PART II
QUANTITATIVE MRI BIOMARKERS
QUANTITATIVE ASSESSMENT OF BRAIN IRON BY R2* RELAXOMETRY IN PATIENTS WITH CLINICALLY ISOLATED SYNDROME AND RELAPSING–REMITTING MULTIPLE SCLEROSIS

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ABSTRACT

BACKGROUND: Increased iron deposition has been implicated in the pathophysiology of multiple sclerosis (MS), based on visual analysis of signal reduction on T2-weighted images. R2* relaxometry allows to assess brain iron accumulation quantitatively.

OBJECTIVE: To investigate regional brain iron deposition in patients with a clinically isolated syndrome (CIS) or relapsing–remitting MS (RRMS) and its associations with demographical, clinical, and conventional magnetic resonance imaging (MRI) parameters.

METHODS: We studied 69 patients (CIS, n = 32; RRMS, n = 37) with 3T MRI and analyzed regional R2* relaxation rates and their correlations with age, disease duration, disability, T2 lesion load, and normalized brain volumes.

RESULTS: Basal ganglia R2* relaxation rates increased in parallel with age ($r = 0.3–0.6; P < 0.01$) and were significantly higher in RRMS than in CIS ($P < 0.05$). Using multivariate linear regression analysis, the rate of putaminal iron deposition was independently predicted by the patients’ age, disease duration, and gray matter atrophy.

CONCLUSIONS: Quantitative assessment by R2* relaxometry suggests increased iron deposition in the basal ganglia of MS patients, which is associated with disease duration and brain atrophy. This technique together with long-term follow-up thus appears suited to clarify whether regional iron accumulation contributes to MS morbidity or merely reflects an epiphenomenon.
INTRODUCTION

With normal aging, regions of the brain, particularly the basal ganglia, tend to accumulate nonhemin iron, primarily in the form of ferritin. Ferritin is a storage protein that contains up to 5000 ferric (Fe3+) ions and does not cross the blood–brain barrier. Abnormal iron deposition in the brain has been implicated in the pathophysiology of various neurodegenerative CNS disorders (Bartzokis, et al. 2004). Although iron is essential for normal neuronal metabolism, excessive iron levels can exert neurotoxic effects by the formation of free radicals (Campbell, et al. 2001, Gutteridge. 1992). From several observations, excessive iron deposition has also been proposed to play a role in multiple sclerosis (MS). Drayer (Drayer, et al. 1987) and Grimaud (Grimaud, et al. 1995) were the first to report on a regionally specific signal reduction on T2-weighted brain magnetic resonance imaging (MRI) images in MS, which was believed to indicate increased iron deposition. Bakshi et al. analyzed in more detail the frequency, location, and clinical significance of T2 shortening in a larger cohort of MS patients (Bakshi, et al. 2000). In this study, T2 hypointensity was found to be more pronounced in the thalamus, putamen, caudate nuclei, and in the rolandic cortex, and moreover to be associated with advanced disability. Further studies of this group, linked gray matter T2 shortening to brain atrophy (Bakshi, et al. 2001, Bakshi, et al. 2002) and cognitive impairment (Brass, et al. 2006). The authors also suggested that gray matter T2 shortening predicted the evolution of brain atrophy in untreated relapsing–remitting MS (RRMS) patients (Bermel, et al. 2005). Altogether, these data give further credence to a possible pathophysiologic role of iron in MS. Although early investigations in this direction suffered from the methodological drawback of deducing iron concentrations from a visual grading of the reduction of signal intensity on T2-weighted images, more recent studies have documented the extent of T2 hypointensity in a quantitative manner (Bermel, et al. 2005, Brass, et al. 2006, Tjoa, et al. 2005). The use of specific MRI sequences at higher (≥3T) field strengths may serve to further increase the sensitivity of depicting iron-related signal changes in the brain. This comes from the fact that the very densely packed ferric ions that are present in ferritin cause local changes of the magnetic susceptibility (Haacke, et al. 2005, Schenck. 2003). As a consequence, the water molecules surrounding the ferritin core experience a higher magnetic field and, thus, a shortening of the relaxation times when diffusing through the local field gradients. These effects become increasingly apparent with higher field strengths. Also, iron is detectable especially when it provokes a paramagnetic effect occurring with a mineralized state such as in the form of ferritin and hemosiderin. Current approaches to assess brain iron in a more quantitative manner are, therefore, based either on susceptometry or on relaxation time mapping, or they focus on a combined approach such as the magnetic field correlation (MFC) technique (Stankiewicz, et al. 2007).

$R^*_{2}$ relaxation rate mapping is among the interesting candidates for iron mapping. On the basis of a gradient echo sequence with multiple echoes, this technique is readily available on modern MRI scanners. Provided a reasonable number of echoes and adequate handling of macroscopic susceptibility effects, robust $R^*_{2}$ maps can be obtained within a clinically acceptable acquisition time. We therefore decided to use this technique in a larger series of patients with a clinically isolated syndrome (CIS) or RRMS to search for differences in regional brain iron concentrations and to use it to reassess the suggested associations of iron deposition with clinical and morphologic features of the disease.
PATIENTS AND METHODS

Study participants were prospectively enrolled from our MS outpatient department. Inclusion criteria were a diagnosis of a CIS (Miller, et al. 2008) or of a RRMS (Polman, et al. 2005), regular follow-up visits and the patients’ willingness, capacity and consent to undergo detailed clinical testing, and a comprehensive 3T MRI examination. Demographical and clinical data recorded included age, gender, age at disease onset, disease duration, and treatment. Disability was measured with the Expanded Disability Status Scale (EDSS) (Kurtzke. 1983). From the documented relapses, we calculated the annualized relapse rate as a measure of clinical disease activity. Relapses were defined as the appearance or reappearance of at least one neurological symptom or as the worsening of an old symptom attributed to MS that lasted for at least 24 h and was preceded by a relatively stable or improving neurological state of at least 30 days.

In all, 32 patients with a CIS and 37 with RRMS fulfilled these criteria and contributed to the analysis (for demographical and clinical data, see Table 1). A total of 6 CIS patients received interferon-β therapy. Of the 21 treated RRMS patients, 14 received interferon-β, 4 glatiramer acetate, 2 natalizumab, and 1 intravenous immunoglobulins.

Magnetic resonance imaging

Patients underwent MRI on a 3 Tesla system (Siemens Tim Trio, Siemens Medical Systems, Erlangen, Germany) using a 12-element receiver coil. Structural imaging included a fast Fluid attenuated inversion recovery (FLAIR) sequence (TR/TE/TI = 9000/70 ms/2500 ms, in plane resolution = 0.9 × 0.9 mm², slice thickness = 3 mm) and a T1-weighted 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence with 1 mm isotropic resolution (TR/TE/TI/FA = 1.9 s/2.19 ms/0.9s/9°). For R2* mapping, a spoiled 3D Fast Low Angle Shot (FLASH) sequence (TR/FA = 86 ms/20°) with 12 equally spaced echoes (bipolar readout gradient with echo spacing of 4.92 ms, in plane resolution = 0.9 × 0.9 mm², slice thickness = 4 mm, whole brain coverage) was used.

Image analysis

All image analyses were performed by trained and experienced technicians and interpreters, blinded to clinical information.

<table>
<thead>
<tr>
<th>Table 1. Clinical and demographical data</th>
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</thead>
<tbody>
<tr>
<td>All patients</td>
</tr>
<tr>
<td>N (percent female)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Age at disease onset (years)</td>
</tr>
<tr>
<td>Disease duration (years)</td>
</tr>
<tr>
<td>Annualized relapse rate</td>
</tr>
<tr>
<td>EDSS</td>
</tr>
<tr>
<td>N treated patients (percent)</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; RRMS, relapsing–remitting multiple sclerosis; N, number of patients; n.s., statistically not significant (P > 0.05); NA, not applicable; EDSS, Expanded Disability Status Scale (Kurtzke. 1983).

*Median (interquartile range).
Regional $R2^*$ mapping
To eliminate image shifts caused by the bipolar data acquisition, all subsequent echoes provided by the FLASH sequence were registered with the first echo. Then, $R2^*$ maps were calculated voxelwise by fitting a single exponential decay curve and by considering the contribution of non-Gaussian image noise with a least square approach proposed by St Pierre (St Pierre, 2003) and described in detail by St Pierre et al. (St Pierre, et al. 2004) and He et al. (He, et al. 2008).

On the basis of high-resolution MPRAGE scan, seven deep gray matter structures (thalamus, caudate nuclei, putamen, pallidum, hippocampus, amygdale, and nucleus accumbens) and the brainstem were segmented fully automatically for all subjects using FIRST, which is a segmentation and registration algorithm based on deformable models from FSL (Smith, et al. 2004). The resulting masks of these structures were eroded by 1 pixel to avoid overlapping with adjacent regions and used to define these regions in the fit $R2^*$ data sets. Then, mean $R2^*$ values and standard deviations were calculated for each structure by masking the $R2^*$ maps and by averaging the values from both hemispheres. A representative $R2^*$ map of the putamen, based on a 3T MRI is shown in Figure 1.

Atrophy

Figure 1. $R2^*$ mapping. The first echo of the multiecho FLASH series and the corresponding $R2^*$ map (overlay) is shown. The higher $R2^*$ in the putamen reflects a higher iron load.
image to determine the registration scaling); this is done primarily to obtain the volumetric scaling factor to be used as normalization for head size. Next, tissue type segmentation with partial volume estimation is carried out (Zhang, et al. 2001) to calculate the total volume of brain tissue (including separate estimates of volumes of gray matter, white matter, peripheral gray matter, and ventricular CSF).

Lesion load
MS lesions were outlined on a transparency overlaid on hard copies of the FLAIR sequence. Using these templates, lesion masks were then created using the DISPImage programme (Plummer, 1992). The lesion load was calculated by multiplying the area of all masks by the slice thickness.

Statistical analysis
Statistical analyses were performed using SPSS 15.0 (SPSS Inc., Chicago, Illinois, USA). Distribution of data was tested by the Kolmogorov–Smirnov test. Comparisons between groups were performed by Mann–Whitney U test or t test according to the statistical distribution of the data. In the combined patient groups, Spearman and Pearson correlations were performed to calculate the correlation coefficients between the imaging and the clinical data. Multivariate linear regression models were applied to identify the factors predicting R2* changes and volumetric data. All regression models were controlled for age.

RESULTS
Automatic measurement of R2* in seven deep and cortical gray matter structures and the brainstem in our cohort yielded no significant difference between the left versus the right hemispheric R2* rates in the respective brain regions. The mean and standard deviations of averaged values for both hemispheres are given in Table 2. As can be seen, there was evidence for a significantly higher iron accumulation in the basal ganglia, including putamen, pallidum, and caudate nuclei, in patients with RRMS compared to those with a CIS (Table 2).

Because of evidence that iron deposition may be more extensive in men than in premenopausal women of comparable age, we also performed separate analyses for both sexes. The results showed higher R2* values in the basal ganglia of both male and female

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>CIS</th>
<th>RRMS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pallidum</td>
<td>34.2 (2.8)</td>
<td>33.0 (2.9)</td>
<td>35.2 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Putamen</td>
<td>26.0 (3.1)</td>
<td>24.7 (2.7)</td>
<td>27.2 (3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Caudate nuclei</td>
<td>24.6 (2.9)</td>
<td>23.6 (2.7)</td>
<td>25.4 (2.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Thalamus</td>
<td>20.5 (1.1)</td>
<td>20.3 (1.3)</td>
<td>20.6 (1.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Amygdala</td>
<td>32.8 (9.1)</td>
<td>34.6 (9.7)</td>
<td>31.3 (8.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>42.9 (11.2)</td>
<td>43.3 (11.3)</td>
<td>42.6 (11.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>24.2 (4.9)</td>
<td>24.9 (5.7)</td>
<td>23.6 (4.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Brain stem</td>
<td>21.2 (5.0)</td>
<td>22.1 (5.8)</td>
<td>20.5 (4.2)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; RRMS, relapsing–remitting multiple sclerosis; n.s., statistically not significant (P > 0.05). R2* rates [s^-1] are given as mean (standard deviation).
patients with RRMS compared to those with CIS (data not shown) but more robust differences in males. Given the relatively small patient numbers for these sub-analyses, this finding will have to be confirmed in a larger patient cohort. No significant differences were seen in the other brain regions analyzed.

CIS and RRMS patients differed regarding other MRI metrics (Table 3) including lesion load and several measures of brain atrophy (whole brain, whole gray matter, and cortex and ventricular volumes). As expected, T2 lesion volume and brain atrophy were significantly more pronounced in RRMS compared to CIS patients (Table 3). No significant differences between CIS and RRMS were found in regard to white matter atrophy.

When assessing correlations of R2* relaxation rates with demographic and clinical variables of both patient groups combined, we found a strong increase with age. This effect was most apparent in the putamen (r = 0.6; P < 0.001) (Figure 2), globus pallidus (r = 0.5; P < 0.001), and the caudate nuclei (r = 0.3; P < 0.01). Longer disease duration correlated with higher iron levels in the putamen (r = 0.5; P < 0.001), globus pallidus (r = 0.4; P < 0.001), and the caudate nuclei (r = 0.3; P < 0.005). No significant correlations were found between the EDSS and the R2* relaxation rates.

Volumes of whole brain, whole gray matter, and cortex correlated negatively with R2* relaxation rates in the putamen (r = −0.5 to −0.6; P < 0.001), globus pallidus (r = −0.5 to −0.6; P < 0.001), and the caudate nuclei (r = −0.6; P < 0.001). No significant differences were found in the other brain regions analyzed.

**Table 3. Morphological data**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>CIS</th>
<th>RRMS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain volume</td>
<td>1604.2 (87.9)</td>
<td>1643.7 (66.3)</td>
<td>1571.1 (90.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gray matter volume</td>
<td>851.9 (73.7)</td>
<td>883.4 (50.5)</td>
<td>825.4 (80.1)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Cortex volume</td>
<td>697.0 (57.5)</td>
<td>724.2 (44.8)</td>
<td>674.2 (57.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White matter volume</td>
<td>752.3 (49.6)</td>
<td>760.3 (56.0)</td>
<td>745.6 (43.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Ventricular volume</td>
<td>371.9 (21.8)</td>
<td>28.0 (14.0)</td>
<td>44.8 (24.2)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Lesion load</td>
<td>10.0 (3.0-24.0)</td>
<td>4.1 (1.9-11.8)</td>
<td>17.6 (7.3-31.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CIS, clinically isolated syndrome; RRMS, relapsing–remitting MS; n.s., statistically not significant (P > 0.05). Values [cm³] are given as mean (standard deviation) or as ‘median (interquartile range).
P < 0.001), and the caudate nuclei (r = −0.3; P < 0.05) while ventricular volumes correlated positively with R2* relaxometry measures in the putamen (r = 0.5; P < 0.001), globus pallidus (r = 0.4; P < 0.005), and the caudate nuclei (r = 0.3; P < 0.05). Figure 3 shows the correlation of putaminal iron levels with gray matter atrophy (r = −0.6; P < 0.001). Increased lesion load was associated with higher R2* relaxation rates in the putamen (r = 0.4; P = 0.001) and globus pallidus (r = 0.5; P < 0.001).

Using a multivariate linear regression model, putaminal R2* relaxation rates were independently predicted by age, disease duration, and gray matter atrophy (Table 4). EDSS and the annualized relapse rate did not enter this model. Accordingly, when assessing predictors of gray matter atrophy, we used linear regression analysis to identify lesion load and iron deposition in the putamen as independent variables (Table 4).

![Figure 3. Graph showing the correlation of putaminal R2* relaxation rates with whole gray matter atrophy. Reduced gray matter volumes are associated with higher putaminal iron levels measured by R2* relaxometry (r = −0.6; P < 0.001).](image)

**Table 4. Multivariate linear regression model**

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Independent variable</th>
<th>Beta</th>
<th>Rho</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R2* putamen</td>
<td>age (years)</td>
<td>0.4</td>
<td>0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Disease duration (years)</td>
<td>0.2</td>
<td>0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Gray matter volume cm³</td>
<td>-0.3</td>
<td>-0.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Lesion load cm³</td>
<td>-0.0</td>
<td>0.3</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

| Gray matter volume cm³ | age (years) | -0.2 | -0.5 | n.s.          |
|                        | R2* putamen  | -0.3 | -0.6 | <0.05         |
|                        | Disease duration (years) | -0.2 | -0.5 | n.s.          |
|                        | Lesion load cm³ | -0.3 | -0.5 | <0.05         |

All multivariate linear regression models were controlled for age. R2* in the putamen was independently predicted by disease duration and gray matter atrophy. R2* putamen and lesion load were identified as independent factors predicting gray matter atrophy; n.s., statistically not significant.
DISCUSSION

This study provides a strong quantitative confirmation of earlier reports on increased iron levels with advancing stages of MS (Bakshi, et al. 2002, Drayer, et al. 1987, Ge, et al. 2007, Hammond, et al. 2008). R2* relaxation rates in the putamen, globus pallidus, and the caudate nuclei were significantly increased in RRMS compared to CIS. Furthermore, disease duration was identified as an independent predictor of the extent of putaminal iron accumulation. This is in line with earlier studies that estimated brain iron levels from visual interpretation of the T2 signal reduction (Bakshi, et al. 2000) and with a most recent investigation performed at 7T (Hammond, et al. 2008). In this investigation, high resolution gradient-echo phase images for quantification of local field shifts were used to show pathologically increased iron deposition in the basal ganglia of MS patients, which was associated with disease duration (Hammond, et al. 2008). Because our patients’ R2* relaxation rates were not compared with those of healthy individuals, we cannot rule out that the R2* relaxation rates in brain regions with no significant differences between CIS and RRMS are increased in MS patients. This needs to be investigated further.

Another major finding is the link between iron deposition and brain atrophy, which has been suggested earlier by correlations between T2 hypointensity and brain atrophy (Bakshi, et al. 2001, Bakshi, et al. 2001, Bakshi, et al. 2002, Bermel, et al. 2005) and which is now corroborated by our quantitative R2* measurements. In this context, it is important to note that local R2* changes do not only reflect changes in brain iron load. Other sources of local magnetic field gradients, for example, a higher density of venules or macroscopic susceptibility effects such as those observed at air-tissue boundaries, may also increase the apparent R2* rate. However, provided appropriate shimming, R2* can be expected to scale with the paramagnetic effect of highly ordered ferric ions (Yao, et al. 2009). R2* is the fastest transverse relaxation rate and is the sum of R2’ and R2. R2’ arises from the transverse relaxation mechanisms that reflect the reversible signal loss associated with the local field inhomogeneities while R2 reflects the non-reversible relaxation effects. Therefore, R2’ is assumed to be the most sensitive relaxation parameter for iron deposition (Gelman, et al. 1999). However, R2’ mapping would require simultaneous mapping of R2* and R2. The assessment of R2 with a multiecho spin-echo sequence is time consuming and it is also limited by the specific absorption rate at 3 Tesla. Therefore, in this study, we used a gradient echo approach that allows fast whole brain R2* mapping in only a few minutes. In addition, fitting a single exponential decay function into 12 echoes enables a robust estimation of T2*.

Our quantitative approach identified age as an important factor of iron accumulation in the deep gray matter nuclei, especially the basal ganglia. This highlights the importance of considering age as a covariate in analyses of cerebral iron accumulation. In this context, it should be emphasized that, in our cohort, age was not significantly different between CIS and RRMS patients.

The exact underlying pathophysiological mechanism(s) leading to increased iron deposition in the deep gray matter areas and the implications of this finding are still a matter of debate. Iron deposits have been described in macrophages and reactive microglia of MS brain tissue (LeVine. 1997), and increased CSF ferritin levels were reported in patients with progressive MS (LeVine, et al. 1999). Increased iron levels can exert toxic effects by the formation of free radicals (Gutteridge. 1992) and may subsequently lead to neurodegeneration (Campbell, et al. 2001).
Earlier reports described a relation between lesion volume and brain iron deposition based on iron detection by T2 hypointensities (Bakshi, et al. 2001) and MFC (Ge, et al. 2007). In contrast to these studies, we could not identify T2 lesion volume as an independent factor influencing R2* relaxometry rates although a significant linear correlation between R2* relaxation rates in the putamen as well as globus pallidus and T2 lesion volume was present.

We identified increased gray matter atrophy as an independent predictor of putaminal R2* relaxation rates indicative of higher amounts of iron. Such an association was not found in respect to white matter atrophy. This suggests iron deposition to be related to the degenerative rather than the inflammatory components of MS, although one might also argue that a potential impact of cortical lesions was not sufficiently assessed with the applied techniques. From pathological data, however, we do not expect a high rate of cortical lesions in the investigated cohort.

MRI T2 hypointensities of deep gray matter areas have previously been associated with advanced neurological disability (Bakshi, et al. 2000, Bakshi, et al. 2002, Tjoa, et al. 2005). In the currently published study by Hammond et al. local field shifts from iron at 7T did not correlate with advanced disability (Hammond, et al. 2008). These findings are in line with the results of the current study where R2* rates were not significantly associated with the EDSS. However, this does not necessarily contradict earlier findings, as we studied patients within a very small range of lower EDSS scores. Also, the deep gray matter nuclei may not be the most sensitive region for assessing correlations of iron deposition with disability. For this purpose, cortical measurements would be preferable but they are problematic for R2* mapping due to macroscopic field gradients that occur at transitions between tissues with different magnetic susceptibility. As increased iron deposition has previously been linked to impaired cognitive performance (Brass, et al. 2006, Ge, et al. 2007), further studies are needed to investigate whether brain iron levels estimated by the current approach are related to cognitive impairment in MS patients.

Unfortunately, our study cannot serve to clarify whether the excess of iron in gray matter areas is a primary cause of tissue damage and neurodegeneration or merely an epiphenomenon of pathophysiological processes occurring during the progression of MS (Stankiewicz, et al. 2007). Nevertheless, our multiregional analysis indicates that iron accumulation with increasing MS duration does not occur in a diffuse manner but that the basal ganglia appear to be preferentially affected. Considering that the corticospinal tract traverses the basal ganglia, it is tempting to speculate that increasing rates of iron deposition could ultimately contribute to the chronic progressive phase of MS. The strong correlation between R2* relaxation rates and age – apparently also a crucial factor for the onset of chronic progression – and the observed correlations with gray matter atrophy may support this hypothesis. Clearly, this will require long-term follow-up studies and a more detailed regional analysis. As we have demonstrated, the R2* relaxation technique can be a useful tool for such investigations.
REFERENCES


