Received: 26 June 2017 | Accepted: 29 June 2017

DOI: 10.1002/jbio.201700165

Journal of BIOPHOTONICS

LETTER

Resting-state functional connectivity measured by diffuse correlation spectroscopy

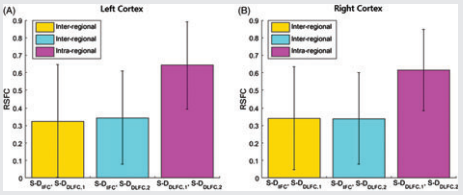
Jun Li | Chien-Sing Poon | Jeremy Kress | Daniel J. Rohrbach | Ulas Sunar*

Department of Biomedical, Industrial and Human Factors, Wright State University, Dayton, Ohio

*Correspondence
Ulas Sunar, Department of Biomedical, Industrial and Human Factors, Wright State University, 3640 Colonel Glenn Highway, Dayton, OH 45435.
Email: ulas.sunar@wright.edu

Funding information
Ohio Third Frontier, Grant/Award number: 667750

Near-infrared diffuse correlation spectroscopy (DCS) is used to record spontaneous cerebral blood flow fluctuations in the frontal cortex. Nine adult subjects participated in the experiments, in which 8-minute spontaneous fluctuations were simultaneously recorded from the left and right dorsolateral and inferior frontal regions. Resting-state functional connectivity (RSFC) was measured by the temporal correlation of the low frequency fluctuations. Our data shows the RSFC within the dorsolateral region is significantly stronger than that between the inferior and dorsolateral regions, in line with previous observations with functional near-infrared spectroscopy. This indicates that DCS is capable of investigating brain functional connectivity in terms of cerebral blood flow.



KEYWORDS
cerebral blood flow, diffuse correlation spectroscopy, resting-state functional connectivity, spontaneous activity

1 | INTRODUCTION

Resting-state functional connectivity (RSFC) indicates spontaneous activity of the brain showing high synchronization in functionally related regions, adjacent or even remote regions. This fact was first uncovered by a functional magnetic resonance imaging (fMRI) study where the low frequency (<0.1 Hz) spontaneous blood-oxygenation-level dependent (BOLD) signals between the bilateral motor areas were observed to be correlated [1]. Subsequent fMRI studies further demonstrated RSFC not only in the motor cortex, but also in various other functional regions, such as frontal, temporal and visual cortex [2–6]. In very recent years, functional near-infrared spectroscopy (fNIRS) has been applied to RSFC studies [7–12] and has revealed RSFC in terms of hemoglobin, such as oxyhemoglobin (HbO_2) and deoxyhemoglobin (Hb). Since BOLD and hemoglobin signals reflect oxygenation levels of the cerebral blood in the related cortical regions, hemoglobin-based RSFC signals are comparable to those revealed by fMRI in terms of BOLD signal [13]. In addition to these cerebral blood oxygenation parameters, cerebral blood flow is another key hemodynamic parameter closely associated with cortical activity. It has been well demonstrated that an optical technique called diffuse correlation spectroscopy (DCS) is capable of noninvasively detecting blood flow related parameters in human brain [14–21]. Recently, superficial optical blood flow measurements were performed by using laser speckle contrast imaging to map RSFC in the mouse brain [22]. However, to our best knowledge, there is no published study using DCS to measure RSFC in human brain. To achieve a better understanding of resting-state brain activity, cerebral blood flow might be a useful parameter to investigate. In this study, we used DCS to noninvasively measure the blood flow in human cortex in resting-state and reveal DCS-based RSFC.

Jun Li and Chien-Sing Poon contributed equally to this study.

2 | MATERIALS AND METHODS

2.1 | Diffuse correlation spectroscopy

The details of the DCS technique can be found in more recent reviews [14, 20, 23]. Briefly, DCS is an optical technique originally used for investigating dynamics in a turbid medium such as colloidal suspension or living tissue [19, 20, 24, 25]. Based on the high coherence of laser light, DCS measures the emitted light intensity autocorrelation function, whose decay rate reflects the dynamics of "scatterers"—in this case moving blood cells in tissue [14, 19, 23]. In this study, the DCS system consists of 2 continuous wave laser sources (785 nm, CrystaLaser, Reno, Nevada) with coherence length larger than 10 m, 8 NIR-optimized single photon counting modules (SPCM-NIR, Excelitas, Quebec, Canada), and a custom-built 8-channel auto-correlator board (Correlator.com). Two multimode fibers (1000 μm core diameter, numerical aperture (NA) of 0.39) are used to guide the laser light to the scalp, while 8 single-mode fibers (5 μm core diameter, NA of 0.22) are used to collect the emitted light from the scalp.

To characterize relative cerebral blood flow, blood flow index (BFI, cm^2/s) was quantified as detailed before [14, 20]. The BFI was obtained by using a semi-infinite diffusion model to fit the recorded autocorrelation function, which has the information about blood flow and optical parameters [14, 19]. For the quantification of BFI, the Brownian motion model was adopted [19, 26]. Optical parameters at 785 nm for each subject were obtained by using a spatially resolved frequency-domain NIRS system (OxiplexTS, ISS Inc, Champaign, IL, USA) operating at 690 nm and 830 nm. Optical parameters at 830 nm were assumed to be the same as those at 785 nm, thus only BFI was fit to the autocorrelation data.

2.2 | Subjects and experimental protocol

Nine adult subjects (8 males) were recruited at Wright State University to participate in this experimental study. All subjects were right-handed. The average age was 29.3 (±2.7) years. During the experiment, subjects were sitting on a comfortable chair in a dark room, and asked to close their eyes and remain silent. An 8-minute spontaneous activity [11, 27] was recorded using DCS from the frontal cortex with 2-second integration time (ie, DCS signal or the time intensity autocorrelation function was computed with 2 seconds of integration time, with a photon sampling rate of 5 MHz). In this experiment, all optical probes were located on both side of the dorsolateral frontal cortex (DLFC) except for the S-D_{IFC} optode, which was located at the inferior frontal cortex (IFC), as shown in Figure 1. A reference channel (ie, S-D_s) with short source-detector spacing (1 cm) was used for recording DCS signal from the superficial tissue on both side of the DLFC. For the sake of reproducibility, 5 subjects were randomly selected for 2 subsequent measurements at different times within about 1 hour of the original experiment. The locations of optical probes were determined with reference to the international electroencephalogram (EEG) 10-20 system. In order to accurately locate the probes, we measured the surface distance from the nasion to inion of each subject with a tape to ensure the EEG cap was correctly positioned over the head according to the EEG 10-20 montage. After DCS measurements, the optical parameters at 690 and 830 nm were measured for each subject by using a spatially resolved frequency-domain NIRS system (OxiplexTS, ISS Inc).

The experimental protocol was approved by the Institutional Review Board at Wright State University and informed consent was obtained from each participant prior to the experiment.

2.3 | Data analysis

Each time-series of the BFI was first detrended by a second order polynomial fit to remove the slow drift [13], and then a zero-phase second order Butterworth filter with a passband of 0.009 to 0.08 Hz was applied [7, 11, 27]. Due to the short source-detector spacing, S-D_s channel sampled

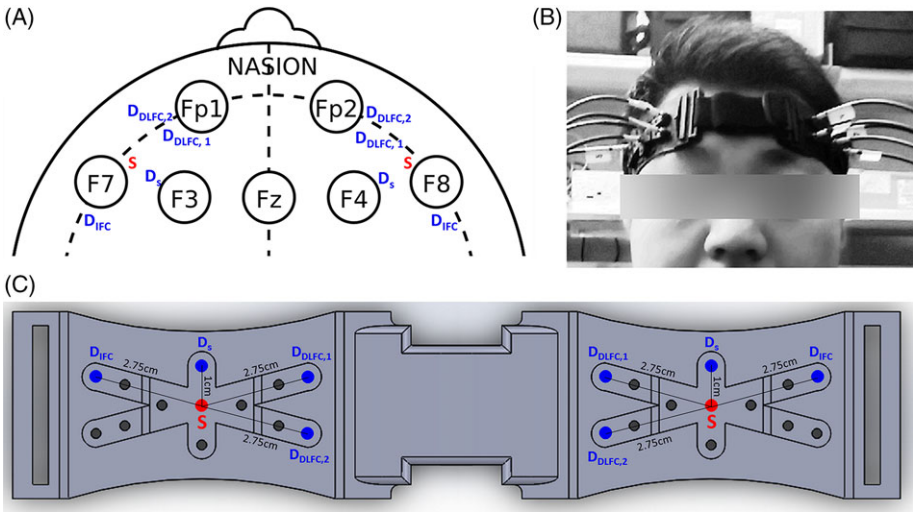


FIGURE 1 A, Locations of sources (red) and detectors (blue) in reference to the international EEG 10-20 system. The source-detector distance was 2.75 cm for S-$D_{DLFC,1}$, S-$D_{DLFC,2}$, S-D_{IFC} and 1.0 cm for S-D_s. B, An example of the placement of the probe on the subject. C, The placement of each optode on the probe in (B)

mainly the BFI in the scalp. This superficial scalp signal was also included when sampled by S-$D_{DLFC,1}$, S-$D_{DLFC,2}$ and S-D_{IFC} with larger source-detector spacing, resulting in inaccurate correlation between these channels. To suppress this interference, a linear regression model was used to remove this superficial component from the BFI of these channels [27]. To show the effectiveness of the data processing, Figure 2 presents an example of BFI signals before and after the processing.

Before regression, the Pearson correlation coefficients between these channels are r(S-D_s, S-D_{IFC}) = 0.131, r(S-D_s, S-$D_{DLFC,1}$) = 0.216, r(S-D_s, S-$D_{DLFC,2}$) = 0.279, r(S-D_{IFC}, S-$D_{DLFC,1}$) = 0.310, r(S-D_{IFC}, S-$D_{DLFC,2}$) = 0.492, r(S-$D_{DLFC,1}$, S-$D_{DLFC,2}$) = 0.766. After regression, the correlation coefficients are r(S-D_s, S-D_{IFC}) = 0.001, r(S-D_s, S-$D_{DLFC,1}$) = 0.003, r(S-D_s, S-$D_{DLFC,2}$) = 0.003, r(S-D_{IFC}, S-$D_{DLFC,1}$) = 0.291, r(S-D_{IFC}, S-$D_{DLFC,2}$) = 0.478, r(S-$D_{DLFC,1}$, S-$D_{DLFC,2}$) = 0.752. Since the long separation channels contain the superficial component, S-D_{IFC}, S-$D_{DLFC,1}$ and S-$D_{DLFC,2}$ are over-correlated before the regression. After the regression, there is nearly no correlation between the long-separation and short-separation channels, implying the scalp signal is removed from the long-separation channels. Since S-$D_{DLFC,1}$ and S-$D_{DLFC,2}$ channels were located at DLFC, the correlation coefficient indicated the intra-regional RSFC in DLFC. The correlation coefficient between the S-D_{IFC} channel—which was located at the IFC—and the channels located in the DLFC (S-

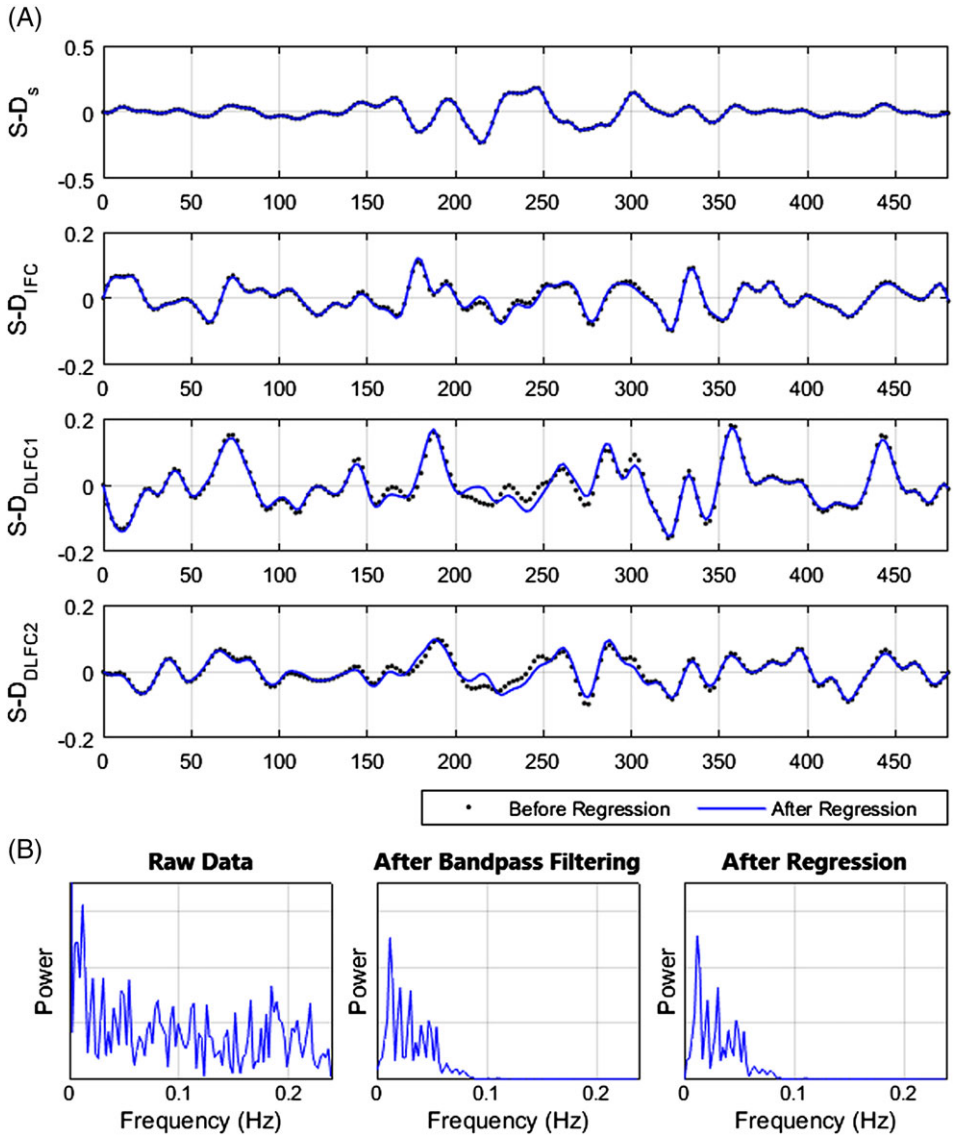


FIGURE 2 A, BFI of each channel before and after the regression with the BFI of S-D_s as the regressor. Before the regression, the correlation coefficients r(S-D_s, S-D_{IFC}) = 0.131, r(S-D_s, S-$D_{DLFC,1}$) = 0.216, r(S-D_s, S-$D_{DLFC,2}$) = 0.279, r(S-D_{IFC}, S-$D_{DLFC,1}$) = 0.310, r(S-D_{IFC}, S-$D_{DLFC,2}$) = 0.492, r(S-$D_{DLFC,1}$, S-$D_{DLFC,2}$) = 0.766. After the regression, the correlation coefficients r(S-D_s, S-D_{IFC}) = 0.001, r(S-D_s, S-$D_{DLFC,1}$) = 0.003, r(S-D_s, S-$D_{DLFC,2}$) = 0.003, r(S-D_{IFC}, S-$D_{DLFC,1}$) = 0.291, r(S-D_{IFC}, S-$D_{DLFC,2}$) = 0.478, r(S-$D_{DLFC,1}$, S-$D_{DLFC,2}$) = 0.752. B, An example of the changes in the $D_{DLFC,1}$ channel's power spectrum after each process, showing the suppression of systemic global signal, such as Mayer wave approximately 0.1 Hz

$D_{DLFC,1}$ and S-$D_{DLFC,2}$) indicated the interregional RSFC. To test statistical significance of the correlation coefficients, each correlation coefficient was first converted to a Z value by Fisher's transform, and then a z-test was performed.

3 | RESULTS

The intra-regional (within the DLFC) RSFC is much stronger than the interregional (between the DLFC and IFC), as shown in Figure 3. The z-test shows that there is a significant difference between the intra-regional and interregional results ($P \leq .0002$) on both side of the cortex. The power analysis with a power of 0.8 and the significance level at 0.05 shows the actual power is 0.82 with the sample size of 8, which indicates the sample size of this study ($N = 9$) is sufficient enough for statistical significance. For reproducibility, 5 of the 9 subjects were selected to perform 2 more measurements at different times. This resulted in an average of r(S-D_{IFC}, S-$D_{DLFC,1}$) = 0.33 ± 0.25, r(S-D_{IFC}, S-$D_{DLFC,2}$) = 0.31 ± 0.22, r(S-$D_{DLFC,1}$, S-$D_{DLFC,2}$) = 0.52 ± 0.27 on the left cortex and r(S-D_{IFC}, S-$D_{DLFC,1}$)- = 0.30 ± 0.26, r(S-D_{IFC}, S-$D_{DLFC,2}$) = 0.27 ± 0.24, r(S-$D_{DLFC,1}$, S-$D_{DLFC,2}$) = 0.50 ± 0.21 on the right cortex, which is within the group average results shown in Figure 3. The observation that the intra-regional RSFC is stronger than the interregional RSFC is consistent with our previous data (eg, HbO_2-based RSFC: 0.81 ± 0.10 vs 0.16 ± 0.28; Hb-based: 0.45 ± 0.26 vs 0.25 ± 0.25; HbT-based: 0.80 ± 0.12 vs 0.19 ± 0.28) using fNIRS [28], which showed that the average RSFC in DLFC was stronger than RSFC between DLFC and IFC [12].

4 | DISCUSSION AND CONCLUSION

The DLFC and IFC are anatomically adjacent, but each has a distinct function. The DLFC plays important roles in working memory, sustaining attention, holding spatial information "on-line", emotion regulation and executive functions [29, 30]; while the IFC is a part of the language area of the brain, mainly responsible for language production [31, 32]. Therefore, each belongs to a different functional network, which is also manifested by the weaker RSFC between these 2 regions. This weaker interregional connectivity has previously been uncovered by fNIRS studies; here it is revealed in the present study using DCS.

In this study, although the error was substantial, the reproducibility of measurements showed that the intra-RSFC was always stronger than the inter-RSFC on each subject at all of the measurement times despite the variations. This is also consistent with the observation that the correlation coefficient between the 2 sites in DLFC for both hemispheres is significantly larger than zero (ie, 0.64 ± 0.25 for the left, 0.62 ± 0.23 for the right, z-test: $P < .05$). On each subject, the left and right optodes that are symmetric to each other also showed no significant difference (z-test: $P > .8$). This further suggests that the intra-RSFC was always stronger than the inter-RSFC, since both left and right side has no significant difference and follows the same trend of a stronger intra-RSFC, which decreases the likelihood that this is a false positive. It should be noted that the purpose of this pilot study is not mapping RSFC with DCS, but for demonstrating that the DCS technique is capable of uncovering RSFC in the cortex.

In a quantitative comparison to fNIRS-based RSFC, the average degree of CBF-based RSFC for left intra-DLFC

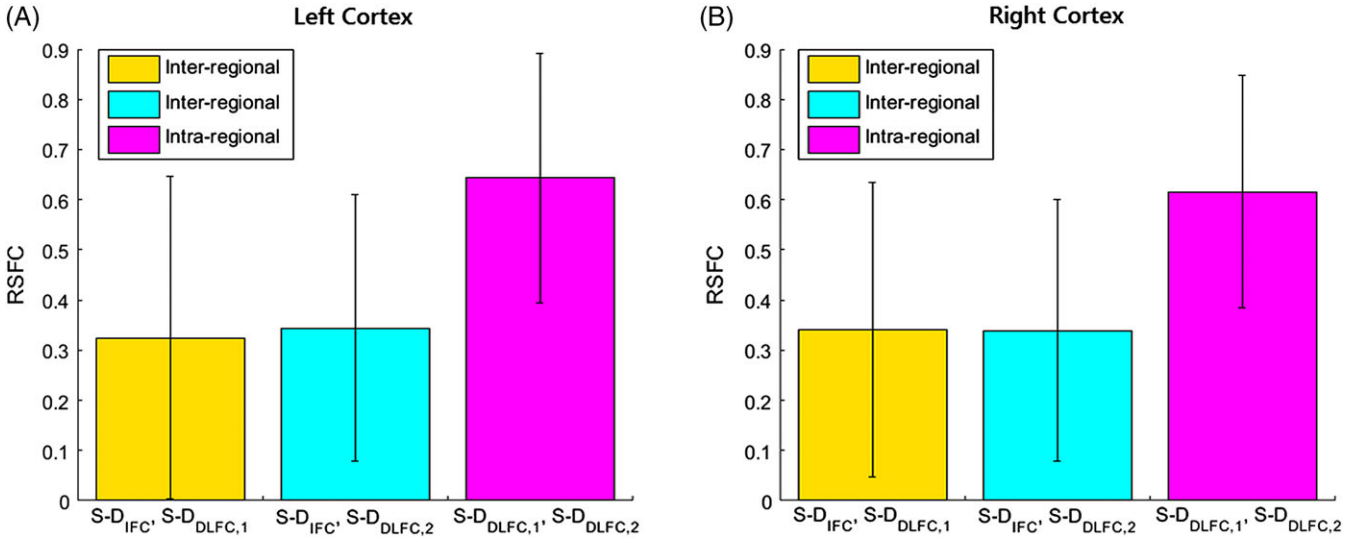


FIGURE 3 A, Group average for interregional (0.32 ± 0.32), (0.34 ± 0.27) and intra-regional RSFC (0.64 ± 0.25) on the left cortex. B, Inter-regional (0.34 ± 0.29), (0.34 ± 0.26) and intra-regional RSFC (0.62 ± 0.23) on the right cortex. The error bar is the SD across all subjects. The z-test shows the difference between the intra- and interregional RSFC on both cortex is significant with $P \leq .0002$, while there was no significant difference between the left and right cortex (z-test: $P > .8$)

(0.64 ± 0.25) and right intra-DLFC (0.62 ± 0.23) is greater than Hb-based RSFC (0.45 ± 0.26), but smaller than HbO_2-based (0.81 ± 0.10) or HbT-based RSFC (0.80 ± 0.12). For the interregional RSFC between the DLFC and IFC, either CBF-based or fNIRS-based RFSC shows a lower degree of connectivity. This observation might imply that, within a functional region of resting brain, HbO_2 (or HbT) signal is more correlated than cerebral blood flow (CBF) signal.

In contrast to fNIRS, which provides information on cerebral blood oxygenation, DCS provides measure on cerebral blood flow, another key variable of hemodynamics associated with brain activity. Since blood oxygenation and flow are unique measures of neural activity, it is useful to include both of these hemodynamic variables into RSFC studies to achieve more comprehensive understanding of the resting brain. Although other imaging modalities, such as positron emission tomography and MRI (through exogenous contrast agent or endogenous tracer with magnetic labeling) are capable of measuring cerebral blood flow, DCS can provide a noninvasive measure of blood flow, making it a very useful tool for studying function as well as the resting brain.

One of the main challenges of the DCS technique is that most DCS measurements of blood flow are slow, with sampling rates ranging from 0.3 to 1 Hz [33]. Thus, physiologic contributions such as heart rate and Mayer wave need to be carefully removed by using suitable signal processing algorithms. In the perspective of technology development, there is a recent interest on fast blood flow measurements with real-time software correlators [33], which showed the feasibility of data acquisition rates at 50 to 100 Hz. High temporal resolution measurements can improve identification and removal of motion artifacts, which is highly desired in clinical settings.

In conclusion, DCS has been used for the first time to uncover RSFC in the frontal cortex, and it is found that the intra-RSFC in DLFC is stronger than inter-RSFC between DLFC and IFC. This observation is consistent with the fact that each of these 2 cortical regions plays a distinct role in brain function, and agrees with previous fNIRS findings. Hence, our study indicates that DCS is applicable to investigating resting brain states, and might provide additional understanding of RSFC.

ACKNOWLEDGMENTS

We acknowledge financial support from the Ohio Third Frontier to the Ohio Imaging Research and Innovation Network (OIRAIN, 667750).

REFERENCES

[1] B. Biswal, F. Z. Yetkin, V. M. Haughton, J. S. Hyde, *Magn. Reson. Med.* **1995**, *34*, 537.
[2] A. L. Cohen, D. A. Fair, N. U. F. Dosenbach, F. M. Miezin, D. Dierker, D. C. Van Essen, B. L. Schlaggar, S. E. Petersen, *Neuroimage* **2008**, *41*, 45.
[3] H. D. Xiang, H. M. Fonteijn, D. G. Norris, P. Hagoort, *Cereb. Cortex* **2010**, *20*, 549.
[4] M. S. Koyama, C. Kelly, Z. Shehzad, D. Penesetti, F. X. Castellanos, M. P. Milham, *Cereb. Cortex* **2010**, *20*, 2549.
[5] X. N. Zuo, C. Kelly, J. S. Adelstein, D. F. Klein, F. X. Castellanos, M. P. Milham, *Neuroimage* **2010**, *49*, 2163.
[6] C. E. Pizoli, M. N. Shah, A. Z. Snyder, J. S. Shimony, D. D. Limbrick, M. E. Raichle, B. L. Schlaggar, M. D. Smyth, *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 11638.
[7] B. R. White, A. Z. Snyder, A. L. Cohen, S. E. Petersen, M. E. Raichle, B. L. Schlaggar, J. P. Culver, *Neuroimage* **2009**, *47*, 148.
[8] C. M. Lu, Y. J. Zhang, B. B. Biswal, Y. F. Zang, D. L. Peng, C. Z. Zhu, *J. Neurosci. Methods* **2010**, *186*, 242.
[9] Y.-J. Zhang, C.-M. Lu, B. B. Biswal, Y.-F. Zang, D.-L. Peng, C.-Z. Zhu, *J. Biomed. Opt.* **2010**, *15*, 47003.
[10] H. Zhang, L. Duan, Y.-J. Zhang, C.-M. Lu, H. Liu, C.-Z. Zhu, *Neuroimage* **2011**, *55*, 607.
[11] J. Li, L. Qiu, *Biomed. Opt. Express* **2014**, *5*, 587.
[12] C.-C. Chuang, C.-W. Sun, *Biomed. Opt. Express* **2014**, *5*, 2503.
[13] L. Duan, Y. J. Zhang, C. Z. Zhu, *Neuroimage* **2012**, *60*, 2008.
[14] T. Durduran, A. G. Yodh, *Neuroimage* **2014**, *85*, 51.
[15] J. Li, G. Dietsche, D. Iftime, S. E. Skipetrov, G. Maret, T. Elbert, B. Rockstroh, T. Gisler, *J. Biomed. Opt.* **2005**, *10*, 44002.
[16] J. Li, M. Ninck, L. Koban, T. Elbert, J. Kissler, T. Gisler, *Opt. Lett.* **2008**, *33*, 2233.
[17] S. A. Carp, G. P. Dai, D. A. Boas, M. A. Franceschini, Y. R. Kim, *Biomed. Opt. Express* **2010**, *1*, 553.
[18] M. Diop, K. Verdecchia, T.-Y. Lee, K. St Lawrence, *Biomed. Opt. Express* **2011**, *2*, 2068.
[19] R. C. Mesquita, T. Durduran, G. Yu, E. M. Buckley, M. N. Kim, C. Zhou, R. Choe, U. Sunar, A. G. Yodh, *Philos. Trans. A Math. Phys. Eng. Sci.* **2011**, *369*, 4390.
[20] E. M. Buckley, A. B. Parthasarathy, P. E. Grant, A. G. Yodh, M. A. Franceschini, *Neurophotonics* **2014**, *1*, 1.
[21] J. Selb, D. A. Boas, S.-T. Chan, K. C. Evans, E. M. Buckley, S. a. Carp, *Neurophotonics* **2014**, *1*, 1.
[22] K. M. Bergonzi, A. Q. Bauer, P. W. Wright, J. P. Culver, *J. Cereb. Blood Flow Metab.* **2015**, *35*, 367.
[23] G. Yu, *Curr. Med. Imaging Rev.* **2012**, *8*, 194.
[24] G. Maret, P. E. Wolf, *Z. Phys. B - Condens. Matter* **1987**, *65*, 409.
[25] D. A. Boas, L. E. Campbell, and A. G. Yodh. Scattering and imaging with diffusing temporal field correlations. *Physical Review Letters* **1995**, *75*:1855–1858.
[26] C. Cheung, J. P. Culver, K. Takahashi, J. H. Greenberg, A. G. Yodh, *Phys. Med. Biol.* **2001**, *46*, 2053.
[27] R. C. Mesquita, M. A. Franceschini, D. A. Boas, *Biomed. Opt. Express* **2010**, *1*, 324.
[28] J. Li, L. N. Qiu, *J. South China Norm. Univ.* **2016**, *48*, 67.
[29] N. Ramnani, A. M. Owen, *Nat. Rev. Neurosci.* **2004**, *5*, 184.
[30] J.-B. Pochon, *Cereb. Cortex* **2001**, *11*, 260.
[31] M. A. Gernsbacher, M. P. Kaschak, *Annu. Rev. Psychol.* **2003**, *54*, 91.
[32] P. Hagmann, L. Cammoun, R. Martuzzi, P. Maeder, S. Clarke, J. P. Thiran, R. Meuli, *Hum. Brain Mapp.* **2006**, *27*, 828.
[33] D. Wang, A. B. Parthasarathy, W. B. Baker, K. Gannon, V. Kavuri, T. Ko, S. Schenkel, Z. Li, Z. Li, M. T. Mullen, J. A. Detre, A. G. Yodh, *Biomed. Opt. Express* **2016**, *7*, 776.

How to cite this article: Li J, Poon C-S, Kress J, Rohrbach D, Sunar U. Resting-state functional connectivity measured by diffuse correlation spectroscopy. *J. Biophotonics.* 2017;e201700165. https://doi.org/10.1002/jbio.201700165