

The meaning and interpretation of ALFF and fALFF

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The meaning and interpretation of ALFF and fALFF

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19 **Abstract**

20 The amplitude of low-frequency fluctuations (ALFF) and its fractional counterpart (fALFF) are
21 widely reported measures of resting-state fMRI signals, but their precise physiological
22 interpretation has not been established. We derive expressions for ALFF and fALFF using a
23 closed-form hemodynamic transfer function which allows the resting-state BOLD spectrum to be
24 expressed explicitly in terms of cerebral blood volume, venous transit time, oxygen extraction
25 and the coupling between flow and oxygen consumption. We demonstrate that ALFF and fALFF
26 do not reflect the same physiological phenomena. ALFF can be related to baseline metabolism
27 via a power law, whereas fALFF is a bounded, saturating function that in practice largely reflects
28 signal-to-noise ratio. fALFF is confined to lie between $\sqrt{r}$ and $\sqrt{\rho_L}$, where r is the fraction of the
29 available signal bandwidth chosen for analysis and ρ_L is the fraction of true BOLD signal power
30 falling in it. Every reported fALFF value must lie between two bounds that are determined by the
31 acquisition protocol as well as the hemodynamic response function. Both limits change with the
32 acquisition parameters without changes in neural function, so, for example, fALFF is not
33 comparable across studies that differ in repetition time or scan length. We evaluate the sensitivity
34 of each measure to baseline metabolism, and show in an appendix that the alternative
35 convention, in which Fourier amplitudes rather than powers are summed, gives different bounds
36 and a stronger dependence on repetition time. We also examine how fALFF and ALFF behave
37 when when signal fluctuations arise from fluctuations in vascular parameters without any
38 accompanying metabolic change.

39

1. Introduction

Resting-state fMRI is used routinely to characterize brain function in health and disease, and among the simplest and most widely adopted metrics derived from a resting-state time series are the amplitude of low-frequency fluctuations, ALFF (1), and its fractional counterpart, fALFF (2). At least two definitions of these quantities are in use. We first define ALFF as the square root of the BOLD power spectrum integrated over a low-frequency band, conventionally 0.01–0.08 Hz, and fALFF as the ratio of ALFF to the same quantity evaluated over the whole available range of frequencies. This definition seems to be preferred because it has a more direct physical interpretation.(2) The alternative and original definitions, adopted in some widely used software, sums the Fourier amplitudes across the band rather than taking the root of the summed power. The two are quantitatively not equivalent but reveal similar limitations in the value of fALFF, and our analysis is repeated for the second convention in Appendix A. The conclusions are unchanged in substance. Both ALFF and fALFF can be mapped voxelwise, and their values compared between regions or groups. Both are usually interpreted as reflecting the intensity of spontaneous neural activity.

The rationale for using fALFF is that normalisation is expected to reduce the impact of contributions from physiological and thermal noise (3). However the interpretation of both ALFF and fALFF in terms of underlying physiology has not been adequately addressed. Both are defined empirically, and it is commonly assumed that the amplitudes of low-frequency BOLD fluctuations vary monotonically with the amplitudes of variations in underlying neural activity. To date there has been little attempt to provide a model that connects neural metabolic changes to the BOLD signal that can be evaluated in the frequency domain in a resting state.

In a recent paper (4) we revised the balloon model of Buxton and colleagues (5) and derived a closed-form analytic hemodynamic response function for the BOLD effect. This model incorporates an explicit transfer function $H(\omega)$ that relates fractional changes in the cerebral metabolic rate of oxygen to fractional changes in the BOLD signal. The system is linear and stationary so the resting-state BOLD power spectrum can be quantitatively described and ALFF and fALFF can be predicted and interpreted from theory. Here we describe the transfer function and derive analytic expressions for ALFF and fALFF. We then show how they are related to baseline metabolism and how they also depend on acquisition parameters, from which we then define the regimes in which they convey useful information. However, the accuracy of several details of the revised balloon model is not essential for the validity of our descriptions of ALFF and fALFF below.

2. Theory

2.1 The signal and its transfer function

The derivations of the revised model are given in our recent paper (4). The BOLD signal from a voxel is written in the form of Obata et al. (6), valid when the activation-induced change in transverse relaxation rate (ΔR_2^*) multiplied by the echo time (TE) remains small, so that

$$\frac{\delta S}{S} = V_0 \left[k_1(1 - q) + k_2 \left(1 - \frac{q}{v} \right) + k_3(1 - v) \right] \quad (1)$$

where $\delta S/S$ is the measured fractional change in the MRI signal, V_0 is the resting venous blood volume fraction, v the venous blood volume and q the total venous deoxyhemoglobin content, both normalised to their resting values, and k_1, k_2, k_3 are constants determined by field strength, echo time and resting oxygen extraction fraction E_0 . At 3 T with $TE = 30$ ms, $E_0 \approx 0.34$ and an

83 intravascular-to-extravascular signal ratio of 1.43, these take the values $k_1 = 3.54$, $k_2 = 0.37$
84 and $k_3 = -0.43$.

85 Linearising (1) and the balloon equations about the resting state, and writing δm for the
86 fractional change in the cerebral metabolic rate of oxygen (CMRO₂), the steady-state response is
87 given as

$$88 \quad \frac{\delta S}{S} = M G \delta m, \quad M = V_0(k_1 + k_3), \quad G = n(\beta_D - \alpha) - \beta_D \quad (2)$$

89 Here M is the calibration constant of Davis et al. (7), the maximum attainable BOLD change;
90 $\beta_D = (k_1 + k_2)/(k_1 + k_3)$ is its field-dependent exponent, which for the constants above takes
91 the value 1.256; α is a parameter relating blood flow and volume (8), which in the revised model
92 is not independent but is fixed by venous distensibility; and $n \equiv \delta f / \delta m$ is the steady-state
93 coupling ratio between fractional changes in cerebral blood flow and in oxygen consumption, for
94 which calibrated-BOLD studies report values of 2–3 (9, 10). The quantity G is a metabolic gain,
95 and it vanishes at $n_{\text{crit}} = \beta_D / (\beta_D - \alpha)$. Below that coupling ratio an increase in CMRO₂
96 produces a *negative* BOLD change. For the purposes of the rest of this report, the only essential
97 relationship is that $\frac{\delta S}{S} \propto \delta m$.

98 The corresponding dynamic relation depends on a frequency domain transfer function $H(\omega)$,
99 whose impulse response in the time domain is the hemodynamic response function (HRF). Its
100 closed form is given in (4). For present purposes only two of its properties matter. It is low-pass
101 (i.e. it falls off at high frequency), and its shape is set by selected time constants, which include a
102 venous transit time τ_0 , a viscoelastic time constant τ_v and flow-control time constants, which
103 together determine its frequency spectrum.

104 2.2 The resting-state spectrum

105 For a linear, time-invariant system, spontaneous fluctuations in oxygen consumption have a
106 power spectral density $P_m(\omega)$. These in turn drive the BOLD spectrum $P_S(\omega)$.

$$107 \quad P_S(\omega) = (MG)^2 |H(\omega)|^2 P_m(\omega) + N_0 \quad (3)$$

108 where N_0 is the power spectral density of thermal noise, taken as white.

109 Let Ω denote the whole sampled frequency band and $L \subset \Omega$ the band that is included in fALFF,
110 conventionally 0.01–0.08 Hz. The sampled band Ω runs from the lowest resolvable frequency
111 $f_{\min} = 1/T_{\text{scan}}$, set by T_{scan} , the scan duration, to the Nyquist frequency $f_{\text{Nyq}} = 1/(2 \text{TR})$, set by
112 the repetition time. Define

$$113 \quad r = \frac{|L|}{|\Omega|} \quad (4)$$

114 the fraction of total bandwidth occupied by the analysis band, and

$$115 \quad \rho_L = \frac{\int_L |H(\omega)|^2 P_m(\omega) d\omega}{\int_\Omega |H(\omega)|^2 P_m(\omega) d\omega} \quad (5)$$

116 the fraction of BOLD signal power falling in it. The distinction between r and ρ_L is key in that
117 the signal is low-pass filtered by the hemodynamic response and so is concentrated at low
118 frequency, making $\rho_L > r$, whereas white noise is spread evenly and contributes in proportion to
119 bandwidth.

120 2.3 Expressions for ALFF and fALFF

121 The noise power in Ω is $N_0|\Omega|$ while that in L is $r N_0|\Omega|$. ALFF is here defined as the square root
122 of the integrated power in the analysis band and fALFF divides it by the same quantity over the
123 whole band. If we denote the *total* signal power in Ω as P_{sig} then

$$124 \quad \text{ALFF} = \sqrt{\rho_L P_{\text{sig}} + r N_0 |\Omega|}, \quad \text{fALFF} = \frac{\text{ALFF}}{\sqrt{P_{\text{sig}} + N_0 |\Omega|}} \quad (6)$$

125 The total-band signal-to-noise ratio is given by

$$126 \quad \theta = \frac{P_{\text{sig}}}{N_0 |\Omega|} \quad (7)$$

127 So dividing numerator and denominator in (6) by the total noise power and using (7)

$$128 \quad \text{fALFF} = \sqrt{\frac{\theta \rho_L + r}{\theta + 1}} \quad (8)$$

129 Differentiating the ratio inside the root,

$$130 \quad \frac{d}{d\theta} \left(\frac{\theta \rho_L + r}{\theta + 1} \right) = \frac{\rho_L - r}{(\theta + 1)^2} > 0 \quad (9)$$

131 so fALFF increases monotonically with signal-to-noise as long as $\rho_L > r$. In the limits,

$$132 \quad \theta \rightarrow 0: \text{fALFF} \rightarrow \sqrt{r}, \quad \theta \rightarrow \infty: \text{fALFF} \rightarrow \sqrt{\rho_L} \quad (10)$$

133 so that fALFF is bounded between $\sqrt{r}$ and $\sqrt{\rho_L}$ and every measured value must lie between

134 them. The lower level is fixed by the choices of analysis band and of acquisition. Widening the

135 analysis band, whether by lowering its lower cut-off or by raising its upper cut-off, raises both

136 bounds and hence the measured value, while narrowing it lowers them; shortening TR lowers the

137 floor and hence the measured value. The ceiling depends on the choice of the analysis band,

138 which should be selected based on the HRF.

139 **2.4 Dependence on baseline metabolism**

140 Equation (2) predicts that spontaneous CMRO₂ fluctuations of standard deviation σ_m will

141 produce BOLD fluctuations of standard deviation $MG\sigma_m$. From Parseval's theorem, $P_{\text{sig}} =$

142 $(MG\sigma_m)^2$ so

$$143 \quad \theta = \frac{(MG\sigma_m)^2}{N_0 |\Omega|} \quad (11)$$

144 In calibrated BOLD, the maximum attainable BOLD change is $M \propto V_0 \cdot [\text{dHb}]^{\beta_D}$, the exponent
 145 arising because the relaxation of extravascular water depends nonlinearly on deoxyhemoglobin
 146 concentration, $[\text{dHb}]$. The baseline venous deoxyhemoglobin concentration is proportional to
 147 the resting extraction fraction, $E_0 = \text{CMRO}_{2,0}/(\text{CBF}_0 C_a)$, where C_a is the arterial oxygen
 148 concentration and CBF_0 is baseline blood flow, so

$$149 \quad M \propto V_0 \left(\frac{\text{CMRO}_{2,0}}{\text{CBF}_0 C_a} \right)^{\beta_D} \quad (12)$$

150 Baseline metabolism modulates M and therefore also affects fALFF through θ as $\theta \propto M^2$.

151 However, we can define a metabolism-sensitivity index as

$$152 \quad \frac{d \ln \text{fALFF}}{d \ln \text{CMRO}_{2,0}} = \beta_D \left[\frac{\theta \rho_L}{\theta \rho_L + r} - \frac{\theta}{\theta + 1} \right] \quad (13)$$

153 which indicates that changes in fALFF with $\text{CMRO}_{2,0}$ depend on signal to noise rather than
 154 underlying physiology. ALFF, by contrast, is the unnormalised numerator of (6). In the limit
 155 when BOLD signal dominates the noise it is directly proportional to $MG\sigma_m$ and obeys a power
 156 law,

$$157 \quad \text{ALFF} \propto \text{CMRO}_{2,0}^{\beta_D} \quad (14)$$

158 Equation (14) is the limiting form at high signal-to-noise ratio. Differentiating the numerator of
 159 (6) in the same way as (13) gives the sensitivity index as

$$160 \quad \frac{d \ln \text{ALFF}}{d \ln \text{CMRO}_{2,0}} = \beta_D \frac{\theta \rho_L}{\theta \rho_L + r} \quad (15)$$

161 which agrees with (14) as $\theta \rightarrow \infty$. Comparison with (13) shows that the two sensitivities share
 162 the same leading term, and that normalisation subtracts the corresponding quantity for the whole

163 band. The ratio of the two sensitivities is $= \left[1 - \frac{\theta + \frac{r}{\rho_L}}{\theta + 1} \right]$. ALFF is therefore always the more

sensitive of the two, but it attains the full power law of (14) only when the analysis band is dominated by signal rather than by noise. Thus ALFF can be related to baseline metabolism through a power law at high signal-to-noise ratio, whereas fALFF is a bounded, saturating readout of signal-to-noise ratio.

3. Methods

BOLD signal time series and noise were simulated and evaluated numerically. All spectral integrals were evaluated as discrete sums over uniformly spaced frequency bins.

Spontaneous CMRO₂ fluctuations were modelled with a power spectral density proportional to $1/f$, in line with the reported spectral character of resting-state fluctuations.

The two relevant frequency bands were defined explicitly by the acquisition. The analysis band was 0.01–0.08 Hz. The sampled band ran from $f_{\min} = 1/T_{\text{scan}}$ to $f_{\text{Nyq}} = 1/(2 \text{ TR})$ for different choices of times, with a reference acquisition of $\text{TR} = 2 \text{ s}$ and $T_{\text{scan}} = 600 \text{ s}$.

4. Results

4.1 The bounds at a typical acquisition

For the reference acquisition ($\text{TR} = 2 \text{ s}$, ten-minute scan) the analysis band occupies a fraction $r = 0.28$ of the sampled bandwidth but contains $\rho_L = 0.54$ of the BOLD signal power. fALFF is therefore confined to $0.531 \leq \text{fALFF} \leq 0.736$.

The dynamic range available is 0.205, and the lower bound is reached by a voxel containing no signal whatever. A voxel at a typical signal-to-noise ratio, $\theta \approx 0.05$, has $\text{fALFF} = 0.542$, only 6

183 % of the way from the floor to the ceiling, far closer to the noise floor than to the ceiling because
184 $\theta \ll 1$ and the measure saturates.

185 The origin of the ceiling is shown in Fig. 1 (left). The transfer function is low-pass, but the
186 neural drive itself varies steeply at low-frequency. Recomputing ρ_L with a white neural spectrum
187 instead of $1/f$ raises it from 0.542 to 0.791, and raises the ceiling correspondingly from 0.736 to
188 0.889. Thus the ceiling is a joint property of the HRF and of the spectrum of spontaneous
189 activity.

190 **4.2 Both limits depend on the acquisition**

191 r depends on the Nyquist frequency, and so the noise floor depends on repetition time. Table 1
192 and Fig. 1 (centre) illustrate these dependences. Shortening TR from 2 s to 0.5 s widens the
193 sampled band fourfold, so the analysis band occupies a smaller fraction of it and the floor falls
194 from 0.531 to 0.265. The ceiling is unaffected because the additional bandwidth contains almost
195 no signal.

196 This illustrates a basic weakness in the interpretation of fALFF. Holding the total-band signal-to-
197 noise ratio θ fixed, so that identical degrees of brain activity are being compared, fALFF = 0.542
198 at TR = 2 s and 0.304 at TR = 0.5 s, a change of -44 %. Nothing about the brain has changed. If
199 the thermal noise rises as TR is shortened, the fall is larger still. fALFF values from acquisitions
200 of different speed are not subject to the same constraints, which must be borne in mind when, for
201 example, comparing multiband with single shot acquisitions.

202 Table 1. Dependence of the fALFF bounds on repetition time, for a ten-minute scan.

TR (s)	f_{Nyq} (Hz)	r	ρ_L	$\sqrt{r}$	$\sqrt{\rho_L}$	fALFF at $\theta = 0.05$
0.50	1.000	0.070	0.542	0.265	0.736	0.304
0.72	0.694	0.101	0.542	0.318	0.736	0.349
1.00	0.500	0.140	0.542	0.375	0.736	0.399
1.50	0.333	0.211	0.542	0.459	0.736	0.476
2.00	0.250	0.282	0.542	0.531	0.736	0.542
2.50	0.200	0.353	0.542	0.594	0.736	0.602
3.00	0.167	0.424	0.542	0.651	0.736	0.656

203

204 4.3 The ceiling depends on scan duration

205 A second dependence is less obvious and may not have been emphasized before. For
206 spontaneous activity with a $1/f$ -like spectrum, the total-band signal power grows as the lowest
207 resolved frequency is reduced. Lengthening a scan adds power to the denominator of (5) but not
208 to the numerator, because the added frequencies lie below the analysis band. The maximum
209 value therefore falls with scan duration, as shown in Table 2 and Fig. 1 (right). For a strict $1/f$
210 drive the denominator diverges as $f_{\min} \rightarrow 0$, but in practice the divergence is limited by
211 detrending and filtering before the spectrum is computed.

212 Table 2. Dependence of the fALFF maximum on scan duration, at TR = 2 s.

T_{scan}	$f_{\min}$ (Hz)	ρ_L	Max = $\sqrt{\rho_L}$	fALFF at $\theta = 0.05$
3 min	0.00556	0.755	0.869	0.556
5 min	0.00333	0.639	0.800	0.548
10 min	0.00167	0.542	0.736	0.542
15 min	0.00111	0.476	0.690	0.539
30 min	0.00056	0.431	0.657	0.536

The ceiling falls from 0.869 to 0.657 as the scan lengthens from three to thirty minutes. The effect for a typical acquisition is modest because $\theta \ll 1$ but it is systematic, and it acts in the opposite direction to the intuition that longer scans give better estimates.

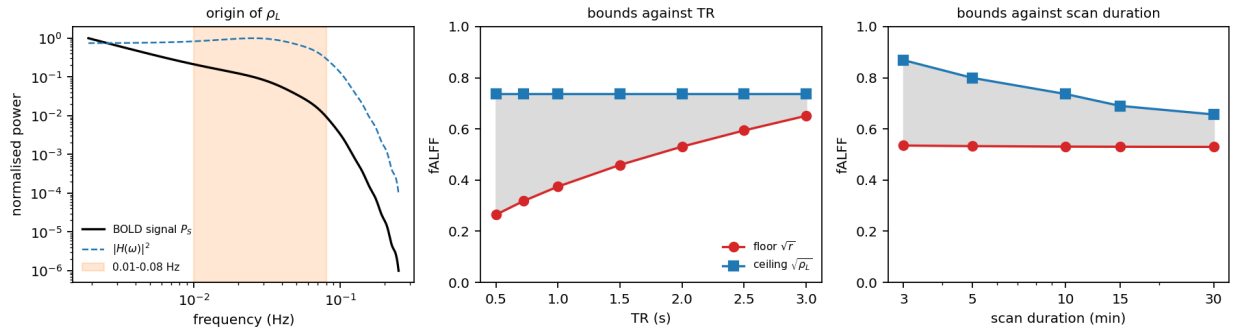


Fig. 1. The bounds on $fALFF$. (Left) The BOLD signal power spectrum (black), obtained from the fitted transfer function driven by a $1/f$ neural spectrum, and $|H(\omega)|^2$ alone (blue, dashed); the shaded region is the 0.01–0.08 Hz analysis band. ρ_L , and hence the $fALFF$ ceiling, is the fraction of the black curve lying in the shaded band, and depends on the neural spectrum as well as on hemodynamics. (Centre) The noise floor $\sqrt{r}$ (red) falls as the repetition time shortens, while the ceiling $\sqrt{\rho_L}$ (blue) is unchanged; the shaded region is the attainable range. (Right) The ceiling falls with scan duration because a $1/f$ drive adds power below the analysis band. In all three panels the physiology is identical throughout.

4.4 Sensitivity to baseline metabolism

Evaluating (13) and (15) for the reference acquisition, a 20 % higher baseline CMRO2 at fixed CBF raises ALFF by 2.0 % and $fALFF$ by 0.9 %. Both are small because both expressions include the factor $\theta\rho_L/(\theta\rho_L + r)$, the fraction of the power in the analysis band that is signal rather than noise, which is only 0.088 at $\theta = 0.05$. ALFF is nonetheless the more sensitive of the two by a factor of 2.2, and the disparity grows with signal-to-noise ratio: as $\theta \rightarrow \infty$ the $fALFF$ sensitivity falls back to zero while that of ALFF approaches the full power-law exponent β_D , so that the same 20 % change in baseline metabolism would raise ALFF by 26 % in a noise-free measurement. ALFF has a power-law dependence on baseline metabolism and is affected by

noise but not bounded by it. fALFF is bounded by it, and at realistic signal-to-noise ratios is confined near its lower bound.

Normalisation of fALFF makes it less susceptible to some types of noise but it compresses the measure into a narrow interval whose endpoints are set by the acquisition. The two measures provide different information, and the common practice of reporting them as interchangeable alternatives, or of preferring fALFF simply because it is normalised, is not supported by these considerations.

4.5 What a difference in fALFF can mean

From the above it follows that a difference in fALFF between two groups or two regions is consistent with several possible causes. These include a difference in the amplitude of spontaneous metabolic fluctuations, a difference in baseline oxygen extraction, hence in M , because of different resting blood flow, a difference in resting venous blood volume fraction V_0 , a difference in thermal noise, possibly modified by coil design or sensitivity, or a difference in acquisition parameters. Only the first is a statement about neural activity. Moreover, the flow-volume exponent α affects the metabolic gain G in (2), and can be related to vascular stiffness. Conditions that stiffen the venous bed, including ageing and hypertension, are therefore predicted to alter the sensitivity of ALFF and fALFF independent of any differences in neural activity.

5. Discussion

Our purpose has been to establish what ALFF and fALFF measure in light of a model that connects neural events to the BOLD signal. From this it is clear that ALFF and fALFF are not

255 alternative measures of the same physiology. ALFF scales as a power law in baseline
256 metabolism with exponent $\beta_D \approx 1.26$, whereas fALFF is a bounded, saturating function of
257 signal-to-noise ratio.

258 Every fALFF value is a position between two bounds that are not set by physiology. The floor
259 $\sqrt{r}$ is fixed by the analysis band and the sampling rate, the ceiling $\sqrt{\rho_L}$ by the hemodynamic
260 response together with the spectrum of spontaneous activity. At the signal-to-noise ratios typical
261 of resting-state acquisitions, fALFF sits near its floor, so much of the between-voxel variance in
262 an fALFF map may not reflect differences in neural activity. As a corollary, comparisons cannot
263 be made across acquisitions even with normalisation.

264 The dependence on TR is strong, such that a 44 % change in fALFF may be seen in a typical
265 comparison between TR = 2 s and TR = 0.5 s, even with fixed physiology. The dependence on
266 scan duration is smaller but systematic. Neither is corrected by the normalisation that defines
267 fALFF, which is what introduces the dependence on r , and hence on TR.

268 We suggest that studies reporting fALFF state the repetition time, the scan duration and the
269 analysis band alongside the values, and that comparisons across sites or across time be restricted
270 to acquisitions matched in all three. In addition, the bounds $\sqrt{r}$ and $\sqrt{\rho_L}$ should be reported
271 alongside group means, so measured values are placed in context within the attainable range.

272 ALFF is the preferred indicator of changes in underlying metabolism but neither fALFF nor
273 ALFF can be interpreted in terms of underlying activity directly without additional data.

274 Our analysis assumes white thermal noise and neglects physiological noise, which adds power
275 outside the analysis band and lowers fALFF independently of CMRO₂. The coupling ratio n is
276 treated as fixed, whereas if it varies with baseline metabolism the gain G is not constant and (2)

277 acquires a further term. The $1/f$ form of the neural drive is a model, and because the maximum
278 fALFF value depends on it, a different spectral form would give different numerical bounds
279 while leaving the existence of the bounds unchanged.

280

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311

312

313 **Appendix A. ALFF and fALFF under the amplitude convention**

314 **A.1 Two definitions**

315 Section 2.3 defines ALFF as the square root of the BOLD power integrated over the analysis
316 band. An equally common definition, and the one originally introduced by Zang et al. (1) and
317 Zou et al. (2), instead sums the Fourier *amplitudes* across the band,

$$318 \quad \text{ALFF}^{(1)} = \int_L A(f) df, \quad \text{fALFF}^{(1)} = \frac{\int_L A(f) df}{\int_\Omega A(f) df} \quad (\text{A1})$$

319 where $A(f) = |X(f)|$ is the modulus of the Fourier transform $X(f)$ of the voxel time series. The
320 definition of Section 2.3 is an L^2 (root-sum-of-squares) statistic, (A1) is an L^1 (sum-of-moduli)
321 statistic. AFNI implements both and distinguishes them by names as 3dRSFC and 3dAmpToRSFC,
322 ALFF and fALFF are the L^1 pair of (A1), while RSFA and fRSFA are the L^2 pair used earlier
323 (10). The further distinction between the sum and the mean of $A(f)$ over the band — Zang et
324 al. take the mean, AFNI the sum — is a constant factor $|L|$ that merely cancels in fALFF and
325 rescales ALFF.

326 The square root lies inside the integral in (A1) and outside it in (6) and every difference derived
327 below follows from that one change.

328 **A.2 The amplitude spectrum**

329 For a Gaussian process observed over a finite record, the real and imaginary parts of $X(f)$ are
330 independent and zero-mean with variance $P_S(f)/2$, so that $A(f)$ is Rayleigh distributed with

$$331 \quad E[A(f)] = 1/2 \sqrt{\pi} \sqrt{P_S(f)}, \quad E[A(f)^2] = P_S(f) \quad (\text{A2})$$

332 Writing $P_s(f) = s(f) + N_0$ with $s(f) = (MG)^2 |H(f)|^2 P_m(f)$ as in (3), the expected amplitude
 333 spectrum is proportional to

$$334 \quad u(f) = \sqrt{s(f) + N_0} \quad (\text{A3})$$

335 Signal and noise combine in power and are only then square-rooted. We can define integrals as

$$336 \quad I_X = \int_X u(f) df, \quad J_X = \int_X \frac{df}{u(f)}, \quad X \in \{L, \Omega\} \quad (\text{A4})$$

337 so that, up to the common factor $1/2\sqrt{\pi}$,

$$338 \quad \text{ALFF}^{(1)} = I_L, \quad \text{fALFF}^{(1)} = \frac{I_L}{I_\Omega} \quad (\text{A5})$$

339 In the noise-dominated limit, $s \ll N_0$ throughout Ω , so $u \rightarrow \sqrt{N_0}$, a constant, and $I_X \rightarrow |X|\sqrt{N_0}$.

340 In the signal-dominated limit $u \rightarrow \sqrt{s}$. Hence

$$341 \quad \theta \rightarrow 0: \text{fALFF}^{(1)} \rightarrow \frac{|L|}{|\Omega|} = r, \quad \theta \rightarrow \infty: \text{fALFF}^{(1)} \rightarrow \rho_L^{(1)} \equiv \frac{\int_L \sqrt{s} df}{\int_\Omega \sqrt{s} df} \quad (\text{A6})$$

342 and every measured value must lie between them,

$$343 \quad r \leq \text{fALFF}^{(1)} \leq \rho_L^{(1)} \quad (\text{A7})$$

344 Comparison with (10) shows that both bounds change in actual values.

345 The floor is r rather than $\sqrt{r}$, because the amplitude of every frequency is the same for pure
 346 white noise, so the fraction of total amplitude falling in L is exactly the fraction of the bandwidth
 347 that L occupies. The upper limit is $\rho_L^{(1)}$, the fraction of the *amplitude* rather than of the power
 348 spectrum lying in L . Taking the square root before integrating weights weak frequencies more

349 heavily relative to strong ones, so the spectrum above the analysis band contributes more to the
 350 denominator and $\rho_L^{(1)} < \sqrt{\rho_L}$.

351 **A.3 Sensitivity to baseline metabolism**

352 Write $s(f) = \theta g(f)$ with $\int_{\Omega} g \, df = 1$, so that $\theta = \theta/(N_0|\Omega|)$.

353 From (A3), $\theta g/u = u - N_0/u$. With $\theta \propto M^2$ and $M \propto \text{CMRO}_{2,0}^{\beta_D}$ from (12),

$$354 \quad \frac{d\ln\text{ALFF}^{(1)}}{d\ln\text{CMRO}_{2,0}} = \beta_D \varphi_L^{(1)}, \quad \frac{d\ln\text{fALFF}^{(1)}}{d\ln\text{CMRO}_{2,0}} = \beta_D (\varphi_L^{(1)} - \varphi_{\Omega}^{(1)}) \quad (\text{A10})$$

355 where

$$356 \quad \varphi_X^{(1)} = 1 - \frac{N_0 J_X}{I_X} \quad (\text{A11})$$

357 is the amplitude-weighted fraction of band X that is signal rather than noise, running from 0
 358 when noise dominates to 1 when signal dominates.

359 The results (A10) have the same format as those of Section 2.4. Rewriting (13) and (15) in the
 360 same notation,

$$361 \quad \frac{d\ln\text{ALFF}}{d\ln\text{CMRO}_{2,0}} = \beta_D \varphi_L^{(2)}, \quad \frac{d\ln\text{fALFF}}{d\ln\text{CMRO}_{2,0}} = \beta_D (\varphi_L^{(2)} - \varphi_{\Omega}^{(2)}) \quad (\text{A12})$$

362 with $\varphi_L^{(2)} = \theta \rho_L / (\theta \rho_L + r)$ and $\varphi_{\Omega}^{(2)} = \theta / (\theta + 1)$. The two conventions therefore differ only
 363 in how the effective signal fraction φ is computed. Thus, ALFF attains the full power-law
 364 exponent β_D only as $\varphi_L \rightarrow 1$, that is, only at high signal-to-noise ratio; in particular $\text{ALFF}^{(1)} \rightarrow$
 365 $\int_L \sqrt{s} \, df \propto M$ in that limit. In addition, normalisation subtracts φ_{Ω} , so fALFF is necessarily the

less sensitive of the two measures, and the ratio $(\varphi_L - \varphi_\Omega)/\varphi_L$ measures the effect of normalisation.

A.4 Numerical evaluation

The quantities above were evaluated with the transfer function, the $1/f$ drive and the frequency bands of Section 3. Table A1 compares the two conventions at the reference acquisition.

Table A1. The reference acquisition ($TR = 2$ s, ten-minute scan, $\theta = 0.05$) under the two conventions.

Quantity	L^2 , Section 2.3	L^1 , equation (A1)
Floor	$\sqrt{r} = 0.531$	$r = 0.282$
Ceiling	$\sqrt{\rho_L} = 0.736$	$\rho_L^{(1)} = 0.632$
Attainable range	0.205	0.350
fALFF at $\theta = 0.05$	0.542	0.288
Position within range	5.6 %	1.8 %
$d\ln\text{ALFF}/d\ln\text{CMRO}_{2,0}$	0.110	0.108
$d\ln\text{fALFF}/d\ln\text{CMRO}_{2,0}$	0.050	0.055
ALFF change for 20 % higher $\text{CMRO}_{2,0}$	+2.0 %	+2.0 %
fALFF change for 20 % higher $\text{CMRO}_{2,0}$	+0.9 %	+1.0 %

Tables A2 and A3 repeat Tables 1 and 2 for the amplitude convention.

376 *Table A2. Dependence of the amplitude-convention bounds on repetition time, for a ten-minute scan. The*
377 *floor is r , the ceiling $\rho_L^{(1)}$.*

TR (s)	r	$\rho_L^{(1)}$	fALFF ⁽¹⁾ at $\theta = 0.05$	fALFF at $\theta = 0.05, L^2$
0.50	0.070	0.628	0.081	0.304
0.72	0.101	0.628	0.111	0.349
1.00	0.140	0.628	0.150	0.399
1.50	0.211	0.629	0.219	0.476
2.00	0.282	0.632	0.288	0.542
2.50	0.353	0.637	0.358	0.602
3.00	0.424	0.646	0.427	0.656

378

379

380 *Table A3. Dependence of the amplitude-convention ceiling on scan duration, at $TR = 2$ s.*

T_{scan}	$\rho_L^{(1)}$	fALFF ⁽¹⁾ at $\theta = 0.05$	Ceiling $\sqrt{\rho_L}, L^2$
3 min	0.714	0.297	0.872
5 min	0.671	0.293	0.805
10 min	0.632	0.288	0.736
15 min	0.616	0.287	0.703
30 min	0.597	0.285	0.656

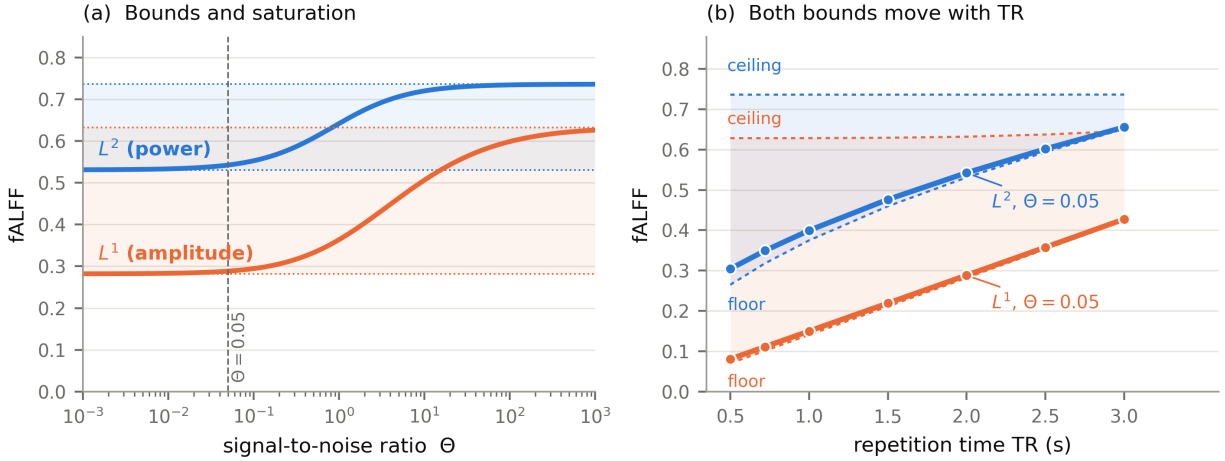


Fig. A1. ALFF and fALFF under the two conventions. (a) fALFF as a function of the total-band signal-to-noise ratio Θ for the reference acquisition, under the L^2 convention of Section 2.3 (blue) and the L^1 convention of (A1) (orange). Dotted lines and shading mark the attainable range in each case; the dashed vertical line is $\Theta = 0.05$. The L^1 range is the wider of the two, but a typical voxel sits closer to its floor. (b) Both bounds as functions of repetition time for a ten-minute scan, with the value attained at $\Theta = 0.05$ shown by the marked curves. The floor rises steeply with TR under both conventions, and approximately in proportion to TR under the L^1 convention.

A.5 Conclusions

The two definitions do not agree quantitatively but have similar limitations. For the reference acquisition the same voxel yields $fALFF = 0.542$ under the L^2 definition and 0.288 under the L^1 definition, a factor of 1.88 . Values are not comparable across studies that use different software or definitions. Papers reporting fALFF should state which definition was used.

The amplitude convention has a wider attainable range but saturates sooner. Its range, 0.350 , is 1.7 times the 0.205 available under the L^2 convention, mostly because the floor drops from $\sqrt{r}$ to r . In practice, for example if $\Theta = 0.05$, the measured value sits 1.8% of the way from floor to ceiling, against 5.6% under the L^2 convention. Normalising by amplitude rather than by power produces fALFF values that mainly reflect the signal-to-noise ratio.

399 The dependence on acquisition parameters is worse. The dependence on scan duration is
400 reduced. The ceiling falls by 16 % between three and thirty minutes against 25 % under the L^2
401 convention. The recommendation of Section 5, that TR, scan duration, analysis band and the two
402 bounds be reported alongside any fALFF value, still applies.

403 The sensitivities to baseline metabolism in Table A1 differ between the conventions by less than
404 a tenth of their value, and (A10) and (A12) are the same expression evaluated with different
405 weights. The choice of convention changes the scale of fALFF and the strength of its dependence
406 on the acquisition; it does not change how much it reports neural activity.

407

408

409 **Appendix B. Fluctuations of non-metabolic origin**

410 We have assumed the spontaneous BOLD signal fluctuations are driven by fluctuations in the
411 cerebral metabolic rate of oxygen. Resting cerebral blood flow and blood volume, however, may
412 also vary for reasons other than changes in oxygen consumption e.g. because of vasomotion and
413 Mayer waves, fluctuations in arterial blood pressure and CO₂, autoregulatory adjustments, and
414 changes in vessel tone. These could potentially produce BOLD signal changes and so affect
415 ALFF and fALFF.

416 The linearised relation on which (2) rests is

$$417 \quad \frac{\delta S}{S} = M[(\beta_D - \alpha) \delta f - \beta_D \delta m] \quad (\text{B1})$$

418 where δf and δm are the fractional changes in cerebral blood flow and in CMRO₂. Section 2
419 assumes the two are coupled, $\delta f = n \delta m$, which substituted into (B1) returns $\delta S/S = MG \delta m$
420 with $G = n(\beta_D - \alpha) - \beta_D$. Instead, more generally we may write

$$421 \quad \delta f = n \delta m + \delta f_v \quad (\text{B2})$$

422 in which δf_v is a flow fluctuation that is not driven by oxygen consumption. Substituting (B2)
423 into (B1),

$$424 \quad \frac{\delta S}{S} = M(G \delta m + G_v \delta f_v), \quad G = n(\beta_D - \alpha) - \beta_D, \quad G_v = \beta_D - \alpha \quad (\text{B3})$$

425 The calibration constant M measures how much deoxyhemoglobin is available to be modulated
426 and is indifferent to what does the modulating. The two driving processes are distinguished by
427 their respective gains.

428 An independent fluctuation of venous blood volume at fixed deoxyhemoglobin content can be
 429 added in the same way. Linearising (1) with respect to v at fixed q gives a third term
 430 $V_0(k_2 - k_3) \delta v$, which for the constants of Section 2.1 is $0.795 V_0 \delta v$ against $M\beta_D =$
 431 $V_0(k_1 + k_2) = 3.900 V_0$ for a fractional change in deoxyhemoglobin content. Volume thus has
 432 much weaker effects (by a factor of about five), and for the remainder of this appendix non-
 433 metabolic fluctuations are represented by δf_v alone, but qualitatively nothing below depends on
 434 that simplification.

435 The G factors for vascular flow and metabolic effects behave quite differently. G depends on the
 436 flow–metabolism coupling ratio n and vanishes at $n_{\text{crit}} = \beta_D/(\beta_D - \alpha) = 1.43$. G_v does not
 437 depend on n at all. For equal fractional fluctuations the ratio of the two contributions is

438
$$\frac{G_v}{G} = \frac{\beta_D - \alpha}{n(\beta_D - \alpha) - \beta_D} \quad (\text{B4})$$

439 which equals unity at $n = 1 + n_{\text{crit}} = 2.43$. Table B1 evaluates this ratio over the range of n
 440 commonly reported from calibrated BOLD.

n	G	G_v	G_v/G	σ_v/σ_m for equal BOLD power
1.50	0.058	0.876	15.1	0.07
1.80	0.321	0.876	2.73	0.37
2.00	0.496	0.876	1.77	0.57
2.50	0.934	0.876	0.94	1.07
3.00	1.372	0.876	0.64	1.57

Table B1. The metabolic and non-metabolic gains, for $\beta_D = 1.256$ and $\alpha = 0.38$. The last column is the ratio of fluctuation amplitudes at which the two contribute equal BOLD power.

Over the range 2–3 quoted in Section 2.1 the two gains are within a factor of two of one another, and below about $n = 2.4$ the non-metabolic drive is the more effective. Reported vasomotion amplitudes may thus contribute substantially to the BOLD signals.

Treating the two drives as uncorrelated, (3) becomes

$$P_S(\omega) = M^2[G^2|H_m(\omega)|^2P_m(\omega) + G_v^2|H_v(\omega)|^2P_v(\omega)] + N_0 \quad (\text{B5})$$

where H_v is the transfer function from a flow input to the BOLD signal. If the drives are partly correlated a cross-term $2M^2GG_v \text{Re}[H_m H_v^* S_{mv}]$ may be added. H_v and H_m likely overlap in frequency content but need not be identical.

The non-metabolic share of the total BOLD signal power is

$$\lambda = \frac{G_v^2 \int_{\Omega} |H_v|^2 P_v d\omega}{G^2 \int_{\Omega} |H_m|^2 P_m d\omega + G_v^2 \int_{\Omega} |H_v|^2 P_v d\omega} \quad (\text{B6})$$

P_{sig} , θ and r retain their definitions unchanged, so the only quantity that is affected is ρ_L , which becomes a weighted mixture

$$\rho_L = (1 - \lambda) \rho_L^m + \lambda \rho_L^v \quad (\text{B7})$$

of the band fractions of the two components taken separately.

Equations (6) to (10) remain valid as before. fALFF is still bounded between $\sqrt{r}$ and $\sqrt{\rho_L}$, still increases monotonically with θ provided $\rho_L > r$, still saturates, and still carries the same dependence on repetition time and scan duration. The presence of non-metabolic fluctuations changes the value of the ceiling but not its existence.

Equation (6) has $\text{ALFF} = \sqrt{\rho_L P_{\text{sig}} + r N_0 |\Omega|}$. We now however have two separable contributions to the signal power so we now write

$$P_L = P_L^m + P_L^v \text{ where } P^m = (1 - \lambda)P_{\text{sig}}, \quad P^v = \lambda P_{\text{sig}}, \quad P_L^m = (1 - \lambda)\rho_L^m P_{\text{sig}}, \quad P_L^v = \lambda\rho_L^v P_{\text{sig}}$$

The sum of the last two, divided by P_{sig} , is (B7). Dividing numerator and denominator by $N_0 |\Omega|$ and using $\theta = P_{\text{sig}}/(N_0 |\Omega|)$ converts $P_L + N_L$ to $\theta\rho_L + r$, P_L^m to $\theta(1 - \lambda)\rho_L^m$ and P_L^v to $\theta\lambda\rho_L^v$.

M multiplies both terms of (B3), so both parts of P_L scale as M^2 and $dP_L/d\ln M = 2P_L$. From (12), $d\ln M/d\ln \text{CMRO}_{2,0} = \beta_D$ at fixed CBF_0 , C_a and V_0 , so $dP_L/d\ln \text{CMRO}_{2,0} = 2\beta_D P_L$ so

$$\frac{d\ln \text{ALFF}}{d\ln \text{CMRO}_{2,0}} = \beta_D \frac{P_L}{P_L + N_L} = \beta_D \frac{\theta\rho_L}{\theta\rho_L + r} = \beta_D \varphi_L$$

σ_m affects P_L^m and $dP_L/d\ln \sigma_m = 2P_L^m$; likewise $dP_L/d\ln \sigma_v = 2P_L^v$ so

$$\frac{d\ln \text{ALFF}}{d\ln \sigma_m} = \frac{P_L^m}{P_L + N_L} = \frac{\theta(1 - \lambda)\rho_L^m}{\theta\rho_L + r} = \varphi_L^m, \quad \frac{d\ln \text{ALFF}}{d\ln \sigma_v} = \frac{P_L^v}{P_L + N_L} = \frac{\theta\lambda\rho_L^v}{\theta\rho_L + r} = \varphi_L^v$$

Adding the two

$$\varphi_L^m + \varphi_L^v = \frac{\theta[(1 - \lambda)\rho_L^m + \lambda\rho_L^v]}{\theta\rho_L + r} = \varphi_L$$

As $\text{fALFF}^2 = (P_L + N_L)/(P_{\text{sig}} + N_0 |\Omega|)$,

$$\frac{d\ln \text{fALFF}}{d\ln \sigma_m} = \varphi_L^m - \frac{\theta(1 - \lambda)}{\theta + 1}, \quad \frac{d\ln \text{fALFF}}{d\ln \sigma_v} = \varphi_L^v - \frac{\theta\lambda}{\theta + 1}$$

The upper limits on ALFF and fALFF are not a property of the hemodynamics alone but depend on λ which describes where the non-metabolic power spectrum overlaps or is different relative to

478 the analysis band. The ceiling arises from both the hemodynamic response and the spectrum of
479 spontaneous activity.

480 If the non-metabolic drive shares the $1/f$ shape of the metabolic one, the two are spectrally
481 identical and fALFF does not change. The lowest value is fixed by the acquisition, so fALFF is
482 insensitive not only to the amplitude of the physiological signal but also to its origin. fALFF
483 cannot distinguish a metabolic from a vascular fluctuation.

484 If a fraction λ of the BOLD power is of non-metabolic origin and all of it is ascribed to
485 metabolism, the inferred amplitude of spontaneous CMRO₂ fluctuation is too large by
486 $(1 - \lambda)^{-1/2}$: 15 % at $\lambda = 0.25$ and a factor of two at $\lambda = 0.75$. More seriously, a difference in
487 vasomotion amplitude, in arterial CO₂ variability, in blood pressure variability or in
488 neurovascular coupling will appear in an ALFF map as though it were a difference in
489 spontaneous neural activity.