Seminar paper

Cognitive and brain science

Iron, Lipid & R1 correlation

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Abstract

Quantitative magnetic resonance imaging (qMRI) provides biophysical parametric measurements allowing for noninvasive mapping of the aging human brain. One of the qMRI parameter is T1, longitudinal relaxation time, the time constant which determines the rate at which excited protons return to equilibrium. The literature indicates that lipids have strongly affect the contrast of brain qMRI maps. The iron content and water fraction (WF) of cellular compartments are also known as influence the qMRI parameters. There have been a few quantitative attempts to find a relationship between lipid content and T1. Additionally, it is unclear how much iron content contributes to T1 tissue contrast. In this research, we aim to find the best describes the relationship between iron and lipid to R1.

Introduction

Advances in the field of magnetic resonance imaging (MRI) have led to the development of quantitative MRI (qMRI). qMRI provides biophysical parametric measurements that are useful in the investigation and diagnosis of normal and abnormal aging (Callaghan, et al., 2014; Yeatman, Wandell & Mezer, 2016; Gracien et al., 2017).

qMRI is aimed at the direct measurement of the physical tissue properties.
Tissue can be characterized by two different relaxation times - T1 and T2. T1 (longitudinal relaxation time) is the time constant which determines the rate at which excited protons return to equilibrium. In this study we will focus on the longitudinal relaxation rate (R1=1/T1). It is a measure of the time taken for spinning protons to realign with the external magnetic field. (Neurology, 2016).

qMRI enables the creation of parametric maps which allows a reliable comparison of brain structure across different time points and different MRI scanners, making it possible to assess normal brain development, as well as pathological conditions.

The human brain is comprised mainly of water (70–80%), proteins (8–11%) and lipids (5 15%) (add ref). The distribution of these molecules varies between brain regions, across lifespan, and in different pathological states. Lipids are known to strongly affect the contrast of brain qMRI maps. (Shtangel & Mezer, 2020)

Iron is an important metal involved in various physiological processes, such as ATP generation and DNA replication (Chang, 2019; Mills et al., 2010; Qian & Ke, 2019).

Particularly, iron is essential for a variety of neurological processes (McCarthy & Kosman, 2015; Rouault, 2013). Iron transport in the brain is effectuated by several pathways; namely, transferrin-dependent iron transport, non-transferrin bound iron (NTBI) mobilization, uptake and export by and from neurons, oligodendrocytes, astrocytes, and microglia (Hohnholt & Dringen, 2013; Roy Sarkar & Dutta, 2019). Furthermore, Ferritin is the main iron storage protein, conformed by two types of subunits, H type (heavy) and L type (light), which co-assemble into a supramolecular spherical-shaped protein (Chang, 2019). The iron content and water fraction (WF) of cellular compartments are thought to influence the qMRI parameters (Shtangel & Mezer, 2020).

There have been a few quantitative attempts to find a relationship between lipid content and T1 (Bot et al., 2004; Mottershead et al., 2003; Schmierer et al., 2004). Due to restricts in conventional imaging techniques in directly measuring the lipids concentration, the relationship between T1 and lipids remain vogue. Additionally, it is unclear how much iron content contributes to T1 tissue contrast (Gelman et al., 2001). The literature regarding iron and T1 contrast is controversial: data showing a clear relationship between brain T1 and iron concentration (Ogg and Steen, 1998; Vymazal et al., 1995) contradict other publications showing no significant correlation of T1 and iron (Steen et al., 2000).

The main objective of this work was to deduce a model representing the effect of lipids and iron on qMRI parameters, specifically R1 (1/T1).

Methods

Data collection

This study describes a phantom system designed to assess the contribution of various membrane lipids and irons to qMRI parameters using a clinical human scanner. Three lipid types have been chosen: phosphatidylcholine (PC), phosphatidylcholine sphingomyelin (PC_SM), and phosphatidylcholine cholesterol (PC_Chol). In addition, 3 iron types have been chosen for the experiment: Fe2, Ferritin, Transferrin.

The phantom systems composed of several boxes; each contains approximately 29 test tubes. Common to each box in the lipid type and iron type. Each test tube in each box contains different concentration of lipid and different concentration of iron, as seen in fig. 1.

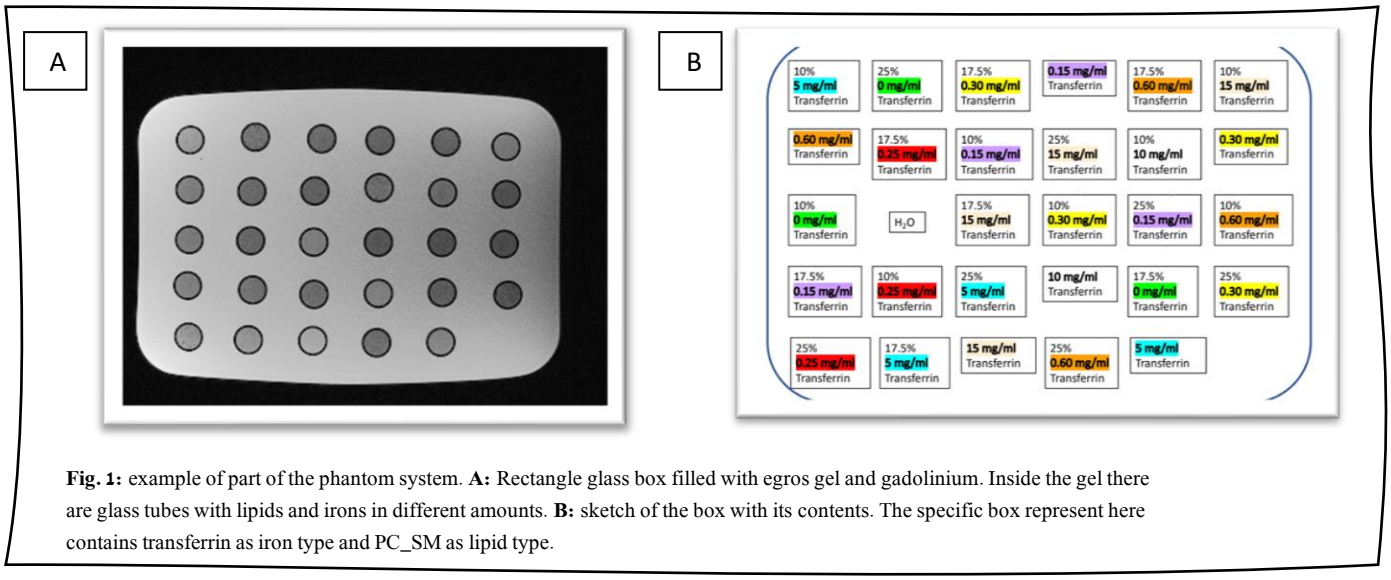

Fig. 1: example of part of the phantom system. **A:** Rectangle glass box filled with egros gel and gadolinium. Inside the gel there are glass tubes with lipids and irons in different amounts. **B:** sketch of the box with its contents. The specific box represent here contains transferrin as iron type and PC_SM as lipid type.

Each box scanned in 3 T MRI machine, and qMRI parameters were established. The entire data of the phantom system is represented in a csv file as seen in fig. 2, contains all the samples information, and the qMRI parameters as received from qMRI analyses.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q
1	[Protein](mg/ml)	iron [mg/ml]	lipid [%]	MTV exp	R1 [1/sec]	R2s [1/sec]	MTV [fraction]	R2 [1/sec]	MT [p.u.]	type	estimation [mg/	iron type	Lipid type	ExpNum	Fe] sigma [mg/ml	Date	Exp. Folder nam
2	0	0	10	0.1	0.367098478	0.003427238	0.089390428	2.96297588	0.00391594	PC+Chol+Fe2	0.0000	Fe2	PC_Choles	1	0.0000	10.12.19	PC_Chol_Fe_1(
3	0	0.15	17.5	0.175	1.281386236	0.00457829	0.14862217	4.78468786	0.006907897	PC+Chol+Fe2	0.1500	Fe2	PC_Choles	1	0.1500		
4	0	0.6	25	0.25	2.65315135	0.013634661	0.240180643	8.23043163	0.007324512	PC+Chol+Fe2	0.6000	Fe2	PC_Choles	1	0.6000		
5	0	0.05	0	0	0.329832368	-9.01334E-05	-0.013546626	1.76211518	-0.000342001	Fe2	0.0500	Fe2	PC_Choles	1	0.0500		
6	0	0.3	17.5	0.175	1.834075168	0.00699874	0.126721888	5.61798578	0.005469975	PC+Chol+Fe2	0.3000	Fe2	PC_Choles	1	0.3000		
7	0	0.3	0	0	0.633609147	0.001351296	-0.000888862	3.0534457	-6.25996E-05	Fe2	0.3000	Fe2	PC_Choles	1	0.3000		
8	0	0	25	0.25	0.592734978	0.010961047	0.275886846	4.72813326	0.012138631	PC+Chol+Fe2	0.0000	Fe2	PC_Choles	1	0.0000		
9	0	0.25	0	0	0.493848493	0.000376406	-0.010080424	2.45399863	0.000359091	Fe2	0.2500	Fe2	PC_Choles	1	0.2500		
10	0	0.05	17.5	0.175	0.750882823	0.004305815	0.169796811	3.60360366	0.007378913	PC+Chol+Fe2	0.0500	Fe2	PC_Choles	1	0.0500		
11	0	0.3	10	0.1	2.180984699	0.006359395	0.130476372	6.51465274	0.004760396	PC+Chol+Fe2	0.3000	Fe2	PC_Choles	1	0.3000		
12	0	0.25	25	0.25	1.658634983	0.00876514	0.23682036	6.0422848	0.010123455	PC+Chol+Fe2	0.2500	Fe2	PC_Choles	1	0.2500		
13	0	0.6	17.5	0.175	2.768887169	0.010160625	0.167370712	8.06453547	0.006439343	PC+Chol+Fe2	0.6000	Fe2	PC_Choles	1	0.6000		
14	0	0.15	10	0.1	1.147384627	0.004041637	0.105632023	4.33839451	0.004343224	PC+Chol+Fe2	0.1500	Fe2	PC_Choles	1	0.1500		
15	0	1	0	0	1.494054506	0.004055194	0.024929104	5.36193461	0.001527849	Fe2	1.0000	Fe2	PC_Choles	1	1.0000		
16	0	0.05	25	0.25	0.842075043	0.008849045	0.242251104	4.77326997	0.012483551	PC+Chol+Fe2	0.0500	Fe2	PC_Choles	1	0.0500		
17	0	0	10	0.1	0.382233151	0.003213436	0.077758948	2.16216242	0.004182086	PC+Chol+Fe2	0.0000	Fe2	PC_Choles	1	0.0000		
18	0	0.05	17.5	0.175	0.762224151	0.005649447	0.181561389	4.00000044	0.007826045	PC+Chol+Fe2	0.0500	Fe2	PC_Choles	1	0.0500		
19	0	0.15	25	0.25	1.054876318	0.010700769	0.244766773	5.6022421	0.010445322	PC+Chol+Fe2	0.1500	Fe2	PC_Choles	1	0.1500		
20	0	0	17.5	0.175	0.475479431	0.007354696	0.182084621	3.05342234	0.008516913	PC+Chol+Fe2	0.0000	Fe2	PC_Choles	1	0.0000		
21	0	0.6	10	0.1	3.181948591	0.010960248	0.130255312	8.88887102	0.005301018	PC+Chol+Fe2	0.6000	Fe2	PC_Choles	1	0.6000		
22	0	0.25	17.5	0.175	1.488582835	0.006967736	0.155875101	4.66200339	0.006717807	PC+Chol+Fe2	0.2500	Fe2	PC_Choles	1	0.2500		
23	0	0.8	0	0	1.240634721	0.003136427	-0.01177233	4.64037191	0.00062741	Fe2	0.8000	Fe2	PC_Choles	1	0.8000		
24	0	0.15	25	0.25	1.078673729	0.009811247	0.241549351	5.08906071	0.009822066	PC+Chol+Fe2	0.1500	Fe2	PC_Choles	1	0.1500		
25	0	0.6	0	0	1.035235318	0.003508214	-0.012988652	4.35729995	0.000658026	Fe2	0.6000	Fe2	PC_Choles	1	0.6000		
26	0	0.05	10	0.1	0.617838319	0.003592084	0.081873383	3.00750283	0.003701782	PC+Chol+Fe2	0.0500	Fe2	PC_Choles	1	0.0500		
27	0	0.15	0	0	0.424632422	0.000650831	0.035031049	2.20994179	-0.000287742	Fe2	0.1500	Fe2	PC_Choles	1	0.1500		
28	0	0.25	10	0.1	1.509560911	0.004632622	0.096799733	4.88997429	0.004299738	PC+Chol+Fe2	0.2500	Fe2	PC_Choles	1	0.2500		
29	0	0.3	25	0.25	1.970620144	0.012155837	0.285428587	6.60060459	0.010578382	PC+Chol+Fe2	0.3000	Fe2	PC_Choles	1	0.3000		
30	0	0	25	0.25	0.338275552	0.007270488	0.22703061	4.59770414	0.000697194	PC+Fe2	0.0000	Fe2	PC	2	0.0000	30.10.19	PC_Fe_301019
31	0	0.3	0	0	0.605951816	0.000902777	0.012496483	2.87769071	0.000267144	Fe2	0.3000	Fe2	PC	2	0.3000		
32	0	0.25	25	0.25	1.091587123	0.010066123	0.226835081	5.30504451	0.001023545	PC+Fe2	0.2500	Fe2	PC	2	0.2500		
33	0	0	10	0.1	0.308433589	0.004230988	0.10190572	2.43902641	-2.59339E-05	PC+Fe2	0.0000	Fe2	PC	2	0.0000		
34	0	0.05	25	0.25	0.483213056	0.007377667	0.193518585	3.46620423	0.000427813	PC+Fe2	0.0500	Fe2	PC	2	0.0500		
35	0	0.25	10	0.1	1.060574208	0.005699485	0.076094729	5.24935809	0.000862248	PC+Fe2	0.2500	Fe2	PC	2	0.2500		
36	0	0.05	0	0	0.332805677	-0.001274485	-0.003531639	1.82648487	-0.000185845	Fe2	0.0500	Fe2	PC	2	0.0500		
37	0	0.15	10	0.1	0.705169857	0.003815084	0.110850459	3.91389348	0.000913524	PC+Fe2	0.1500	Fe2	PC	2	0.1500		
38	0	0	17.5	0.175	0.337929585	0.008873406	0.207902827	3.6764707	0.000103426	PC+Fe2	0.0000	Fe2	PC	2	0.0000		
39	0	0.15	25	0.25	0.841071732	0.008540202	0.211134403	4.61893798	0.000825125	PC+Fe2	0.1500	Fe2	PC	2	0.1500		

Fig. 2: The entire data after MRI scans. Represented in csv worksheet, 10 experiments (boxes) were scanned. In total, 3 iron types; Fe2, Ferritin, Transferrin, 3 lipid types; PC_SM, PC, PC_Choles, 4 lipid concentrations; 0, 10, 17.5, 25 and several iron concentrations according to iron type.

Pre-processing of the data

Out of 10 experiments (273 samples), 2 were disqualified. 1 experiment was disqualified due to inaccurate amounts of substances and the other was disqualified due to the fact it contains protein that was irrelevant for the current research.

Outliers

To detect outliers, calculation of Z-score was made. Z-score is a statistical measure represent the number of standard deviations away from the mean that a certain data point is. The equation of Z-score calculated as follows: $Z = \frac{x-\mu}{\sigma}$ where μ=mean of the R1 values X; σ=Standard deviation of the R1; X= R1. Z-score values greater than or less than + 3 or − 3, respectively, are considered outliers (Misra et al., 2019; Tabachnick & Fidell, 2013).

Visualization of the outliers was created by using box plot. A boxplot is another convenient approach to identifying univariate outliers (Field & Miles, 2010; Tukey, 1977) which graphically depicting groups of numerical data through their quartiles. It has lines extending vertically from the boxes (whiskers) indicating variability outside the upper and lower quartiles. As seen in fig. 3, outliers can be detected outside the upper quartiles.

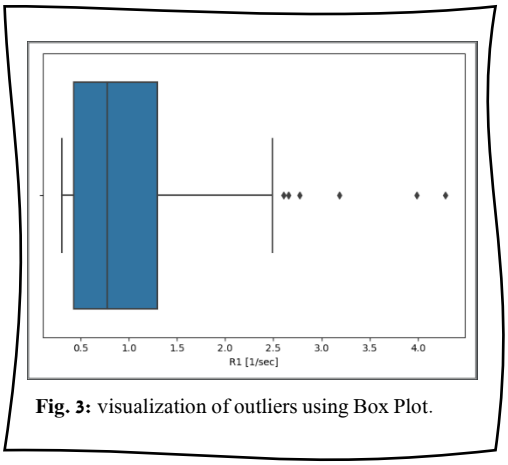

Fig. 3: visualization of outliers using Box Plot.

After calculating Z-score for the R1 values, values with distance of 3 SD and more from the mean, were disqualified (3 samples).

After performing pre-processing methods on the data, 163 samples remain.

Relationship between the variables.

To assess the relationship between the independent variables and the dependent variable, Pearson's correlation coefficient was calculated. The correlation coefficient is a measure of linear correlation between two sets of data (Correlation Coefficient, 2021; Pearson, 1895). The Pearson correlation coefficient calculated by dividing the covariance of the two variables, with the products of their standard deviations. $P = \frac{COV(X,Y)}{\sigma X^{*}\sigma Y}$. The covariance is calculated as follows: $COV(X,Y) = \frac{\mathbb{E}[(X-\mu x)(Y-\mu Y)]}{\sigma X^{*}\sigma Y}$.

Linear Regression Models

Simple linear regression models were created to examine the ability to predict R1 values by iron and lipid concentrations. Linear regression is a linear approach for modelling the relationship between a scalar response and one or more explanatory variables (Freedman, 2009).

In this research, the response is the R1 (1/sec) values, which derived from T1 results ($R1 = 1/T1$), and the explanatory variables are the lipid and iron concentrations.

As mentioned earlier, the research focuses on 3 different iron types: Fe2, Ferritin and Transferrin. In order to address the iron concentration, bound to the proteins (Ferritin, Transferrin), calculation of estimated Fe concentration.

In the first stage, simple and multiple linear regression were calculated. The equations were:

1. R1 = a*[Fe] + b
2. R1 = a*[lipid] + b
3. R1 = a*[Fe] + b*[lipid] + c

In the second stage, multiple linear regression with interaction model was created, based on the calculation R1 = a*[Fe] + b*[lipid] + c*[Fe]*[lipid] + d.

The third stage included linear regression with categorical variables; iron types and lipid types, to understand how the different types affects the relation between the substance's concentration and the target. The calculation of the model was as follows: R1 = a*[lipid]*lipid type + b * [Fe] * iron type + c. To properly use the categorical variables, encoded with dummy variables was established. In this stage, column of every iron type and lipid type added to the data frame. The code '1' presented in the column represented the iron type used in each sample, as well as lipid type (Fig. 4).

Lipid type_PC_SM	Lipid type_PC_Cholest	Lipid type_PC	Iron type_Transferrin	Iron type_Ferritin	Iron type_Fe2	[%] lipid	sigma [mg/ml] [Fe]	
0	1	0	0	0	1	10.0	0.000000	0
0	1	0	0	0	1	17.5	0.150000	1
0	1	0	0	0	1	25.0	0.600000	2
0	1	0	0	0	1	17.5	0.300000	4

Fig. 4: Dummy variables coding. 3 columns of iron types exchange the original column of the iron type, and so for the lipid type. The number 1 was written in the right column fit to the types used in the sample. In this example we can detect 4 samples with iron type Fe2 and lipid type PC_Cholest.

For the convenience, there will be use in this research in the equation R1 = a*[lipid]*lipid type + b*[Fe]*iron type + c when in fact in the current technique, each iron type and each lipid type demonstrated different coefficient. In this way, when the sample involved Fe2 as iron type and PC as lipid type, the regression equation was: R1 = a*[Fe]*Fe2(==1) + b*[lipid]*PC + c. whereas for different iron type **a** coefficient will be different, same as the **b** coefficient.

To evaluate the goodness of fit of a model, R^2 coefficient of determination was calculated (Renaud et al., 2010). R^2 is a statistical measure of how well the regression predictions approximate the real data points. An R^2 of 1 indicates that the regression

predictions perfectly fit the data. $R^2 = \frac{TSS - RSS}{TSS}$ where RSS is the sum of squares of residuals, a measure of the discrepancy between the data and an estimation model and TSS is the total sum of squares - sum over all squared differences between the observations and their overall mean.

Furthermore, the mean absolute error was calculated. The mean absolute error is a way of comparing forecasts with their eventual outcomes (Willmott et al., 2005). The calculation is as follows $MAE = \frac{\sum_{k=1}^{n} |y_i - \hat{y}|}{n}$ where n is the total number of the samples, y_i is specific value from the measured samples and $\hat{y}$ is the predicted value.

Cross validation

Cross-validation is a data resampling method to assess the generalization ability of predictive models and to prevent overfitting (Hastie et al., 2008; Duda et al., 2001).

A central question in supervised learning concerns the accuracy of the resulting model. Overfitting is the case where a model is perfectly adapted to the data set at hand but then unable to generalize well to new, unseen data (Berrar et al., 2013). In this research, leave one out cross-validation technique was obtained. the available learning set is partitioned into n disjoin. The model is trained using $n - 1$ subsets, which, together, represent the training set. Then, the model is applied to the remaining subset, which is denoted as the validation set, and the performance is measured. This procedure is repeated until each of the n subsets has served as validation set. The average of the n performance measurements on the n validation sets is the cross-validated performance. The test error in LOOCV is approximately an unbiased estimate of the true prediction error (Hastie et al., 2008).

Results

Pearson correlation coefficients was calculated for R1 target variable. It can be determined that p value smaller than 0.5 doesn't indicated strong linear relation (Mukaka, 2012; Benesty et al., 2009). The results indicated no significant relationship between R1 and iron concentrations (p= 0.485, N=163), and R1 to lipid concentrations (p=0.086, N=163).

Accordingly, simple Linear regression model created; $R1 = a*[Fe] + b$, $R1 = a*[lipid] + b$. Both models yielded low R^2 values, indicating a model that does not properly

explain the dependent variable by the independent variable (Hamilton, Ghert & Simpson, 2015), as seen in fig. 5.

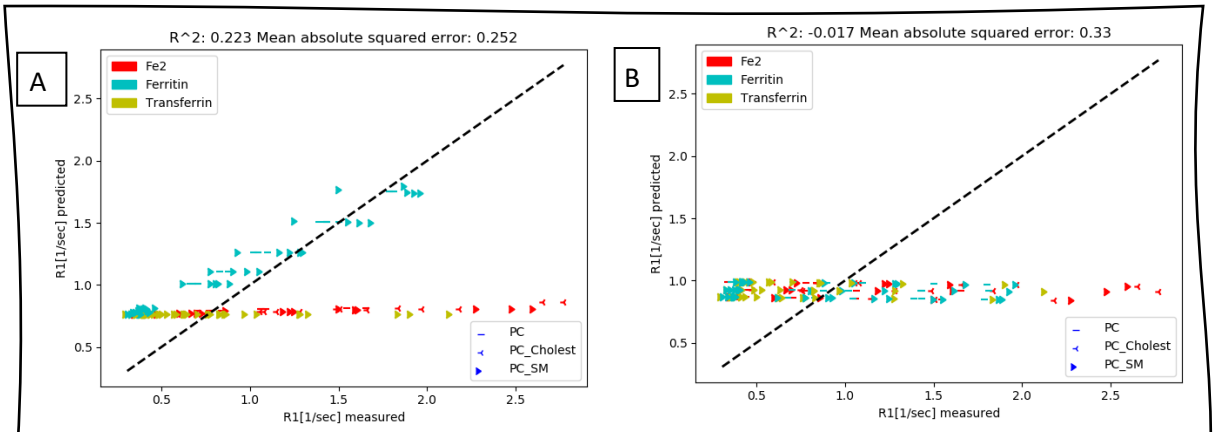

Fig. 5: simple linear regression. **A:** visualization of the measured R1 values towards the predicted R1 values, which predicted by the equation R1 = a*[Fe] + b. The presented values transformed cross-validation evaluation, as mentioned in the methods chapter. The R^2 values appearing in the title, and the MAE values, measured in 1/sec units. **B:** visualization of the measured R1 values towards the predicted R1 values, which predicted by the equation R1 = a*[lipid] + b.

Multiple linear regression and multiple linear regression with interaction were performed to evaluate the abilities of iron concentrations and lipids to predict R1 values as can be seen in Fig. 6.

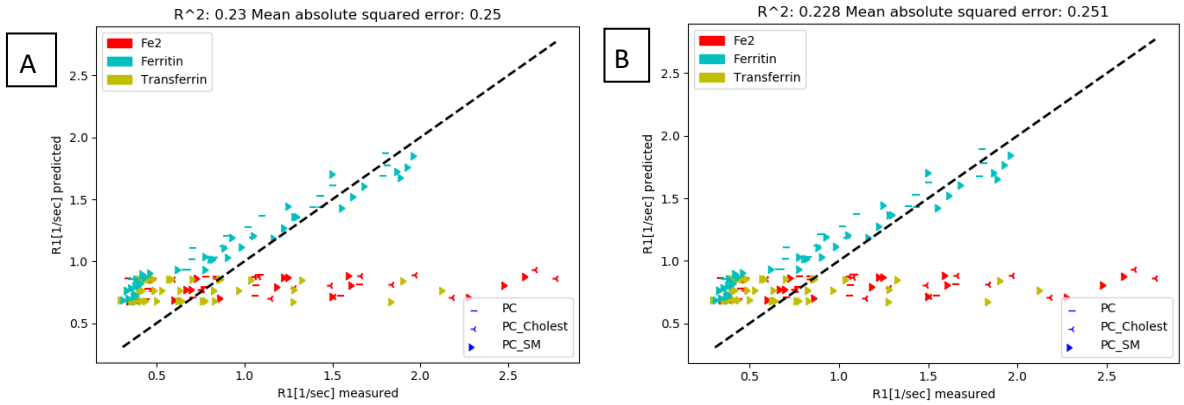

Fig. 6. A: multiple linear regression. visualization of the measured R1 values towards the predicted R1 values, which predicted by the equation R1 = a*[Fe] + b*[lipid] + c. The presented values transformed cross-validation evaluation, as mentioned in the methods chapter. The R^2 values appearing in the title, and the MAE values, measured in 1/sec units. **B:** multiple linear regression with interaction. visualization of the measured R1 values towards the predicted R1 values, which predicted by the equation R1 = a*[Fe] + b*[lipid] + c*[Fe]*[lipid] + d.

It can be identified in fig.6 that groups of samples with the same iron type, and the same lipid type, have common slope, and the clustering of the iron types is more noticeable. We hypothesized that there is an effect of the lipid types and the iron types on the way the substances concentration effects the R1 values.

The data analysis revealed the relationship between the different types of iron and types of lipids. That is, depending on the type of iron and lipid, there is an effect of the iron and lipid concentrations on the target. In other words, using seaborn library, a scatter plot created to visual the effect of iron types and lipid types on the substances concentration in the goal of predicting R1 values. In Fig. 7 one can clearly detect clusters of common types of lipids and irons.

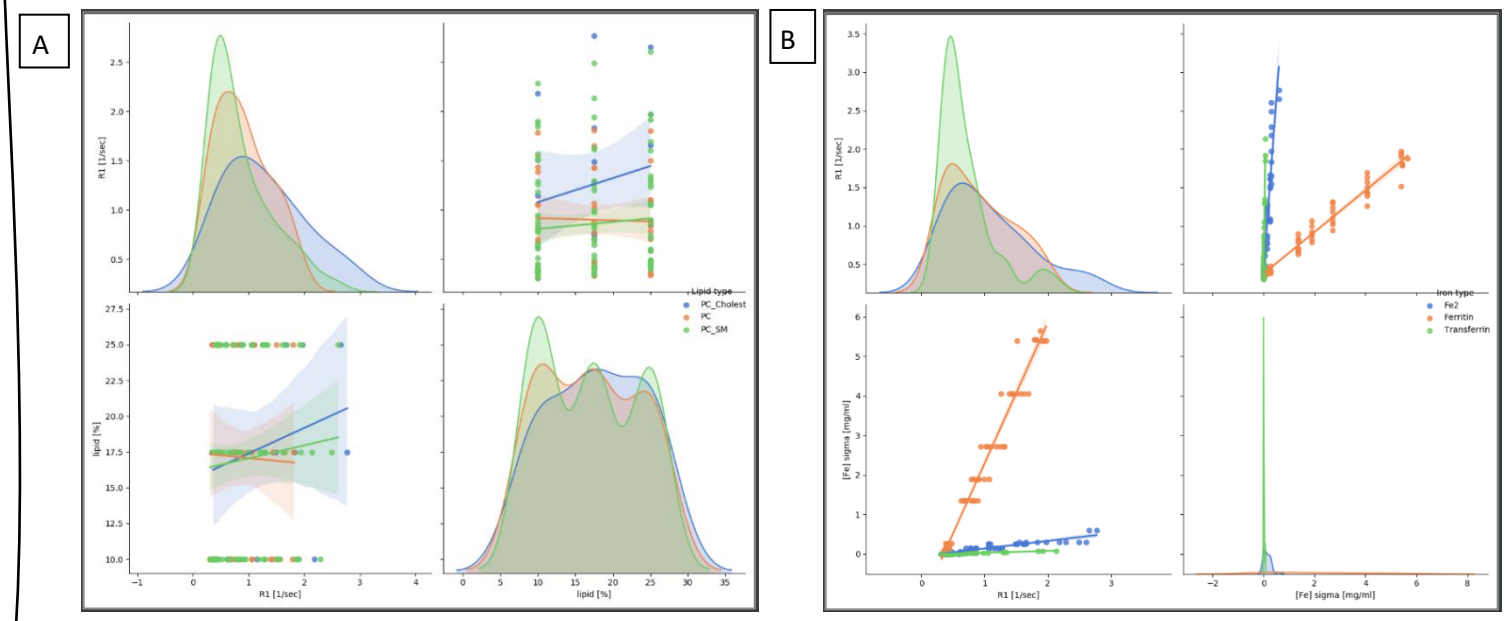

Fig. 7: relations between lipid to R1 and iron to R1 with the effect of lipids and iron types. **A:** pair plot depicting the relationship between lipid concentrations and R1 when common behaviors can be identified for all samples from the same type of lipid. **B:** pair plot depicting the relationship between iron concentrations and R1 when common behaviors can be identified for all samples from the same type of iron.

Due to the last results, linear regression involves interaction between categorical variables (iron types and lipid types) was performed. According to the hypothesis, it was found that when referring to the effect of the types of iron and lipids on the amounts of iron and lipids, respectively, R1 predicted values approximate the real data points very well ($R^2 = 0.926, MAE = 0.024$).

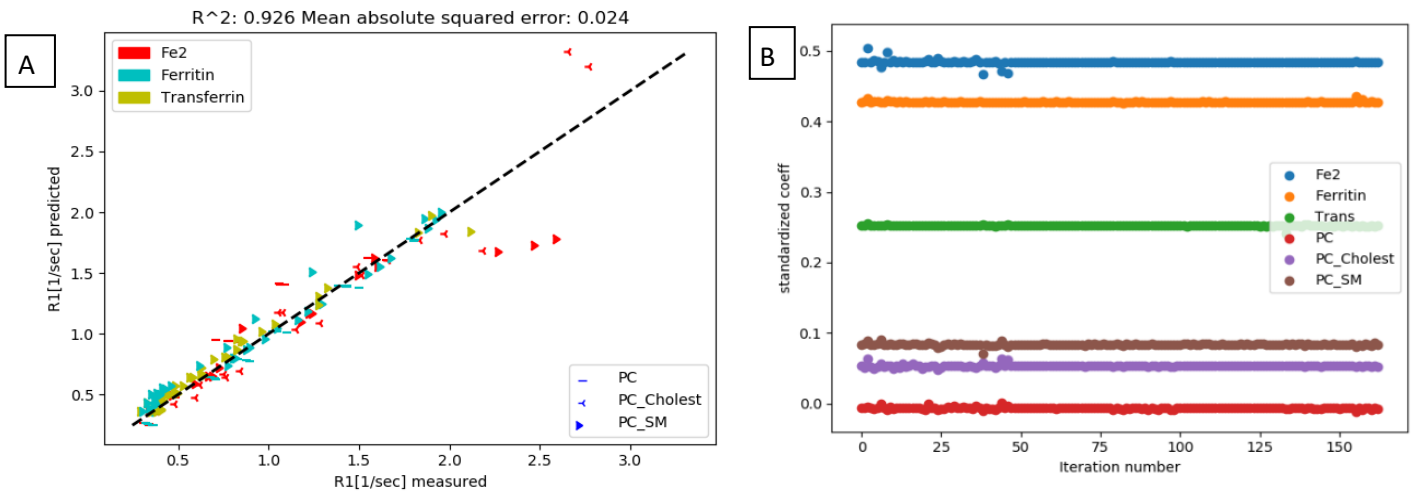

Fig. 8: A: linear regression involves interaction with categorical variables. visualization of the measured R1 values towards the predicted R1 values, which predicted by the equation R1 = a*[Fe]*iron type + b*[lipid]*lipid type + c. The presented values transformed cross-validation evaluation, as mentioned in the methods chapter. The R^2 values appearing in the title, and the MAE values, measured in 1/sec units. **B:** As mentioned, each type of iron and each type of lipid paired with another coefficient. The data was standardized using Z-score technique to be able to compare the different coefficients. The graph represents the coefficient of each type during each one of the cross-validation iterations. It can be identified that Fe2 has the most effect on the target, due to its highest coefficient value.

Discussion

In this research, the goal was to find the best fit model that allows to predict R1 values based on lipid and iron concentrations and types. One positive outcome that can be derived from this experiment, is the possibility of inferring diseases and defects in the human brain, depending on the results of R1. Further studies can deduct from this study the relationship between R1 and iron and lipid concentrations, as well as iron and lipid types. Given that relationship, detecting abnormal values of iron and lipid concentrations, can help in diagnostics neurological symptoms and diseases.

In addition to the findings in the literature (Rooney et al., 2007), in this experiment it was found that the types of iron and lipids also influence R1 values prediction, and not just concentrations. As seen in Fig. 8 B, the iron types have more effect then the lipid type, due to its higher coefficient (Cornell & Berger, 1987).

There are some limitations to this research. First, it can be thought that the data is biased. Out of 10 experiments that have been used in this research, not all the combinations of the lipid types and iron types has been tested. The combinations of Ferritin with PC_Cholest, and Transferrin with PC, and PC_Cholest were not included in the phantom system. Due to that fact, it possible that the results supporting the larger meaning of the iron type, won't be demonstrated in future similar experiments. Second, the concentrations presented in this research, are not correlate exactly to the human brain iron and lipid concentrations. Due to that fact, it would not be accurate to draw conclusions about the human brain based on the results of this study (Yeatman et al., 2014).

Further research can aim to model the relation between iron and lipid to other qMRI parameters. With the full models connecting iron and lipids to qMRI parameters, it will be possible to turn the model and find the right equation for predicting iron and lipid in the human brain. These results can lead to innovation in the world of science and medicine.

The code of the research can be found in the following address: https://github.com/ShirlyEliezer/iron_lipids. In order to download the code to your computer, clone to the desire folder with the command: git clone https://github.com/ShirlyEliezer/iron_lipids

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