Simulating human brain glutamate fMRS at 7.0 T to determine minimum SNR requirements

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Introduction

Glutamate is the main excitatory neurotransmitter in the human brain and is involved in practically all brain functions. ^{1}H-MRS has been used to study normal and abnormal glutamate levels at rest in the human brain[1]. However, despite being present in large concentrations in the brain, the precise quantification of glutamate is limited due to spectral overlap of other metabolites such as glutamine and NAA as well as important J-dephasing related to strong J-coupling. At ultra-high magnetic field strengths (≥ 7T), increased spectral dispersion, weaker J-coupling and increased SNR help mitigate these limitations. Certain abnormalities of brain glutamate metabolism may only surface when a region of the brain is activated. Dynamic changes in metabolite levels can be assessed by fMRS which has been shown to be effective in determining concentration changes in metabolites of the occipital lobe during rest and visual stimulation at 7T [2]. The goal of this work is to determine the minimum SNR necessary to distinguish a certain concentration change in glutamate from rest to activation. This will place lower limits on the minimum number of signal averages required to detect glutamate level changes and hence determine the maximum temporal resolution.

Materials and Methods

A template of *in vivo* spectra acquired with a short-echo time STEAM sequence with TE/TM of 6/32ms at 7T was created using simulations. The template, which can be seen in Figure 1, contains 15 metabolites (NAA, NAAG, Glu, Gln, Gaba, Tau, Cho, PC, GPC, Glc, Cr, PCr, Scy, Myo, and Asp) along with a macromolecular baseline empirically determined to match a previously published macromolecule signature[3]. The template contains a total of 401 resonances plus a reference peak used for determining SNR (matched in concentration and number of protons to the CH_3 singlet of NAA). Chemical shifts, coupling constants, and concentrations were obtained from literature values[4],[5]. Lorentzian linewidths were assumed to be 10Hz for each resonance line of the template. Simulated spectra were generated for two different concentrations of glutamate to imitate rest and active states (rest:10mMol/kg; active: 10.3mMol/kg based on a 3% change observed in literature[2]) in fMRS. NAA SNR's ranged from 2^4 to 2^8 in powers of 2. Although SNR varies within different brain areas, one acquisition of a 8cc voxel *in vivo* at 7T typically has an SNR of at least 2^4. The simulation assumes that the BOLD effect has been accounted for as it was previously shown that this can be done effectively[2]. Pseudo-random noise spectra were added to the simulated spectra to produce 100 different noisy realisations of both glutamate concentrations at each SNR using Datsim, a program developed in-house. The noisy simulated spectra were quantified using Fitman, a spectral quantification algorithm developed in-house and previously described in literature[6]. This iterative algorithm was seeded using values of amplitude, chemical shift, phase (0^{th} and 1^{st} order) and linewidths randomly distributed about the known value based on typical seeding precision of in vivo data. Mean, standard deviation and coefficient of variation (CV) of glutamate concentrations were calculated at each concentration and SNR. The following formula for the smallest detectable difference (%SDD) was used:

$$\%SDD = (z_\alpha + z_\beta) \bullet \sqrt{\frac{CV_1^2}{N_1} + \frac{CV_2^2}{N_2}}$$

where $z_\alpha(0.05, \text{one-tailed})=1.645$, $z_\beta(0.8,\text{two-tailed})=1.28$, and N_1 and N_2 are the number of spectra for rest and activation, respectively. Let $N_1 = N_2 = N$. By letting %SDD =3% the minimum number of spectra to detect a 3% change in glutamate for each SNR can be found. Alternatively, by letting N =1 the smallest detectable difference for one spectrum at a given SNR can also be found.

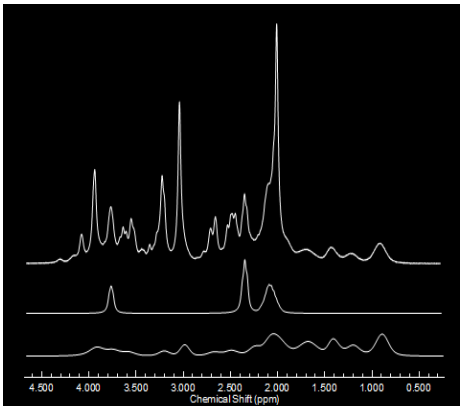

Figure 1. A simulated *in vivo* TE/TM 6/32ms STEAM spectrum at 7T (top) showing glutamate (middle) and the macromolecular baseline (bottom).

Results and Discussion

The relationship between %SDD and SNR derived from the values of CV_1 and CV_2 obtained from simulations can be seen in Figure 3. The intersection point in Figure 3 is 212, which is the minimum SNR required to detect a 3% concentration change in glutamate from the resting to active state with only one spectrum. The minimum number of spectra for each SNR to detect the 3% change is shown in Table 1. If one scan (nt=1) is assumed to have a SNR of 16, then because SNR is proportional to the square root of the number of averages the other nt can be determined as well. Assigning a TR can then allow an estimate of temporal resolution. For example, a TR of 5s will give a temporal resolution of 4 min 15s for an SNR of 16 (5s x 51) for one rest or activation period in one person. One limitation of the simulation is that it assumes that the concentration of glutamate remains constant at different levels during the rest and activation period. The temporal resolution obtained should therefore be considered a lower limit of what can be achieved in vivo. However, the SNR of single in vivo acquisitions is often higher than 16, which, in turn, decreases the minimum required N.

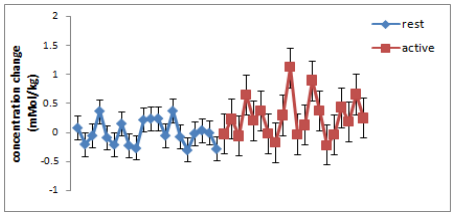

Figure 2. Simulated rest (10.0mMol/kg) and active (10.3mMol/kg) states with SNR=32 and N=20. Differences from the mean value at rest are shown along with standard deviations.

SNR	nt	min N
16	1	51
32	4	13
64	16	4
128	64	2
256	256	1

Table 1. The minimum spectra required to detect a 3% change in the concentration between rest and activation of glutamate with a given SNR. "nt" is the number of transients (assumed) to achieve the SNR.

Conclusion

We have shown that for human brain glutamate fMRS a concentration change of 3% requires a minimum SNR of 212 to detect the change with one spectrum. The best temporal resolution is the time required to acquire 51 spectra per activation state assuming a minimum SNR of 16. This corresponds to 4 min and 15s per state assuming TR=5s. Averaging fMRS time course between subjects would require higher SNR due to additional contribution of inter-subject variability to overall variability.

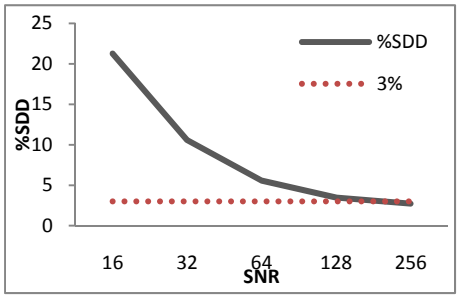

Figure 3. Smallest detectable difference (%SDD) in glutamate between the rested and activated states for a given SNR with N=1. The only SNR from this dataset sensitive enough to detect the actual concentration change of 3% is 256.

References

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