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# The confound of hemodynamic response function variability in resting-state functional MRI studies

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Abstract: Functional magnetic resonance imaging (fMRI) is an indirect measure of neural activity with the hemodynamic response function (HRF) coupling it with unmeasured neural activity. The HRF, modulated by several non-neural factors, is variable across brain regions, individuals and populations. Yet, a majority of resting-state fMRI connectivity studies continue to assume a non-variable HRF. In this article, with supportive prior evidence, we argue that HRF variability cannot be ignored as it substantially confounds within-subject connectivity estimates and between-subjects connectivity group differences. We also discuss its clinical relevance with connectivity impairments confounded by HRF aberrations in several disorders. We present limited data on HRF differences between women and men, which resulted in a 15.4% median error in functional connectivity estimates in a group-level comparison. We also discuss the implications of HRF variability for fMRI studies in the spinal cord. There is a need for more dialogue within the community on the HRF confound, and we hope that our article is a catalyst in the process.

Keywords: BOLD fMRI; HRF; resting state connectivity; aging; sex differences; confound

## 1. Introduction

Functional magnetic resonance imaging (fMRI) has contributed significantly to the advancement of neuroscience, psychiatry, and neurology over the past three decades [1][2][3]. While neural activity can be directly measured *in vivo* through invasive procedures, blood oxygenation level-dependent (BOLD) fMRI is a complex, indirect measure of neural activity [4] (**Fig.1a**), measuring local blood oxygenation variations in response to active neurons. Dilation and constriction of blood vessels modulate this process, which, in turn, is modulated through numerous non-neural and neural factors that are difficult to delineate [5]. The combination of factors that lie between neural activity and BOLD is the hemodynamic response function (HRF) [6][7]. HRF shape is characterized by its amplitude (response height, RH), latency (time-to-peak, TTP) and width (full-width at half max, FWHM) (**Fig.1b**). Representing neurovascular coupling in the BOLD signal, the HRF is modulated by several non-neural factors [5][8] such as hematocrit, variable size/density of vasculature, global magnetic susceptibilities, alcohol/caffeine/lipid ingestion,

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pulse/respiration differences, and partial volume imaging of veins [8][9][10][11][12][13][14][15]. The HRF shape varies across the brain and individuals [9][10][16].

The current 'perspective' article focuses on this HRF variability (HRFv) and its impact on fMRI data processing and subsequent outcome measures within the scope of human fMRI research. This topic is important because thousands of human fMRI studies are published each year, but a significant portion of those do not account for HRFv. Resting-state fMRI (rs-fMRI) and connectivity studies dominate that list. Thus, there is a need for more dialogue within the community on HRFv. We argue that HRFv causes a measurable impact on the BOLD time series, which, if ignored, will confound fMRI outcomes such as connectivity. We substantiate our argument with prior human HRFv research, including those focusing on rs-fMRI connectivity. We also present limited new data (to substantiate our 'perspective') on HRFv across two important demographic variables: age and sex. Lastly, to cover structures of the central nervous system beyond the brain, we also discuss the implications of HRFv for spinal cord fMRI.

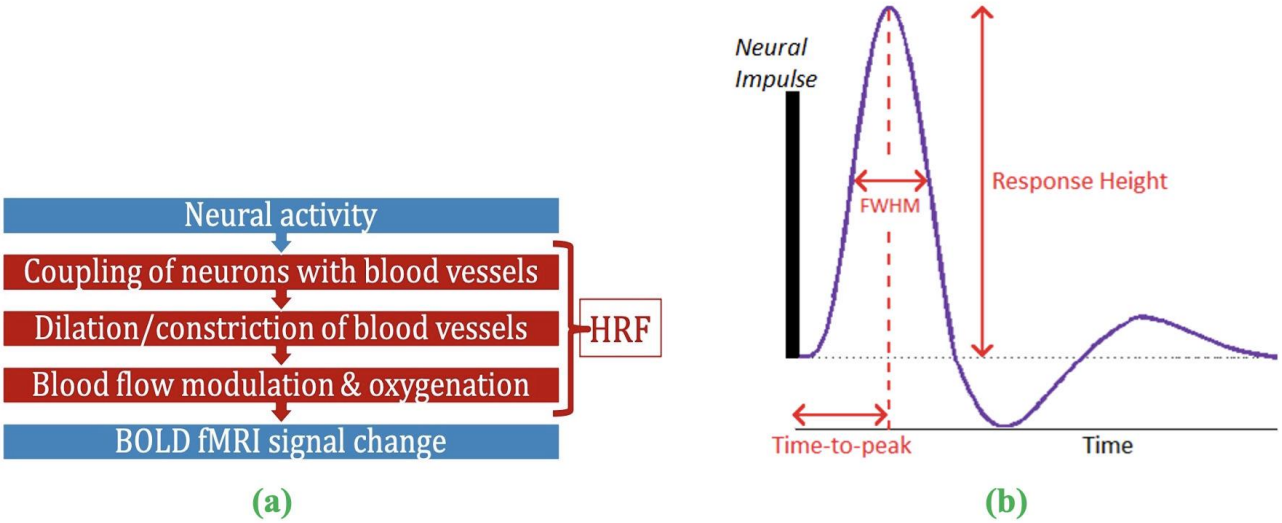


**Figure 1. (a)** FMRI is an indirect measure of neural activity. What stands between them is the hemodynamic response function (HRF). **(b)** The HRF is the BOLD response to a neural impulse. It has a peak (response height) occurring sometime after the neural impulse (time-to-peak) (HRF width = FWHM). The HRF always has this shape (biological), but these parameters are variable.

## 2. The problem of HRF variability

HRFv was first demonstrated in 1998 [10] and further examined in later years [9][17][18][19]. The HRF of a given brain region was identified to be different across individuals, and within a given individual, it was different across brain regions. Non-neural factors affecting the HRF is not merely the concern because a variable known HRF could be accounted for. Instead, the concern is that we do not understand these variable factors (and thus the HRF). The issue is alleviated in task fMRI studies by often modeling the HRF confound as time/dispersion derivatives of the canonical HRF in a general linear model (GLM) framework, which works well since BOLD is time-locked to an external stimulus. However, the outlook is different in rs-fMRI studies, which mostly ignore HRFv. The notion of HRF not being variable enough to be a serious confound was challenging to test, if not impossible, a few years ago because of the inability to estimate the HRF from rs-fMRI data. Necessary technical advancements (e.g., point-process theory [20][21]) have now resulted in rs-fMRI deconvolution techniques that are capable of HRF estimation from resting-state fMRI data [22][23][24][25]. We take a closer look at these techniques next.

## 3. HRF estimation from resting-state fMRI data

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HRF estimation can be straightforward with two known quantities (fMRI and neural activity) and one unknown (HRF). This is possible with simultaneous fMRI and invasive recordings (e.g., [26][27]), which is hardly feasible in humans. Obtaining simultaneous rs-EEG/fMRI data and considering EEG as the neural input to deconvolve fMRI (using AFNI's *3dDeconvolve* [28]) is problematic because generative fMRI models do not consider scalp EEG as properly representing BOLD-inducing neural activity [4]. A viable alternative is estimating HRF latency from a hypercapnic challenge because breath-hold causes vasodilation and modulates cerebral blood flow (CBF) [29][30][31] in the absence of neural activity, allowing us to measure vascular latency. Chang et al. [32] utilized this to correct for vascular latency prior to connectivity analysis. The disadvantage is that an additional breath-hold scan is not always feasible or available. Breath-hold is prone to subjective performance and can be challenging in those with some neurological diseases [33][34]. Moreover, it only measures one aspect of HRF shape (TTP), while the entire HRF impacts BOLD.

To circumvent these concerns, an alternative is to perform blind deconvolution; that is, solve the mathematically ill-posed inverse problem of having two unknowns (HRF and neural activity) and one known (fMRI). This is feasible because the natural limits and biophysics of HRF and fMRI are well understood. HRF estimation then becomes a constrained optimization exercise. Such deconvolution techniques primarily focusing on task fMRI data [35][36][37][38][39][40][41][42] are generally robust to HRF misspecification within a narrow physiological range, but are not viable for estimating voxel-specific HRFs in the entire brain, especially in rs-fMRI data. Whole-brain HRF estimation is preferable with rs-fMRI data because, with task fMRI, a given task does not activate the entire brain uniformly [43], and even among activated voxels, the BOLD response is mostly non-uniform [44], sometimes leading to biologically implausible HRF estimates [43]. Some techniques that might, in principle, be viable for rs-fMRI have never been tested using rs-fMRI data [45][46].

This leaves us with four rs-fMRI deconvolution techniques that have been more widely adopted: (i) Wu et al.'s [22] data-driven rsHRF method [47], (ii) parametric generative state-space models proposed within the stochastic dynamic causal modeling (DCM) framework [48][49][23], (iii) physiologically informed DCM [24] (developed for task fMRI but can be extended to rs-fMRI), and (iv) Total Activation [25] (estimates an "activity-inducing signal" from BOLD, from which it is possible in principle to estimate the HRF by Wiener deconvolution), which has been applied in the brain [50][51] as well as spinal cord [52]. Notably, a substantial number of studies examining HRFv (described later) utilized Wu et al.'s technique [22], hence we describe it briefly here. The Wu et al. technique models rs-fMRI data as event-related time series, with events modeled as point-processes [53]. Then it estimates the best-fit HRF in a least-squares sense, using the BOLD time series at identified events. Finally, the latent neural time series is estimated using Wiener deconvolution from the measured BOLD and the estimated HRF [54]. This technique has been validated using simulations, non-invasive and invasive data [20][22][55][47], and has been applied in many recent papers [55][56][57][58][59][60][61][62]. HRFs separated by four weeks demonstrated moderate test-retest reliability (ICC=0.51) [63], which is impressive by current neuroimaging standards [64]. We next present the impact of HRFv on rs-fMRI data.

## 4. The confound of HRF variability on connectivity estimates

We focus here on functional connectivity (FC) [65] because most rs-fMRI studies investigate FC, or metrics derived from FC such as dynamic connectivity and graph measures. It is, however, notable that the HRF confound has also been investigated for effective connectivity models such as DCM [48], Granger causality [66][67][68][69][45], and multivariate dynamical system models [70][71][72]. Effective connectivity estimated from fMRI data is viable [66][73] as well as accurate [23][26][74][75] only after deconvolution.

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FC studies have, however, largely ignored HRFv either with the assumption that the HRF is similar enough among brain regions and individuals or due to the unavailability of HRF estimation methods. Recent evidence suggests that these assumptions must be re-evaluated. Although researchers have been aware, since the early days of fMRI, that BOLD measures blood oxygenation and not neural activity, the magnitude of HRF confound on FC is being investigated only recently with the availability of deconvolution techniques. We take a closer look at these. It has been demonstrated that the HRF is variable [9][10][55][76][77] and recent reports suggest that ignoring it can introduce confounds in FC estimates [55][57][59][78][79]. In fact, our study reported significant HRFv in the brain's default mode network (DMN) that confounded FC by about 14.7% [55]. This error in FC estimates due to HRFv (FC-error) was smaller for within-lobe FC (12.6%) vs. between-lobes (15.6%), perhaps due to more variable vasculature in the latter case.

The HRF is not only different across individuals, but also different across clinical populations due to impairments in various factors contributing to HRFv. Our prior work has highlighted this in autism [78], post-traumatic stress disorder (PTSD) [57], obsessive-compulsive disorder (OCD) [63], bipolar disorder and schizophrenia [80]. They also demonstrated that HRF impairments are significant enough to confound FC group differences; and sometimes the confound was of a similar order of magnitude as FC impairments in these diseases. Other labs have made similar observations. For example, another study found that HRF alterations confound FC [81]. HRFv also confounded rat FC [82]. Using variable HRFs that are person-specific (vs. fixed HRF) improved connectivity estimates [83]. Taken together, emerging evidence indicates that HRFv is concerning for rs-fMRI connectivity and clinical applications.

## 5. The importance of studying HRF variability

Non-invasive measurements are not as 'clean' as invasive ones. There is always an effort to make fMRI data as 'clean' as possible by maximizing relative variance from neural sources. Examples of such efforts include minimizing physiological/thermal noise through ultra-high-field imaging (≥7T) [84], improved acquisition sequences [85][86], and better denoising [21][87]. Today we are in a reproducibility crisis in functional imaging [88][89][90], indicating that further advancements are needed to make this technology clinically more useful. We still do not understand the substantial intra- and inter-subject variability of fMRI outcomes. Further characterization of this variability is timely to maximize the percentage variance in BOLD explained by the underlying neural activity.

Effective modeling of HRFv could potentially contribute to this effort. Like head motion or physiological noise, HRFv is an undesirable confound reducing fMRI data fidelity. We predict that minimizing HRFv in fMRI data will improve data quality and enhance clinical discovery. Concerns about the HRF confound also exist among the broader neuroscience community. Examples include the viewpoint of cellular neuroscientists [29], special issue articles on HRFv [91], studies on non-neural factors and BOLD [92], and investigating the link between fMRI and neural activity [93].

## 6. Clinical research and HRF variability

Evidence suggests that HRFv is relevant for clinical and geriatric research. HRFs in older adults are different from their younger counterparts. Older adults have longer TTP and shorter RH, largely due to vascular factors [94]. Such change is associated with Alzheimer's disease as well [95]. Longer TTP is also linked to reduced intelligence [96]. Aberrant HRFs have been observed in stress [97], mild traumatic brain injury [98], aging [94][99][100], isolated cervical dystonia [101], and levels of consciousness [102][103]. Such HRF changes are concerning because they are at least partly driven by non-neural factors and can confound FC group differences. Although studying non-neural factors in brain disorders is a valid enterprise, attributing FC group differences entirely to neural activity is problematic. HRFv in neurological disorders is yet to be investigated; however, our prior work in psychiatric conditions (autism [78], PTSD [57], schizophrenia and bipolar [80]) demonstrated that HRF impairments in these conditions invariably confounds FC

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group differences, and the confound can sometimes be of the same order of magnitude as group differences. Taken together, HRFv has implications across a spectrum of cognitive, psychiatric and geriatric domains, and perhaps also in other cases in which HRFv has yet to be investigated.

## 7. Demographic variables and HRF variability

Non-neural factors that affect the HRF also differ across two highly relevant variables – age and sex. Aging causes vascular degradation; blood vessels of older adults are stiffer and less pulsatile, typically resulting in weaker BOLD responses to the same magnitude of neural activity (i.e., shorter RH) as well as longer time for peak BOLD activity (longer TTP) [94][99][100]. There is evidence for altered HRF in older adults [94][99], although the confound of HRFv on young vs. old FC group differences has not yet been studied. There is motivation to hypothesize that accounting for HRFv is essential for minimizing these vascular and other non-neural age-related confounds in rs-fMRI data. In fact, a recent report [99] noted that "*vascular confounds in fMRI studies are common. Despite over 10,000 BOLD-fMRI papers on aging, fewer than 20 have applied techniques to correct for vascular effects*."

Factors affecting the HRF also differ between women and men. Men have lower CBF independent of neural activity [104][105], which affects the HRF [6][106]. Other factors that exhibit sex differences include vascular physiology [107], capillary microcirculation [108], and overall cerebral hemodynamics [109]. Ignoring these factors by assuming a fixed canonical HRF is a potential confound in rs-fMRI studies that report data from both sexes, and/or perform women vs. men group comparisons. Despite this, HRF sex differences have never been directly studied. Hence, we next present limited data in this context.

## 8. Results on HRF differences between sexes and their impact on connectivity

We utilized 7T rs-fMRI data from our earlier HRF study (N=47, 22F/25M, healthy adults) [55] (data made public [110]) (please refer to these publications for data details). Kindly note that since this is a perspective article, we have not presented comprehensive results, but we hope that the results herein will encourage extensive follow-up studies. Briefly, upon standard pre-processing, we extracted mean region-of-interest (ROI) time series from DMN regions defined by the Power-Petersen atlas [1] and estimated FC between all DMN ROI pairs using Pearson's correlation [64][111]. This procedure was repeated for two separate pipelines: data with deconvolution (DC) and no deconvolution (NDC), which differed only in HRFv. We also obtained HRF parameters for each ROI during deconvolution.

We compared ROI-level HRF parameters between men and women ($p$<0.05, FDR corrected). T-test was used for RH, and Wilcoxon rank-sum test was used for discrete variables (TTP, FWHM). There were no RH differences, but men had significantly longer TTP and/or FWHM in four regions (**Table 1**). Longer TTP/FWHM in men could be due to CBF and vascular differences between sexes [104][105][106][107][108][109]. The mean values averaged across all ROIs and subjects were as follows: RH (women=5.01, men=4.77), TTP (women=5.61s, men=5.73s), FWHM (women=5.62s, men=5.79s).

Next, we computed the error in FC group difference T-stats resulting from HRF differences. For this, women vs. men FC stats were performed separately for DC and NDC pipelines, and the percentage difference in resulting statistical maps was computed (**Fig.2**). HRF differences between sexes resulted in a 15.4% median FC error. After thresholding ($p$<0.05, FDR corrected), all three identified FCs were false positives (FC of temporal_inf_L/frontal_sup_L/fusiform_L with temporal_mid_L). Although only four regions and three connections exhibited significant HRF and FC differences, respectively, it must not be inferred that the rest of the regions or connections were unaffected by HRFv. These HRF/FC differences were large enough to be detected for our sample size and data quality, but that does not mean that the difference can be ignored in the other connections. The testament to this fact is that HRF differences between sexes resulted in 15.4% median FC error with contribution even from a vast number of regions/FCs outside of the

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significant ones (**Fig.2**). Our prior work has demonstrated the same [55][57][78][80]. Taken together, a measurable portion of sex differences in DMN were attributable to HRFv.

(a) Comparison of HRF parameters between sexes (regions exhibiting significant differences)

| ROI | HRF parameter | Women vs. men | | Mean (standard deviation) | | Range | |
|---|---|---|---|---|---|---|---|
| | | *p* value | *Z* stat | Women | Men | Women | Men |
| Frontal orbital L | TTP | 0.015 | 2.4 | 4.45 (0.23) | 4.67 (0.13) | [3.73, 4.67] | [4.23, 4.78] |
| | FWHM | 0.025 | 2.2 | 4.44 (0.22) | 4.77 (0.29) | [4.01, 4.99] | [4.11, 5.22] |
| Temporal mid L | TTP | 0.005 | 2.8 | 6.26 (0.17) | 6.59 (0.32) | [5.81, 6.70] | [6.03, 7.06] |
| | FWHM | 0.017 | 2.4 | 6.31 (0.43) | 6.64 (0.41) | [5.63, 6.99] | [6.08, 7.43] |
| Temporal inf L | TTP | 0.023 | 2.3 | 4.12 (0.17) | 4.34 (0.20) | [3.89, 4.56] | [4.12, 4.67] |
| Frontal mid L | FWHM | 0.027 | 2.2 | 5.62 (0.38) | 5.96 (0.35) | [4.83, 6.18] | [5.29, 7.41] |

(b) Error in functional connectivity estimates (women vs. men) resulting from HRF variability

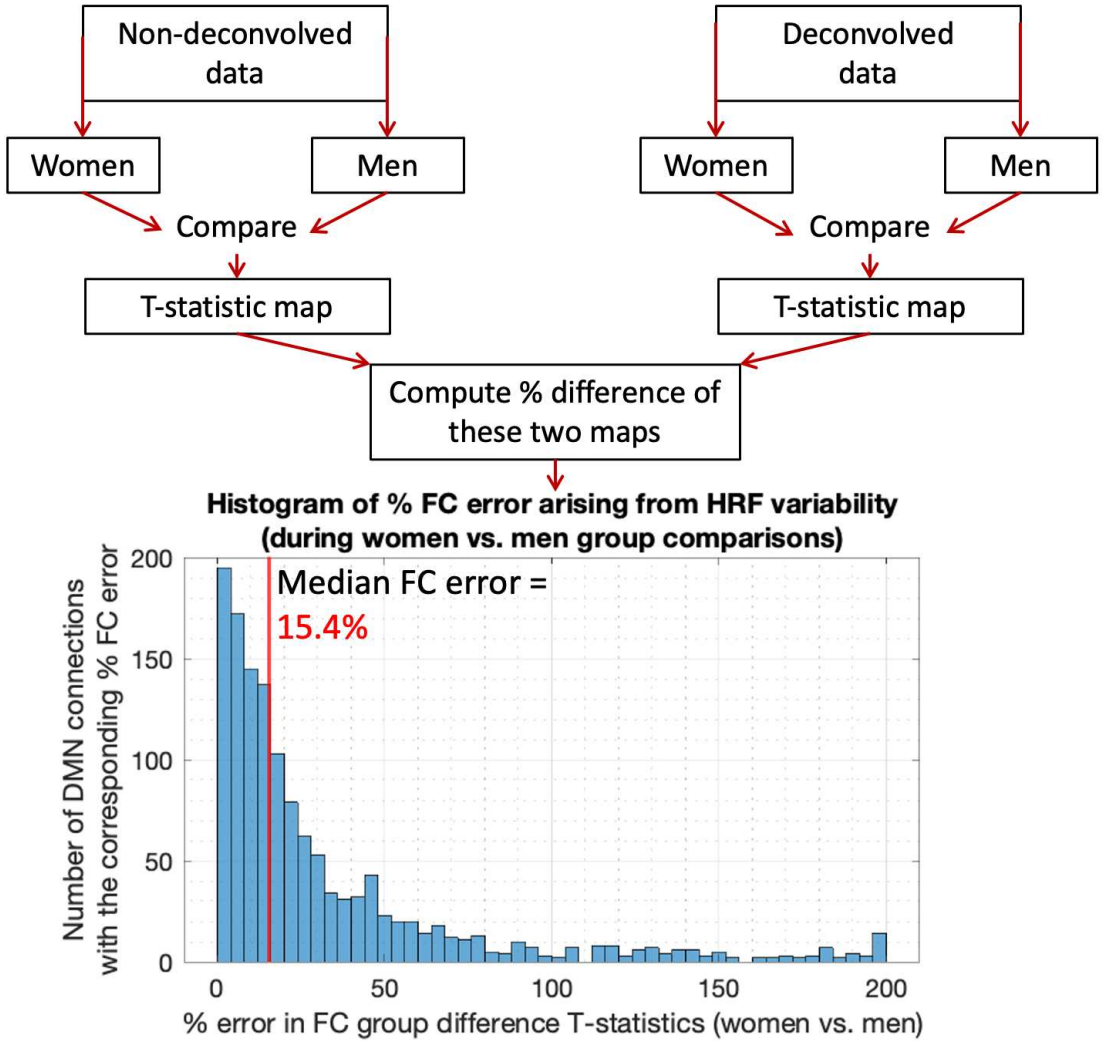


**Figure 2.** A flowchart illustrating our analysis and the final result obtained. The histogram shows the distribution of % FC error arising from men vs. women HRF differences. The median FC error was 15.4%, with a 95% confidence interval of [1.5% – 131.6%].

As a secondary result not related to sex differences, we also report whole-brain-level average metrics of variability in HRF parameters within and between healthy young adult

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subjects, because these were not reported in our earlier publication [55], but they support our conclusions and encourage future work. Of course, for the nature of this article, these results could be more complex and extensive. Using the same FC data, we (i) computed within-subjects variability of each HRF parameter as the mean percentage difference between all ROI pairs; and (ii) computed between-subjects variability of each HRF parameter as the mean percentage difference between all pairs of subjects. We used a t-test for RH and a rank-sum test for TTP/FWHM ($p$<0.05, FDR corrected). Within-subjects, we found on average 14.1% RH variability, 13.5% TTP and 13.4% FWHM variability. L/R orbitofrontal had the largest HRF difference with other regions (86%/65% RH, 43%/24% TTP, 42%/24% FWHM variability), perhaps due to susceptibility [11] and/or vascular [99] differences. Temporal lobe had larger variability than other lobes in RH ($p$=0.034), TTP ($p$=0.039) and FWHM ($p$=0.037). Between-lobe variability was higher than within-lobe in RH ($p$=0.039), TTP ($p$=0.028) and FWHM ($p$=0.041) (possibly due to vastly different vasculature across lobes). Between-subjects HRFv (RH: 29.8%, TTP: 28.5%, FWHM: 28.1%) was larger than within-subjects. The occipital lobe varied significantly less across subjects than other lobes in RH ($p$=0.048) and TTP ($p$=0.045).

## 9. The HRF in the spinal cord

The central nervous system (CNS), which includes the brain and spinal cord, is a single continuous entity. But prior HRF literature is exclusively focused on the brain. Cord rs-fMRI studies have so far not accounted for HRFv, except for a recent study [52]. If systematic brain HRF changes in pathological conditions translate to the cord, it is concerning because the cord is clinically relevant for several neurological diseases (e.g., multiple sclerosis [112], chronic pain [113], amyotrophic lateral sclerosis [114], transverse myelitis [115], ataxia [116], and spinal cord injury [117]). Cord impairments are being discovered in other pathologies (Alzheimer's disease [118] and cerebral palsy [119]), suggesting that more disorders could involve the cord than we currently understand. HRFv could confound cord FC impairments in these diseases. Hence, characterizing HRFv in the spinal cord is clinically relevant and novel.

## 10. Discussion and conclusions

Herein we described prior evidence for HRFv and its confound on rs-fMRI FC and elaborated on this research's importance and clinical relevance. Unexplained variability in BOLD is a more significant concern today than before because connectivity is used in sophisticated contexts such as dynamics [120], single-subject-level prediction [121], laminar fMRI [122], and precision medicine [123]. HRFv matters to a larger extent for all the desired 'precision' and fidelity expected of rs-fMRI today. With fast fMRI acquisition becoming prevalent [86][124], accounting for HRFv is even more critical [16] to determine the neural/vascular origin of fMRI timing differences. Thus far, FC error arising only from spatial HRFv has been quantified, and only in parts of the brain and in small samples [55]. We provided limited data for FC error between sexes. Further research is required to quantify HRFv and FC error across various within- and between-subject comparison scenarios and demographic variables.

In summary, measurements of FC often involve unexplained variance between 40% (ML prediction) and 70% (behavioral association) [121][123]. While the underlying prediction/association models may be statistically significant and perform above chance, there is still a sizeable unexplained variance. We, therefore, argue that the HRF confound, typically in the range of 10–30%, may explain a part of this variance and thus should be commonly accounted for during rs-fMRI data pre-processing.

**Conflicts of Interest:**The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**CRediT (Contributor Roles Taxonomy) – author contributions: D.R.**: Conceptualization, Methodology, Software, Data Analysis, Investigation, Visualization, Writing - Original Draft, Reviewing and Editing. **R.L.B.**: Investigation, Writing - Reviewing and Editing, Supervision. **G.D.**:

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Conceptualization, Methodology, Data Acquisition, Investigation, Writing - Reviewing and Editing, Supervision.

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**Data Availability Statement:**The source data used in this article is already publicly available [110]. Data specifically related to the presented results can be made available upon reasonable request to the corresponding author.

## References

[1] J. D. Power, A. L. Cohen, S. M. Nelson, G. S. Wig, K. A. Barnes, J. A. Church, A. C. Vogel, T. O. Laumann, F. M. Miezin, B. L. Schlaggar and S. E. Petersen, "Functional network organization of the human brain," *Neuron,* vol. 72, no. 4, pp. 665-78, 2011.

[2] P. J. Nathan, K. L. Phan, C. J. Harmer, M. A. Mehta and E. T. Bullmore, "Increasing pharmacological knowledge about human neurological and psychiatric disorders through functional neuroimaging and its application in drug discovery.," *Current opinion in pharmacology,* vol. 14, p. 54–61, 2014.

[3] C. Rosazza and L. Minati, "Resting-state brain networks: literature review and clinical applications.," *Neurological sciences,* vol. 32, no. 5, p. 773–785, 2011.

[4] N. K. Logothetis, J. Pauls, M. Augath, T. Trinath and A. Oeltermann, "Neurophysiological investigation of the basis of the fMRI signal," *Nature,* vol. 412, pp. 150-157, 2001.

[5] F. Biessmann, Y. Murayama, N. Logothetis, K. Müller and F. Meinecke, "Improved decoding of neural activity from fMRI signals using non-separable spatiotemporal deconvolutions," *Neuroimage,* vol. 61, no. 4, pp. 1031-42, 2012.

[6] J. H. Kim and D. Ress, "Arterial impulse model for the BOLD response to brief neural activation," *Neuroimage,* vol. 124(Pt A), pp. 394-408, 2016.

[7] J. V. Duarte, J. M. Pereira, B. Quendera, M. Raimundo, C. Moreno, L. Gomes, F. Carrilho and M. Castelo-Branco, "Early disrupted neurovascular coupling and changed event level hemodynamic response function in type 2 diabetes: an fMRI study," *Journal of Cerebral Blood Flow and Metabolism,* vol. 35, no. 10, pp. 1671-1680, 2015.

[8] H. S. Yang, Z. Liang, J. F. Yao, X. Shen, B. D. Frederick and Y. Tong, "Vascular effects of caffeine found in BOLD fMRI.," *Journal of neuroscience research,* vol. 97, no. 4, p. 456–466, 2019.

[9] D. A. Handwerker, J. M. Ollinger and M. D'Esposito, "Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses," *Neuroimage,* vol. 21, no. 4, pp. 1639-51, 2004.

[10] G. K. Aguirre, E. Zarahn and M. D'esposito, "The variability of human, BOLD hemodynamic responses," *Neuroimage,* vol. 8, no. 4, pp. 360-9, 1998.

[11] R. Buxton, "Introduction to Functional Magnetic Resonance Imaging: Principles and Techniques," *Energy,* vol. 24, no. 2, pp. xi, 523, 2002.

[12] J. Levin, M. Ross, J. Mendelson, M. Kaufman, N. Lange, L. Maas, N. Mello, B. Cohen and P. Renshaw, "Reduction in BOLD fMRI response to primary visual stimulation following alcohol ingestion," *Psychiatry Research,* vol. 82, no. 3, p. 135–46, 1998.

[13] M. D. Noseworthy, J. Alfonsi and S. Bells, "Attenuation of brain BOLD response following lipid ingestion," *Human Brain Mapping,* vol. 20, no. 2, p. 116–121, 2003.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 February 2023 doi:10.20944/preprints202302.0516.v1

[14] Y. Tong and B. D. Frederick, "Tracking cerebral blood flow in BOLD fMRI using recursively generated regressors," *Human brain mapping,* vol. 35, no. 11, p. 5471–5485, 2014.

[15] M. Bernier, S. C. Cunnane and K. Whittingstall, "The morphology of the human cerebrovascular system.," *Human brain mapping,* vol. 39, no. 12, p. 4962–4975, 2018.

[16] L. D. Lewis, K. Setsompop, B. R. Rosen and J. R. Polimeni, "Stimulus-dependent hemodynamic response timing across the human subcortical-cortical visual pathway identified through high spatiotemporal resolution 7T fMRI.," *NeuroImage,* vol. 181, p. 279–291, 2018.

[17] F. M. Miezin, L. Maccotta, J. M. Ollinger, S. E. Petersen and R. L. Buckner, "Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing," *Neuroimage,* vol. 11(6 Pt 1), pp. 735-759, 2000.

[18] J. A. de Zwart, A. C. Silva, P. van Gelderen, P. Kellman, M. Fukunaga, R. Chu, A. P. Koretsky, J. A. Frank and J. H. Duyn, "Temporal dynamics of the BOLD fMRI impulse response.," *NeuroImage,* vol. 24, no. 3, p. NeuroImage, 2005.

[19] S. Badillo, T. Vincent and P. Ciuciu, "Group-level impacts of within- and between-subject hemodynamic variability in fMRI.," *NeuroImage,* vol. 82, p. 433–448, 2013.

[20] E. Tagliazucchi, P. Balenzuela, D. Fraiman and D. R. Chialvo, "Criticality in large-scale brain fMRI dynamics unveiled by a novel point process analysis," *Frontiers in Physiology,* vol. 3, p. 15, 2012.

[21] J. D. Power, B. L. Schlaggar and S. E. Petersen, "Recent progress and outstanding issues in motion correction in resting state fMRI," *Neuroimage,* vol. 105, pp. 536-51, 2015.

[22] G. R. Wu, W. Liao, S. Stramaglia, J. R. Ding, H. Chen and D. Marinazzo, "A blind deconvolution approach to recover effective connectivity brain networks from resting state fMRI data," *Medical Image Analysis,* vol. 17, no. 3, pp. 365-374, 2013.

[23] M. Havlicek, K. J. Friston, J. Jan, M. Brazdil and V. D. Calhoun, "Dynamic modeling of neuronal responses in fMRI using cubature Kalman filtering," *Neuroimage,* vol. 56, no. 4, pp. 2109-28, 2011.

[24] M. Havlicek, A. Roebroeck, K. Friston, A. Gardumi, D. Ivanov and K. Uludag, "Physiologically informed dynamic causal modeling of fMRI data.," *NeuroImage,* vol. 122, p. 355–372, 2015.

[25] F. I. Karahanoğlu, C. Caballero-Gaudes, F. Lazeyras and D. Van de Ville, "Total activation: fMRI deconvolution through spatio-temporal regularization.," *NeuroImage,* vol. 73, p. 121–134, 2013.

[26] O. David, I. Guillemain, S. Saillet, S. Reyt, S. Deransart, C. Segebarth and A. Depaulis, "Identifying neural drivers with functional MRI: an electrophysiological validation," *PLoS Biology,* vol. 23, no. 6, pp. 2683-97, 2008.

[27] Y. Wang, S. Katwal, B. Rogers, J. Gore and G. Deshpande, "Experimental Validation of Dynamic Granger Causality for Inferring Stimulus-evoked Sub-100ms Timing Differences from fMRI," *IEEE Trans Neural Syst Rehabil Eng.,* vol. 25, no. 6, p. 539-546, 2017.

[28] B. Feige, K. Spiegelhalder, A. Kiemen, O. G. Bosch, L. Tebartz van Elst, J. Hennig, E. Seifritz and D. Riemann, "Distinctive time-lagged resting-state networks revealed by simultaneous EEG-fMRI.," *NeuroImage,* vol. 145(Pt A), pp. 1-10, 2017.

[29] C. N. Hall, C. Howarth, Z. Kurth-Nelson and A. Mishra, "Interpreting BOLD: towards a dialogue between cognitive and cellular neuroscience," *Philos Trans R Soc Lond B.,* vol. 371, no. 1705, p. 20150348, 2016.

[30] M. E. Thomason, L. C. Foland and G. H. Glover, "Calibration of BOLD fMRI using breath holding reduces group variance during a cognitive task.," *Human brain mapping,* vol. 28, no. 1, pp. 59-68, 2007.

[31] I. M. McDonough, A. Bender, L. Patihis, E. A. Stinson, S. K. Letang and W. S. Miller, "The Trouble Interpreting fMRI Studies in Populations with Cerebrovascular Risk: The Use of a Subject-Specific

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 February 2023 doi:10.20944/preprints202302.0516.v1

Hemodynamic Response Function in a Study of Age, Vascular Risk, and Memory," *bioRxiv,* p. 512343, 2019.

[32] C. Chang, M. E. Thomason and G. H. Glover, "Mapping and correction of vascular hemodynamic latency in the BOLD signal.," *NeuroImage,* vol. 43, no. 1, p. 90–102, 2008.

[33] V. R. Spano, D. M. Mandell, J. Poublanc, K. Sam, A. Battisti-Charbonney, O. Pucci, J. S. Han, A. P. Crawley, J. A. Fisher and D. J. Mikulis, "CO2 blood oxygen level-dependent MR mapping of cerebrovascular reserve in a clinical population: safety, tolerability, and technical feasibility.," *Radiology,* vol. 266, no. 2, p. 592–598, 2013.

[34] A. L. Urback, B. J. MacIntosh and B. I. Goldstein, "Cerebrovascular reactivity measured by functional magnetic resonance imaging during breath-hold challenge: A systematic review.," *Neuroscience and biobehavioral reviews,* vol. 79, pp. 27-47, 2017.

[35] D. R. Gitelman, W. D. Penny, J. Ashburner and K. J. Friston, "Modeling regional and psychophysiologic interactions in fMRI: the importance of hemodynamic deconvolution.," *NeuroImage,* vol. 19, no. 1, p. 200–207, 2003.

[36] C. Caballero Gaudes, N. Petridou, S. T. Francis, I. L. Dryden and P. A. Gowland, "Paradigm free mapping with sparse regression automatically detects single-trial functional magnetic resonance imaging blood oxygenation level dependent responses.," *Human brain mapping,* vol. 34, no. 3, p. 501–518, 2013.

[37] C. C. Gaudes, N. Petridou, I. L. Dryden, L. Bai, S. T. Francis and P. A. Gowland, "Detection and characterization of single-trial fMRI bold responses: paradigm free mapping.," *Human brain mapping,* vol. 32, no. 9, p. 1400–1418, 2011.

[38] L. Hernandez-Garcia and M. O. Ulfarsson, "Neuronal event detection in fMRI time series using iterative deconvolution techniques.," *Magnetic resonance imaging,* vol. 29, no. 3, p. 353–364, 2011.

[39] K. Bush and J. Cisler, "Decoding neural events from fMRI BOLD signal: a comparison of existing approaches and development of a new algorithm.," *Magnetic resonance imaging,* vol. 31, no. 6, p. 976–989, 2013.

[40] K. Bush, J. Cisler, J. Bian, G. Hazaroglu, O. Hazaroglu and C. Kilts, "Improving the precision of fMRI BOLD signal deconvolution with implications for connectivity analysis.," *Magnetic resonance imaging,* vol. 33, no. 10, p. 1314–1323, 2015.

[41] I. Khalidov, J. Fadili, F. Lazeyras, D. Van De Ville and M. Unser, "Activelets: Wavelets for sparse representation of hemodynamic responses," *Signal Processing,* vol. 91, no. 12, pp. 2810-2821, 2011.

[42] R. Lopes, J. M. Lina, F. Fahoum and J. Gotman, "Detection of epileptic activity in fMRI without recording the EEG.," *NeuroImage,* vol. 60, no. 3, p. 1867–1879, 2012.

[43] A. J. Taylor, J. H. Kim and D. Ress, "Characterization of the hemodynamic response function across the majority of human cerebral cortex," *Neuroimage,* vol. 173, pp. 322-331, 2018.

[44] J. Gonzalez-Castillo, Z. Saad, D. Handwerker, S. Inati, N. Brenowitz and P. Bandettini, "Whole-brain, time-locked activation with simple tasks revealed using massive averaging and model-free analysis," *Proc Natl Acad Sci USA,* vol. 109, no. 14, pp. 5487-92, 2012.

[45] K. R. Sreenivasan, M. Havlicek and G. Deshpande, "Non-parametric hemodynamic deconvolution of fMRI using homomorphic filtering," *IEEE Transactions on Medical Imaging,* vol. 34, no. 5, pp. 1155-63, 2015.

[46] H. Cherkaoui, T. Moreau, A. Halimi and P. Ciuciu, "Sparsity-based Blind Deconvolution of Neural Activation Signal in FMRI," in *IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP)*, Brighton, UK, 2019.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 February 2023 doi:10.20944/preprints202302.0516.v1

[47] G. Wu, N. Colenbier, S. Van Den Bossche, K. Clauw, A. Johri, M. Tandon and D. Marinazzo, "rsHRF: A toolbox for resting-state HRF estimation and deconvolution," *NeuroImage,* vol. 244, p. 118591, 2021.

[48] K. J. Friston, L. Harrison and W. Penny, "Dynamic causal modelling," *Neuroimage,* vol. 19, no. 4, pp. 1273-302, 2013.

[49] K. J. Friston, J. Kahan, B. Biswal and A. Razi, "A DCM for resting state fMRI," *NeuroImage,* vol. 94, no. 100, p. 396-407, 2014.

[50] F. I. Karahanoğlu and D. Van De Ville, "Transient brain activity disentangles fMRI resting-state dynamics in terms of spatially and temporally overlapping networks.," *Nature communications,* vol. 6, p. 7751, 2015.

[51] D. Zöller, C. Sandini, M. Schaer, S. Eliez, D. S. Bassett and D. Van De Ville, "Structural control energy of resting-state functional brain states reveals less cost-effective brain dynamics in psychosis vulnerability.," *Human brain mapping,* vol. 42, no. 7, p. 2181–2200, 2021.

[52] N. Kinany, E. Pirondini, S. Micera and D. Van De Ville, "Dynamic Functional Connectivity of Resting-State Spinal Cord fMRI Reveals Fine-Grained Intrinsic Architecture.," *Neuron,* vol. 108, no. 3, p. 424–435, 2020.

[53] Z. S. Saad, S. J. Gotts, K. Murphy, G. Chen, H. J. Jo, A. Martin and R. W. Cox, "Trouble at rest: how correlation patterns and group differences become distorted after global signal regression," *Brain Connectivity,* vol. 2, no. 1, pp. 25-32, 2012.

[54] G. Glover, "Deconvolution of impulse response in event-related BOLD fMRI," *Neuroimage,* vol. 9, no. 4, pp. 416-29, 1999.

[55] D. Rangaprakash, G.-R. Wu, D. Marinazzo, X. Hu and G. Deshpande, "Hemodynamic response function (HRF) variability confounds resting-state fMRI functional connectivity," *Magnetic Resonance in Medicine,* vol. 80, no. 4, pp. 1697-1713, 2018.

[56] D. Rangaprakash, G. Deshpande, T. Daniel, A. Goodman, J. Robinson, N. Salibi, J. Katz, T. Denney and M. Dretsch, "Compromised Hippocampus-Striatum Pathway as a Potential Imaging Biomarker of Mild Traumatic Brain Injury and Posttraumatic Stress Disorder," *Human Brain Mapping,* vol. 38, no. 6, pp. 2843-64, 2017.

[57] D. Rangaprakash, M. N. Dretsch, W. Yan, J. S. Katz, T. S. Denney and G. Deshpande, "Hemodynamic variability in soldiers with trauma: Implications for functional MRI connectivity studies," *NeuroImage: Clinical,* vol. 16, pp. 409-417, 2017.

[58] M. Boly, S. Sasai, O. Gosseries, M. Oizumi, A. Casali, M. Massimini and G. Tononi, "Stimulus set meaningfulness and neurophysiological differentiation: a functional magnetic resonance imaging study," *PLoS One,* vol. 10, no. 5, p. e0125337, 2015.

[59] D. Rangaprakash, M. N. Dretsch, W. Yan, J. S. Katz, T. S. Denney and G. Deshpande, "Hemodynamic response function parameters obtained from resting-state functional MRI data in soldiers with trauma," *Data in Brief,* vol. 14, pp. 558-562, 2017.

[60] E. Amico, F. Gomez, C. Di Perri, A. Vanhaudenhuyse, D. Lesenfants, P. Boveroux, V. Bonhomme, J. F. Brichant, D. Marinazzo and S. Laureys, "Posterior cingulate cortex-related co-activation patterns: a resting state FMRI study in propofol-induced loss of consciousness," *PLoS One,* vol. 9, no. 6, p. e100012, 2014.

[61] B. Lamichhane, B. M. Adhikari, S. F. Brosnan and M. Dhamala, "The neural basis of perceived unfairness in economic exchanges," *Brain Connectivity,* vol. 4, no. 8, pp. 619-30, 2014.

[62] D. Rangaprakash, M. N. Dretsch, A. Venkatraman, J. S. Katz, T. S. Denney and G. Deshpande, "Identifying Disease Foci from Static and Dynamic Effective Connectivity Networks: Illustration in Soldiers with Trauma," *Human Brain Mapping,* vol. 39, no. 1, pp. 264-287, 2018.

[63] D. Rangaprakash, R. Tadayonnejad, G. Deshpande, J. O'Neill and J. Feusner, "FMRI hemodynamic response function (HRF) as a novel marker of brain function: applications for understanding obsessive-compulsive disorder pathology and treatment response," *Brain Imaging and Behavior,* vol. in press, pp. DOI: 10.1007/s11682-020-00358-8, 2020.

[64] S. Noble, D. Scheinost and R. Constable, "A decade of test-retest reliability of functional connectivity: A systematic review and meta-analysis," *NeuroImage,* vol. 203, p. 116157, 2019.

[65] J. Power, A. Cohen, S. Nelson, G. Wig, K. Barnes, J. Church, A. Vogel, T. Laumann, F. Miezin, B. Schlaggar and S. Petersen, "Functional network organization of the human brain," *Neuron,* vol. 72, no. 4, pp. 665-78, 2011.

[66] G. Deshpande, K. Sathian and X. Hu, "Effect of hemodynamic variability on Granger causality analysis of fMRI," *Neuroimage,* vol. 52, no. 3, pp. 884-96, 2010.

[67] S. Lacey, R. Stilla, K. Sreenivasan, G. Deshpande and K. Sathian, "Spatial imagery in haptic shape perception," *Neuropsychologia,* vol. 60, pp. 144-158, 2014.

[68] C. Feng, G. Deshpande, C. Liu, R. Gu, Y.-J. Luo and F. Krueger, "Diffusion of responsibility attenuates altruistic punishment: A functional magnetic resonance imaging effective connectivity study," *Human Brain Mapping,* vol. 37, no. 2, pp. 663-77, 2015.

[69] B. M. Hampstead, M. Khoshnoodi, W. Yan, G. Deshpande and K. Sathian, "Patterns of effective connectivity between memory encoding and retrieval differ between patients with mild cognitive impairment and healthy older adults," *NeuroImage,* vol. 124, no. A, pp. 997-1008, 2016.

[70] S. Ryali, K. Supekar, T. Chen and V. Menon, "Multivariate dynamical systems models for estimating causal interactions in fMRI," *Neuroimage,* vol. 54, no. 2, pp. 807-23, 2011.

[71] S. Ryali, T. Chen, K. Supekar, T. Tu, J. Kochalka, W. Cai and V. Menon, "Multivariate dynamical systems-based estimation of causal brain interactions in fMRI: Group-level validation using benchmark data, neurophysiological models and human connectome project data," *Journal of Neuroscience Methods,* vol. 268, pp. 142-53, 2016.

[72] S. Ryali, Y. Y. Shih, T. Chen, J. Kochalka, D. Albaugh, Z. Fang, K. Supekar, J. H. Lee and V. Menon, "Combining optogenetic stimulation and fMRI to validate a multivariate dynamical systems model for estimating causal brain interactions," *Neuroimage,* vol. 132, pp. 398-405, 2016.

[73] D. A. Handwerker, J. Gonzalez-Castillo, M. D'Esposito and P. A. Bandettini, "The continuing challenge of understanding and modeling hemodynamic variation in fMRI," *Neuroimage,* vol. 62, no. 2, pp. 1017-23, 2012.

[74] M. Havlicek, J. Jan, M. Brazdil and V. Calhoun, "Dynamic Granger causality based on Kalman filter for evaluation of functional network connectivity in fMRI data," *Neuroimage,* vol. 53, no. 1, pp. 65-77, 2010.

[75] Y. Wang, O. David, X. Hu and G. Deshpande, "Can Patel's τ accurately estimate directionality of connections in brain networks from fMRI?," *Magnetic Resonance in Medicine,* vol. 78, no. 5, pp. 2003-2010, 2017.

[76] S. Tak, J. R. Polimeni, D. J. Wang, L. Yan and J. J. Chen, "Associations of resting-state fMRI functional connectivity with flow-BOLD coupling and regional vasculature.," *Brain connectivity,* vol. 5, no. 3, p. 137–146, 2015.

[77] M. G. Bright, J. R. Whittaker, I. D. Driver and K. Murphy, "Vascular physiology drives functional brain networks.," *NeuroImage,* vol. 217, p. 116907, 2020.

[78] W. Yan, D. Rangaprakash and G. Deshpande, "Aberrant hemodynamic responses in Autism: Implications for resting state fMRI functional connectivity studies," *NeuroImage: Clinical,* vol. 19, pp. 320-330, 2018.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 February 2023 doi:10.20944/preprints202302.0516.v1

[79] W. Yan, D. Rangaprakash and G. Deshpande, "Hemodynamic response function parameters obtained from resting state BOLD fMRI data in subjects with Autism Spectrum Disorder and matched healthy controls," *Data in Brief,* vol. 14, pp. 558-562, 2017.

[80] G. Deshpande, D. Rangaprakash, W. Yan, P. Liddle and L. Palaniyappan, "Characterization of Hemodynamic Alterations in Schizophrenia and Bipolar Disorder and their Effect on Resting-state Functional Connectivity," in *Schizophrenia International Research Society Conference (SIRS)*, Florence, Italy, April 2018.

[81] M. E. Archila-Meléndez, C. Sorg and C. Preibisch, "Modeling the impact of neurovascular coupling impairments on BOLD-based functional connectivity at rest.," *NeuroImage,* vol. 218, p. 116871, 2020.

[82] S. L. Peng, C. M. Chen, C. Y. Huang, C. T. Shih, C. W. Huang, S. C. Chiu and W. C. Shen, "Effects of Hemodynamic Response Function Selection on Rat fMRI Statistical Analyses.," *Frontiers in neuroscience,* vol. 13, p. 400, 2019.

[83] K. A. Duffy, Z. F. Fisher, C. A. M. P. Arizmendi, J. Hopfinger, J. R. Cohen, A. M. Beltz, M. A. Lindquist, M. N. Hallquist and K. M. Gates, "Detecting Task-Dependent Functional Connectivity in Group Iterative Multiple Model Estimation with Person-Specific Hemodynamic Response Functions.," *Brain connectivity,* vol. doi: 10.1089/brain.2020.0864, 2021.

[84] R. L. Barry, S. J. Vannesjo, S. By, J. C. Gore and S. A. Smith, "Spinal cord MRI at 7T," *NeuroImage,* vol. 168, p. 437-451, 2018.

[85] H. Islam, C. Law, K. A. Weber, S. C. Mackey and G. H. Glover, "Dynamic per slice shimming for simultaneous brain and spinal cord fMRI.," *Magnetic resonance in medicine,* vol. 81, no. 2, p. 825–838, 2019.

[86] M. Barth, F. Breuer, P. Koopmans, D. Norris and B. Poser, "Simultaneous multislice (SMS) imaging techniques," *Magn Reson Med.,* vol. 75, no. 1, p. 63-81, 2016.

[87] G. H. Glover, T. Q. Li and D. Ress, "Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR.," *Magnetic resonance in medicine,* vol. 44, no. 1, p. 162–167, 2000.

[88] K. J. Gorgolewski and R. A. Poldrack, "A Practical Guide for Improving Transparency and Reproducibility in Neuroimaging Research.," *PLoS biology,* vol. 14, no. 7, p. e1002506, 2016.

[89] R. A. Poldrack, C. I. Baker, J. Durnez, K. J. Gorgolewski, P. M. Matthews, M. R. Munafò, T. E. Nichols, J. B. Poline, E. Vul and T. Yarkoni, "Scanning the horizon: towards transparent and reproducible neuroimaging research.," *Nature reviews. Neuroscience,* vol. 18, no. 2, p. 115–126, 2017.

[90] Y. Osmanlıoğlu, J. A. Alappatt, D. Parker and R. Verma, "Analysis of Consistency in Structural and Functional Connectivity of Human Brain.," in *Proceedings. IEEE International Symposium on Biomedical Imaging*, 2020.

[91] A. D. Ekstrom, "Regional variation in neurovascular coupling and why we still lack a Rosetta Stone.," *Philosophical transactions of the Royal Society of London. Series B, Biological sciences,* vol. 376, no. 1815, p. 20190634, 2021.

[92] A. Das, K. Murphy and P. J. Drew, "Rude mechanicals in brain haemodynamics: non-neural actors that influence blood flow.," *Philosophical transactions of the Royal Society of London. Series B, Biological sciences,* vol. 376, no. 1815, p. 20190635, 2021.

[93] A. Mishra, C. N. Hall, C. Howarth and R. D. Freeman, "Key relationships between non-invasive functional neuroimaging and the underlying neuronal activity.," *Philosophical transactions of the Royal Society of London. Series B, Biological sciences,* vol. 376, no. 1815, p. 20190622, 2021.

[94] K. L. West, M. D. Zuppichini, M. P. Turner, D. K. Sivakolundu, Y. Zhao, D. Abdelkarim, J. S. Spence and B. Rypma, "BOLD hemodynamic response function changes significantly with healthy aging.," *NeuroImage,* vol. 188, p. 198–207, 2019.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 28 February 2023 doi:10.20944/preprints202302.0516.v1

[95] Z. Y. Shan, A. Vinkhuyzen, P. M. Thompson, K. L. McMahon, G. Blokland, G. I. de Zubicaray, V. Calhoun, N. G. Martin, P. M. Visscher, M. J. Wright and D. C. Reutens, "Genes influence the amplitude and timing of brain hemodynamic responses.," *NeuroImage,* vol. 124(Pt A), p. 663–671, 2016.

[96] A. E. Anderson, M. Diaz-Santos, S. Frei, B. H. Dang, P. Kaur, P. Lyden, R. Buxton, P. K. Douglas, R. M. Bilder, M. Esfandiari, K. J. Friston, U. Nookala and S. Y. Bookheimer, "Hemodynamic latency is associated with reduced intelligence across the lifespan: an fMRI DCM study of aging, cerebrovascular integrity, and cognitive ability.," *Brain structure & function,* vol. 225, no. 6, p. 1705–1717, 2020.

[97] I. G. Elbau, B. Brücklmeier, M. Uhr, J. Arloth, D. Czamara, V. I. Spoormaker, M. Czisch, K. E. Stephan, E. B. Binder and P. G. Sämann, "The brain's hemodynamic response function rapidly changes under acute psychosocial stress in association with genetic and endocrine stress response markers.," *Proceedings of the National Academy of Sciences of the United States of America,* vol. 115, no. 43, p. E10206–E10215, 2018.

[98] A. R. Mayer, T. Toulouse, S. Klimaj, J. M. Ling, A. Pena and P. S. Bellgowan, "Investigating the properties of the hemodynamic response function after mild traumatic brain injury.," *Journal of neurotrauma,* vol. 31, no. 2, p. 189–197, 2014.

[99] K. A. Tsvetanov, R. Henson and J. B. Rowe, "Separating vascular and neuronal effects of age on fMRI BOLD signals.," *Philosophical transactions of the Royal Society of London. Series B, Biological sciences,* vol. 376, no. 1815, p. 20190631, 2021.

[100] A. Yabluchanskiy, A. Nyul-Toth, A. Csiszar, R. Gulej, D. Saunders, R. Towner, M. Turner, Y. Zhao, D. Abdelkari, B. Rypma and S. Tarantini, "Age-related alterations in the cerebrovasculature affect neurovascular coupling and BOLD fMRI responses: Insights from animal models of aging.," *Psychophysiology,* p. e13718, 2020.

[101] B. D. Berman, C. L. S. E. Groth, S. H. Sillau, B. Sutton, K. T. Legget and J. R. Tregellas, "Hemodynamic responses are abnormal in isolated cervical dystonia.," *Journal of neuroscience research,* vol. 98, no. 4, p. 692–703, 2020.

[102] G. R. Wu, C. Di Perri, V. Charland-Verville, C. Martial, M. Carrière, A. Vanhaudenhuyse, S. Laureys and D. Marinazzo, "Modulation of the spontaneous hemodynamic response function across levels of consciousness.," *NeuroImage,* vol. 200, p. 450–459, 2019.

[103] M. Gemma, A. de Vitis, C. Baldoli, M. R. Calvi, V. Blasi, E. Scola, L. Nobile, A. Iadanza, G. Scotti and L. Beretta, "Functional magnetic resonance imaging (fMRI) in children sedated with propofol or midazolam.," *Journal of neurosurgical anesthesiology,* vol. 21, no. 3, p. 253–258, 2009.

[104] M. Ibaraki, Y. Shinohara, K. Nakamura, S. Miura, F. Kinoshita and T. Kinoshita, "Interindividual variations of cerebral blood flow, oxygen delivery, and metabolism in relation to hemoglobin concentration measured by positron emission tomography in humans.," *Journal of cerebral blood flow and metabolism,* vol. 30, no. 7, p. 1296–1305, 2010.

[105] J. Aanerud, P. Borghammer, A. Rodell, K. Y. Jónsdottir and A. Gjedde, "Sex differences of human cortical blood flow and energy metabolism.," *Journal of cerebral blood flow and metabolism,* vol. 37, no. 7, p. 2433–2440, 2017.

[106] A. M. Golestani, L. L. Wei and J. J. Chen, "Quantitative mapping of cerebrovascular reactivity using resting-state BOLD fMRI: Validation in healthy adults," *Neuroimage,* vol. 138, pp. 147-163, 2016.

[107] A. C. Boese, S. C. Kim, K. J. Yin, J. P. Lee and M. H. Hamblin, "Sex differences in vascular physiology and pathophysiology: estrogen and androgen signaling in health and disease.," *American journal of physiology. Heart and circulatory physiology,* vol. 313, no. 3, p. H524–H545, 2017.

[108] V. H. Huxley and S. S. Kemp, "Sex-Specific Characteristics of the Microcirculation.," *Advances in experimental medicine and biology,* vol. 1065, p. 307–328, 2018.

[109] J. N. Barnes, "Sex-specific factors regulating pressure and flow.," *Experimental physiology,* vol. 102, no. 11, p. 1385–1392, 2017.

[110] D. Rangaprakash, G.-R. Wu, D. Marinazzo, X. Hu and G. Deshpande, "Parameterized hemodynamic response function data of healthy individuals obtained from resting-state functional MRI in a 7T MRI scanner," *Data in Brief,* vol. 17, pp. 1175-1179, 2018.

[111] A. F. Mejia, M. B. Nebel, A. D. Barber, A. S. Choe, J. J. Pekar, B. S. Caffo, M. A. Lindquist, "Improved estimation of subject-level functional connectivity using full and partial correlation with empirical Bayes shrinkage.," *NeuroImage,* vol. 172, p. 478–491, 2018.

[112] B. N. Conrad, R. L. Barry, B. P. Rogers, S. Maki, A. Mishra, S. Thukral, S. Sriram, A. Bhatia, S. Pawate, J. C. Gore and S. A. Smith, "Multiple sclerosis lesions affect intrinsic functional connectivity of the spinal cord.," *Brain,* vol. 141, no. 6, p. 1650–1664, 2018.

[113] D. Reckziegel, E. Vachon-Presseau, B. Petre, T. Schnitzer, M. Baliki and A. Apkarian, "Deconstructing biomarkers for chronic pain: context- and hypothesis-dependent biomarker types in relation to chronic pain," *Pain,* vol. 160, no. Suppl 1, p. S37-S48, 2019.

[114] M. de Albuquerque, L. M. Branco, T. J. Rezende, H. M. de Andrade, A. Nucci and M. C. França, "Longitudinal evaluation of cerebral and spinal cord damage in Amyotrophic Lateral Sclerosis," *Neuroimage: Clinical,* vol. 14, p. 269-276, 2017.

[115] L. Cacciaguerra, A. Meani, S. Mesaros and e. al., "Brain and cord imaging features in neuromyelitis optica spectrum disorders," *Ann Neurol.,* vol. 85, no. 3, p. 371-384, 2019.

[116] J. Faber, T. Schaprian, K. Berkan, K. Reetz, M. C. França, T. de Rezende, J. Hong, W. Liao, B. van de Warrenburg and e. al., "Regional Brain and Spinal Cord Volume Loss in Spinocerebellar Ataxia Type 3.," *Movement disorders,* p. in press, 2021.

[117] P. Freund, M. Seif, N. Weiskopf and e. al., "MRI in traumatic spinal cord injury: from clinical assessment to neuroimaging biomarkers," *Lancet Neurol.,* vol. 18, no. 12, p. 1123-1135, 2019.

[118] R. M. Lorenzi, F. Palesi, G. Castellazzi, P. Vitali, N. Anzalone, S. Bernini, M. Cotta Ramusino, E. Sinforiani, G. Micieli, A. Costa, E. D'Angelo and C. Gandini Wheeler-Kingshott, "Unsuspected Involvement of Spinal Cord in Alzheimer Disease.," *Frontiers in cellular neuroscience,* vol. 14, p. 6, 2020.

[119] M. P. Trevarrow, S. E. Baker, T. W. Wilson and M. J. Kurz, "Microstructural changes in the spinal cord of adults with cerebral palsy.," *Developmental medicine and child neurology,* p. in press, 2021.

[120] M. Preti, T. Bolton and D. Van De Ville, "The dynamic functional connectome: State-of-the-art and perspectives," *Neuroimage,* vol. 160, p. 41–54, 2016.

[121] L. Jollans, R. Boyle, E. Artiges, T. Banaschewski, S. Desrivières, A. Grigis, J. L. Martinot, T. Paus, M. N. Smolka, H. Walter, G. Schumann, H. Garavan and R. Whelan, "Quantifying performance of machine learning methods for neuroimaging data.," *NeuroImage,* vol. 199, p. 351–365, 2019.

[122] E. S. Finn, L. Huber and P. A. Bandettini, "Higher and deeper: Bringing layer fMRI to association cortex.," *Progress in neurobiology,* p. 101930, 2020.

[123] E. S. Finn, X. Shen, D. Scheinost, M. D. Rosenberg, J. Huang, M. M. Chun, X. Papademetris and R. T. Constable, "Functional connectome fingerprinting: identifying individuals using patterns of brain connectivity.," *Nature neuroscience,* vol. 18, no. 11, p. 1664–1671, 2015.

[124] C. Preibisch, J. Castrillón, M. Bührer and V. Riedl, "Evaluation of Multiband EPI Acquisitions for Resting State fMRI," *PLoS One,* vol. 10, no. 9, p. e0136961, 2015.