SWI filtered phase images demonstrate that tissue iron in the midbrain correlates with local capillary density

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Introduction: Iron plays a key role in many neurological processes in the brain and in neuro-degenerative disease. We have observed that the filtered phase images in susceptibility weighted imaging (SWI) correlate well with the vascular content of a number of structures in the midbrain. The goal of this work is to demonstrate that the SWI phase (1) corresponds to the local non-heme iron content and not the local venous blood supply.

Materials and methods: SWI images were collected at 1.5T using a fully flow compensated, 3D, gradient echo sequence. The normal acquisition parameters are used: in-plane resolution 0.5mm x 1.0mm; TH = 2mm, FOV = 256mm x 256mm; Nx = 512; Ny = 256; Nz = 48; TE = 40ms; TR = 57ms; FA = 20 degrees. The phase images are high pass filtered. A series of 75 subjects were evaluated for an Alzheimer's study (informed consent was obtained in all cases). The area around the substantia nigra and red nucleus was evaluated over 4 to 5 slices. Five to six slices were evaluated for susceptibility changes based on iron concentration. Results from each slice were then compared to the recent brainstem cadaver analysis by Duvernoy (2). In his work, he presents results from India ink stained cadaver brains over 2mm to 3mm thick slices. To test the hypothesis that the phase values obtained were not due to heme-iron in venous blood (veins or venules), two volunteers were scanned pre and post ingestion of caffeine (a single 200mg NoDoz pill of caffeine) at 4T. The sequence was the same as that described above except that TR = 29, TE = 15, and Ny = 512.

Results: We found that the pattern of capillary density shown in Duvernoy's work (2) is duplicated in the SWI phase images. An example of this one-to-one mapping is shown in Figure 1 for one of the 5 or 6 slices. The red nucleus is seen to contain two regions, a highly vascularized horseshoe area and a central gray matter area, in agreement with Fig.2. The small long dark lines in the crus cerebri are connecting tissue from the substantia nigra. This anatomy changes from 2 mm slice to 2 mm slice and those details would not be evident in thicker slices. The local changes in phase correlate with the darkening patterns in Duvernoy's work (2). Further, we have also seen the connecting pathway, referred to as the fascicula nigrale, that may transport iron between the substantia nigra and globus pallidus. Post caffeine, these images look identical although phase changes in the veins are clearly seen. No changes in intensity in these basal ganglia structures were seen, implying that the source of signal is non-heme iron.

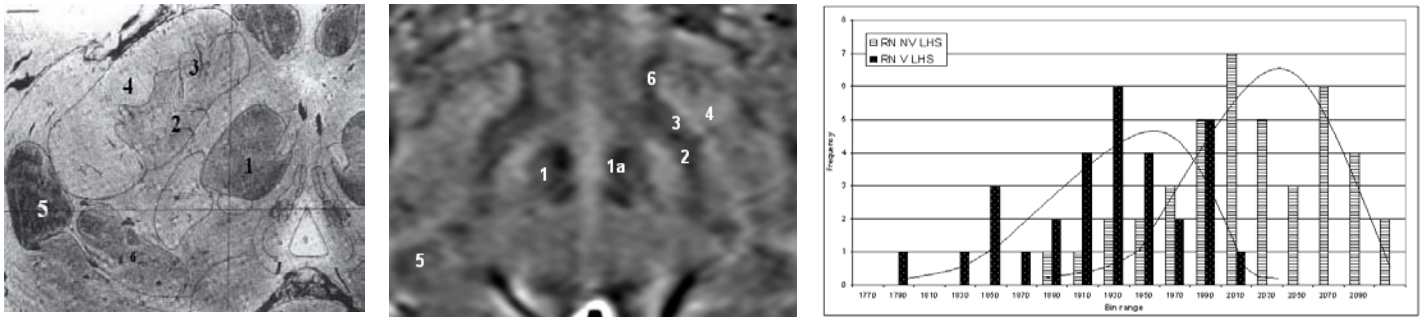

Figure 1: Left hand image: India ink stained cadaver brain. Middle image: Phase image from a normal volunteer. The regions demarcated by numbers are as follows: 1 – the red nucleus, non-vascularized part, 1a – red nucleus, vascularized part, 2 – substantia nigra pars compacta, 3 – substantia nigra pars reticulata; 4 – crus cerebri, 5 – medial geniculate, 6 – Fasicula nigrale connecting the globus pallidus and substantia nigra. The histogram on the right shows the distribution of phase values depending on the region whether the vascularized part (dark dotted) or non-vascularized part (white striped) of the red nucleus. The vascularized part is seen to be significantly shifted to the left (higher iron content) than the non-vascularized part. The error in the means is only 4 phase units while the difference between the mean of the phases is roughly 90 units.

Discussion and Conclusion: The match between the structures shown in the SWI phase filtered images and Duvernoy's work suggests that there is a correspondence between iron, and vascular density. The question then is: "Is the correspondence coming from the fact that the phase behavior is induced by the heme-iron? Or is it because there is iron associated with vessels via the vessel wall or structural elements associated with the vessels themselves?" To answer either question, we needed first to rule out that the signal is a blood oxygen saturation effect (BOLD) from the de-oxygenated blood. This was done by changing the BOLD effect using caffeine and noting that there were no changes in the phase. On the other hand, the India ink staining of Duvernoy's work is used to indicate vascular density. The answer can be validated with a careful histological analysis of human cadaver brains (3). Staining of the brain with Perl's staining and diaminobenzidine intensification indicate that the neuropils associated with both large and small vessels in basal ganglia have iron (3). In fact, some of the iron conglomerates in the neuropils have been shown to be spherical in nature and as large as 0.5 mm in diameter (3). This information supports our hypothesis that there is non-heme iron associated with blood vessels that lead to the contrast seen in SWI phase images. The ability to map this type of iron in the human brain may prove to be a new means to map brain iron associated with vessels and may prove useful in the identification and longitudinal follow-up of patients with neuro-degenerative disease. It may also be a means to follow patho-physiologic changes in iron and identify certain pathways in iron distribution that are still not understood to this day.

References:

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