	43.1 (8.5)
Walhter *et al.* (2011)	PASL 3T	11 (3/8)	35.3 (12.5)	8.9 (13.2)	na	442.5 (241)	54.2 (14.11)
Zhu *et al.* (2015)	pCASL 3T	100 (43/57)	33.6 (8.6)	10.2 (8.2)	na	453.2 (342.9)	71.3 (22.7)
n = 10	pCASL 3T (mode)	Total = 297 Mean = 29.7 Median = 24.5 SD = 26.7	Mean = 36 Median = 36.4 SD = 3.53			Mean = 496.86 Median = 486.05 SD = 127.9	Mean = 54.8 Median = 61.8 SD = 17.7

ASL: arterial spin labeling; CASL: continuous ASL; CLPZ Eq: chlorpromazine equivalents; F: female; ID: illness duration; M: male; na: not available; PASL: pulsed ASL; pCASL: pseudocontinuous ASL; SD: standard deviation; T: Tesla.

Table 3. Divergent results in the articles reviewed. Increases or decreases in rCBF are relative to healthy controls

Brain region	↑CBF	↓CBF
R_MTG	Pinkham *et al.* (2011) n = 30	Scheef *et al.* (2010) n = 11
L_MTG	Zhu *et al.* (2015) n = 100	Walther *et al.* (2011) n = 11
PHG	Scheef *et al.* (2010) n = 11	Walther *et al.* (2011) n = 11
PCN	Scheef *et al.* (2010) n = 11	Pinkham *et al.* (2011) n = 30
Th	Scheef *et al.* (2010) Zhu *et al.* (2015) n = 111	Liu *et al.* (2012) Walther *et al.* (2011) n = 30

rCBF: regional cerebral blood flow; R_MTG: right middle temporal gyrus; L_MTG: left middle temporal gyrus; PHG: parahipoccampal gyrus; PCN: precuneus; Th: thalamus.

Discussion

Taken together, the findings of our review lends support to the disputed hypothesis of hypofrontality in schizophrenia patients[15]. Convergent findings of decreased rCBF were reported in the frontal lobe (FL), left middle frontal gyrus (eMiFG), and inferior frontal gyrus (IFG). These regions are closely related to the regulation of complex behaviors that are impaired in schizophrenia[16]. Pinkham *et al.*[17] found a frontal region with increased rCBF, the right precentral gyrus, but no explanation was given for this finding and no other study in our review found similar results in this region or in any other frontal region.

The anterior cingulate (ACC) is responsible for the integration of cognitive and emotional processes in goal-directed activities. Clinically, these functions are impaired in schizophrenia patients. Convergent results of decreased rCBF in the ACC are consistent with clinical observations and other imaging studies[18].

The occipital lobe is host to both the primary visual area and the visual association area. Deficits in early-stage visual processing have been repeatedly reported in schizophrenia patients[19] and visual hallucinations seem to be associated with dysfunctions in this region[20]. Our review found convergent results regarding the rCBF in three important sub regions of the occipital lobe; the lingual gyrus, cuneus and middle occipital gyrus.

The fusiform gyrus (FF) is an occipitotemporal brain region thought to subserve the processing and encoding of facial stimuli. Several studies have reported that schizophrenia patients show deficits in facial processing[21]. It has been hypothesized that the FF might be the central brain region underlying abnormal facial recognition in schizophrenia[22]. The studies reviewed here provided convergent results of decreased rCBF in the FF, in support to this hypothesis.

Convergent results of decreased rCBF were also found in the parietal lobe, a region that is recruited when one views one's own body compared with a familiar body and which stores representations of the self-face as part of one's awareness of the self-body; in sum, this region supports the ability for self-other discrimination[23,24]. The parietal lobe contains mirror neurons and maintains self-other distinction during empathic interpersonal face-to-face interactions. Studies on self-face processing in schizophrenia have provided mixed results to date[25,26], but our review points to the existence of impairments related to this region.

There is substantial evidence in the literature of abnormal basal ganglia activity in subjects with schizophrenia[27]. The basal ganglia include the following nuclei: caudate nucleus, putamen, nucleus accumbens, globus pallidus, subthalamic nucleus, and the mesencephalic nuclei of the substantia nigra and ventral tegmental area. Through extensive cortical connections, these nuclei are implicated in motor and cognitive functions[28]. For example, affective flattening has been correlated with anterior putamen abnormalities in non-medicated patients[29]. Our finding of increased rCBF in the putamen is in line with the results of studies using other neuroimaging methods and is probably a consequence of antipsychotic use[30].

The middle temporal gyrus (MTG) is involved in several cognitive processes, including language and semantic memory processing, and multimodal sensory integration[31]. Functional deficits in these domains have been reported in schizophrenia, and it appears reasonable to assume therefore that the MTG plays an important role in the physiopathology of schizophrenia[32,33]. However, it is not yet clear whether rCBF in this region is increased or decreased in patients[6]. Among the articles included in our review, Pinkham *et al.*[17] (N = 30) reported increased rCBF in the right MTG in schizophrenia, whereas Scheef *et al.*[14] (N = 11), the only study with unmedicated patients, found decreased rCBF in patients relative to controls. The assumption of an antipsychotic effect to explain these differences is tempting, but the answer remains elusive. Zhu *et al.*[34] (N = 100) found increased rCBF in the left MTG, in contrast with Walther *et al.*[35] (N = 11), who described a decrease in patients. It is possible that increased rCBF in the MTG of schizophrenia patients reflects greater effort to integrate various sensory cues, even passively while at rest. Alternatively, it is also possible that increased rCBF in this region may be related to treatment with antipsychotic medications. The evidence available to date is insufficient to answer these questions.

The parahippocampus is a component of the hippocampal formation, and a key structure for declarative memory[36]. Impaired parahippocampal recruitment during visual-memory encoding has been reported in patients and their siblings[37]. In our review, two small studies with the same sample size found divergent results in this region: while Scheef *et al.*[14] (N = 11) described increased rCBF in this brain region, Walther *et al.*[35] (N = 11) found precisely the opposite. Again, evidence is not enough to determine the rCBF patterns in the parahippocampus of patients with schizophrenia.

The precuneus is located in the posteromedial portion of the parietal lobe and has important connections with the prefrontal cortex, ACC, and many other areas. It is believed to play a central role in the neural network supporting the mental representation of the self[38]. It has also been hypothesized that the precuneus is part of a few highly-connected regions playing a central role in the global topology of the brain network. Studies have shown that functions mediated by the precuneus are impaired in schizophrenia[39]. Scheef *et al.*[14] (N = 11) reported increased rCBF in the precuneus of patients, which is in contrast with Pinkham *et al.*[17] (N = 30). The divergent data available make it impossible to determine rCBF patterns in the precuneus of patients with schizophrenia.

The thalamus is an important region in the bidirectional flow of neuronal signals between cortical and subcortical regions; and it also links different cortical regions via transthalamic pathways[40]. Many studies report a variety of thalamic alterations in schizophrenia, but few have offered consistent findings[41]. Our review showed divergent results regarding the rCBF in the thalamus in schizophrenia, but the studies that found increased rCBF (Scheef *et al.*[14] and Zhu *et al.*[34]), assessed a total of 111 patients against 30 patients assessed by Liu *et al.*[42] and Walther *et al.*[35] The evidence of increased rCBF in the thalamus of schizophrenia patients receives further support from a PET study[43], but the discrepancies should be addressed by future research.

Conclusions

Our review has some limitations that should be taken into account by the reader. First, the qualitative approach for data extraction reduces the strength of our analyses, as our findings could not be the object of statistical treatment. Also, corrections for age, symptomatology, age of onset, illness duration or medication use were not performed. Moreover, schizophrenia research has a few intrinsic limitations related to highly heterogeneity of the disorder, different etiological factors, and the fact that almost every patient is on antipsychotics and recruitment of large samples is a challenge, especially for neuroimaging investigations.

Despite these limitations, the results of our review highlight the differences in the brain metabolism of schizophrenia patients compared to healthy controls and suggest that ASL is a valid and reliable tool for investigations on the neural underpinnings of the disorder. Our findings are consistent with those of previous studies and lend support to the hipofrontality hypothesis at the same time that they are harmonic with the disconnection hypothesis[44] of schizophrenia.

The next logical step for future reviews would thus be a quantitative analysis (meta-analysis) of raw rCBF data, and studies involving larger samples than the ones performed to date will be central for solid conclusions to be reached about the patterns of rCBF in schizophrenia.

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