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The relationship between BOLD signal and autonomic nervous system functions: implications for processing of "physiological noise"☆

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Abstract

Functional magnetic resonance imaging (fMRI) research has revealed not only important aspects of the neural basis of cognitive and perceptual functions, but also important information on the relation between high-level brain functions and physiology. One of the central outstanding questions, given the features of the blood oxygenation level-dependent (BOLD) signal, is whether and how autonomic nervous system (ANS) functions are related to changes in brain states as measured in the human brain. A straightforward way to address this question has been to acquire external measurements of ANS activity such as cardiac and respiratory data, and examine their relation to the BOLD signal. In this article, we describe two conceptual approaches to the treatment of ANS measures in the context of BOLD fMRI analysis. On the one hand, several research lines have treated ANS activity measures as noise, considering them as nothing but a confounding factor that reduces the power of fMRI analysis or its validity. Work in this line has developed powerful methods to remove ANS effects from the BOLD signal. On the other hand, a different line of work has made important progress in showing that ANS functions such as cardiac pulsation, heart rate variability and breathing rate could be considered as a theoretically meaningful component of the signal that is useful for understanding brain function. Work within this latter framework suggests that caution should be exercised when employing procedures to remove correlations between BOLD data and physiological measures. We discuss these two positions and the reasoning underlying them. Thereafter, we draw on the reviewed literature in presenting practical guidelines for treatment of ANS data, which are based on the premise that ANS data should be considered as theoretically meaningful information. This holds particularly when studying cortical systems involved in regulation, monitoring and/or generation of ANS activity, such as those involved in decision making, conflict resolution and the experience of emotion.

Keywords: BOLD signal; Autonomic nervous system functions; Physiological noise

1. Introduction

Blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) is one the most powerful and popular methods for noninvasive examination of whole-brain and regional neural activity patterns. However, the relationship between BOLD fluctuation and pre- or post-synaptic activity at the neural level is nontrivial [1]. BOLD fluctuations in a given area are induced not only by changes in metabolic demand related to neural activity, but also by a wide range of factors that are considered artifacts such as system noise, hardware limitations [2] and confounding effects such as participant's movements inside the scanner. In particular, physiological factors mediating the transfer function between neural and BOLD fluctuations [3] play an important and potentially confounding factor in the interpretation of BOLD data. Determining the impact of these various noise sources on the BOLD signal is an active domain of research (e.g., Ref. [4]).

One of the main external factors known to co-vary with BOLD measurements is a set of physiological parameters reflecting activity in the autonomic nervous system (ANS). The ANS is a part of the nervous system that controls functions such as perspiration, respiration, heart rate and

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blood pressure. It is well documented that fluctuations in these functions are correlated with the BOLD signal [5] and that the impact of such factors may increase in higher field strengths, rendering measurements performed at higher strength marginally advantageous unless this factor is adequately controlled for [6].

Given the sensitivity of BOLD to ANS functions, one of the important technical and theoretical questions facing scientists relying on BOLD measures is to understand how ANS functions are related to changes in the BOLD signal. To date, this issue has been largely addressed by acquiring external measurements of ANS states and examining their relation to the BOLD signal. With progress in the field, it appears that two implicit approaches to the treatment of ANS data have been developed. On the one hand, studies employing an "ANS as noise" approach have mainly treated physiological acquisitions as artifacts, considering them, from a cognitive or theoretical point of view, as nothing but a confounding factor that reduces the power of an analysis or its validity. Work in this line has developed powerful methods to remove ANS effects from the BOLD signal. On the other hand, other work within various neuroscience domains has made important progress in showing that ANS functions such as cardiac pulsation and breathing rate could be considered as cognitively relevant and interesting components of the BOLD signal. Our aim in this review was to track the rationale for these approaches and derive pragmatic conclusions based on these considerations.

2. BOLD: a product of a complex transfer function

The BOLD signal is intrinsically a metabolic effect since it is not directly related to electrophysiological changes induced by neuronal populations. Evidence for its biophysical nature was originally shown in PET studies documenting an uncoupling between cerebral blood flow (CBF) and a metabolic quantity of the oxygen consumption ($CMRO_2$ [7]). Quantitative models characterizing aspects of the BOLD effect were developed on the basis of metabolic variables (e.g., the balloon model [8]). The transfer function thought to mediate between neural activity and BOLD has been termed "hemodynamic response" function (HRF), to underline both its mechanical and its hydrodynamic aspects. Numerous subsequent studies explored factors affecting the vascular aspects of BOLD signal, using methods such as the examination of blood flow and volume variations induced by natural or carbon dioxide calibrated respiration. For example, controlled breathing studies have shown the unique impact of vasodilation on the BOLD response [9,10]. Other work [11] has shown that factors such as baseline CO_2 levels determine the dynamic range of BOLD and CBF responses to stimulations. One of the interesting points raised by such work is the fact that the asymmetric coupling between CBF and CBV is spatially heterogeneous: this leads to different rates of change in BOLD fluctuations across brain regions. Moreover, inter-individual differences could be well accounted for using such parameters given that individuals' BOLD fluctuations could be related to absolute changes in CO_2 partial pressure, and the final results could be more accurate and specific [12]. In all, these studies have served useful in highlighting how breathing induces changes that affect the BOLD signal. In tandem with studies that have used breathing challenges as a method for understanding the relation between BOLD and physiological factors, other work had demonstrated that, although BOLD changes are related to fluctuations in neural activity [13,14], neural activity is not the only factor that causes BOLD fluctuations. In particular, it was recognized that physiology may be one factor affecting ongoing changes in regional metabolism, given that continuous ANS functions like respiration and cardiac rate trends are tightly linked to the process of oxygenation.

3. Physiology as noise

There are a number of ways by which physiological processes can impact BOLD measures, and some of these induce fluctuations that should be treated as noise. For instance, respiration processes may induce systematic motion patterns that reduce the accuracy of BOLD analyses and necessitate correction [15]. One type of movement effect is driven by changes in blood pressure through major vessels, which induces movement in nearby tissues [16]. Respiration-induced effects can translate into head motion [17] but also result in variations in oxygen concentration and susceptibility effects induced due to the breathing process [18]. Given such impact, work treating ANS correlates as noise has developed analysis methods that treat ANS measurements similarly to how motion data are treated during fMRI preprocessing. A number of approaches have been examined, including the removal of ANS covariates in *k*-space or during retrospective processing in the image domain [17] or the joint removal of physiological effects in tandem with head motion [19]. Other work has examined related covariates, including heart-rate variance and respiration variance [20], as well as the effectiveness of various models combining these factors in the context of correction [21].

In practice, a common general method to link physiological time courses with fMRI data is the one in which the phase of the physiological time course is used to produce Fourier expansions of low order. The relation of these expansions with the BOLD data is evaluated using linear fit against the fMRI time series. When considering physiological effects as a source of noise, the image-based method for retrospective correction of physiological motion effects (RETROICOR [17]) is commonly utilized to assess the amount of variance in the fMRI data explained by ANS measures. Given that ANS recordings have a higher temporal resolution than BOLD (e.g., 50 Hz), some researchers have

opted to undersample the measures to the timing of the acquisition repetition time (TR) [22], whereas others account for ANS effects at the single-slice level, which is acquired at a rate given by the repetition time divided by the number of slices: [TR/*N*(slices)] Hz.

In the absence of physiological recording, several researchers have examined the use of proxy measures derived from the BOLD signal itself. The particular issue of whether physiological effects are aptly summarized in the "global mean" of the BOLD signal and whether the global mean can be used as a proxy for physiological parameters has been addressed in several studies [23–25]. Furthermore, a direct comparison, by means of correlation coefficients, between physiological acquisitions and global mean signal showed that for certain participants it was possible to find a reliable correlation between the global mean of the BOLD response and physiological responses [20]. However, we note that interpreting the reliability of correlations in this context is complicated by the fact that both the global mean time series and the physiological data themselves demonstrate strong serial autocorrelation, which makes it difficult to assign reliability values to correlations between the two variables, and this is a topic that should be further addressed. The issue of global mean removal has also been examined by several studies, which suggest that it is best to not partial out this property for various analytic reasons [26] and that, at a minimum, global mean removal should be employed only in those cases where it does not create interpretive confounds. From a theoretical perspective, recent works [25,27] have examined the neuronal correlates of global BOLD fluctuations, by combining local field potentials derived from single-cell recordings and fMRI acquisitions. This work has shown that correlations between the gamma frequency (40–80 Hz) of the LFP spectrum and the fMRI signal are observed over large parts of the cortex. This correlation was found to be significant for neural events recorded in diverse brain areas. The fact that about 10% of the fMRI variance could be related to these transient-induced LFP changes suggests that global signal contains cognitively relevant information and, as such, should not be removed from the signal. One avenue for future work on removal of physiological effects from the BOLD signal is the development of data-driven methods such as independent component analysis (ICA) to identify components in the BOLD signal whose properties match those of physiological time series [28].

The importance of accounting for potential physiological effects on BOLD data has increased with the theoretical focus on understanding resting state processes in the human and primate brain and their relation to cognition. Since many of the fMRI methods for studying the resting state depend on quantifying patterns of spatially synchronized fluctuations in the BOLD response, any factor that may drive correlated BOLD fluctuations should be corrected for in order to determine if the patterns of spatial correlation identified are indeed driven by synchronized neural sources. This is particularly a concern since physiological measures induce correlation between different brain regions [20], and given that motion may induce similar patterns of activity that affect the results of clustering solutions [29] in the resting state [19]. That is, dissociation between "functional connectivity" and "nonfunctional connectivity" is becoming an important domain of inquiry. A number of studies have examined the relation between physiological processes, cortical activity and connectivity among various cortical networks.

The relation between respiration effects and the BOLD signal has been evaluated in different ways: modeled as lagged boxcar functions [30] or considered as factors to be convolved with an HRF in a block design context [31]. The work by Birn et al. [32] examined several interesting aspects of respiration-induced effects on the BOLD signal: they started from the observation that variations in respiration rate occur at frequencies (about 0.03 Hz) similar to those related to resting state connectivity (see, for example, Ref. [33]). They showed that the lagged envelope of the respiration time courses, termed the respiration volume per time (RVT), is an important factor in explaining BOLD fluctuations, both at rest and during a cognitive task [32]. Furthermore, the removal of physiological effects reduced the standard deviation of the signal, suggesting an improvement in data quality. The interrelation between RVT and brain function was examined by probing for correlations between BOLD time series and RVT lagged regressors, obtaining significant values at hemodynamically relevant time lags (about 8 s). An extension of this framework led to the development of a respiration response function [34], which was shown to be a valid basis function for respiration-induced fluctuations across the brain.

Cardiac effects on BOLD have also been examined. Heart rate and heart rate variability over time have been incorporated into the RETROICOR framework to take into account noncyclic effects explained by cardiorespiratory phases, and the impact of these factors was evaluated using connectivity studies [22]. Regressors for noncyclic effects were constructed by lagging physiological acquisitions and choosing the shifts that maximized the correlation with BOLD signal. Additional variance (about 5% more than explained by the initial RETROICOR procedure) was found to be explained by noncyclic effects, including RVT. Importantly, functional connectivity during rest was still reliable after the removal of these effects, suggesting that, even after physiologically induced correlations are removed, some correlation is indeed related to neural activity per se.

Chang et al. [35] aimed to derive a cardiac response function through a deconvolution of the fMRI data. They showed that their model accounted for more variance (taking into account the additional parameter) in about one-third of the brain voxels at rest. This improvement was also spatially heterogeneous; it produced an increase of the connectivity within nodes of the default mode network and a decrease outside it.

The specific issue of the spatial heterogeneity of physiological effects was also examined in several other studies. Saad et al. [36] demonstrated that, due to the spatial heterogeneity of physiological effects, masks of particular brain areas including white matter and cerebrospinal fluid may be constructed from structural images, so that the mean time series from those masks can be used as additional explanatory variables when accounting for physiological noise. A related study demonstrated the use of a completely image-based strategy to remove variance related to global effects [37], and this was shown to improve the data quality of the signal. This particular attention to tissue features suggests that correction of ANS effects could be better performed when considering the particular anatomical context of various brain regions.

The studies we described explored the relationship between autonomic indicants and neural activity by examining correlations between ANS measures and the BOLD response, and their relation to connectivity patterns or BOLD data quality. These relations have also been examined outside the domain of BOLD response. For example, optical topography has been used as noninvasive imaging technique to directly evaluate hemoglobin concentrations (HbCC). Katura et al. [38] acquired optical topography data as well as two autonomic indicants (heart rate and mean arterial blood pressure) at rest to examine the relationship between cardiovascular dynamics and low-frequency HbCC fluctuations in the cortex. They evaluated whether there exists a common low-frequency band where oscillations occur for both the hemodynamic and autonomic functions. The authors also identified a frequency band at around 0.1 Hz that could be distinguished within the hemodynamic behavior from other fluctuation components. Subsequent work showed that this relation could be modulated pharmacologically [39]. Using transfer entropy as a measure of interrelation between HbCC, heart rate and mean arterial pressure, Katura et al. [38] also showed that the low-frequency fluctuations in cerebral oxy- and deoxy-hemoglobin could be associated, in a significant fraction (up to 35%), with ANS indicants. This suggests that, when analyzing BOLD signal fluctuations in this frequency band, ANS influences could be considered as a significant source of fluctuations. Tong and Frederick [40] extended the investigation of low-frequency fluctuations using near-infrared spectroscopy acquisitions (NIRS) combined with fMRI. NIRS extends the information obtainable from fMRI since the former has high temporal resolution (12.5 Hz). The authors observed a correlation between low-frequency oscillations of the NIRS signal and the BOLD responses widely distributed throughout the brain. This correlation, performed between BOLD and down-sampled, multi-lagged versions of the spectroscopy time series, showed a meaningful temporal pattern as well. According to the distributions of correlation in time (about 6 s to travel across the whole brain) and in the space (their arrangement resembled main blood vessel maps), the authors were able to identify the presence of heterogeneous sources for low-frequency fluctuations, including nonneural nature.

Work using fMRI has attempted addressing this issue as well. The BOLD signal itself is related to the fluctuations in HbCC, and the blood volume itself could be related to blood pressure effects. Shmueli et al. [41] studied the relationship between cardiac rate variation time courses and BOLD signal at rest, using correlations and regressions. The ANS indicant they examined was heart rate variability, constructed from the cardiac pulsation time courses. The spectrum of this parameter was shown to be higher in the relevant (about 0.1 Hz) range of frequency. Adding cardiac rate regressors to a RETROICOR framework led to an increase of the variance explained. Furthermore, the spatial distribution of the correlations with cardiac rate variations was not localized around large vessels (as commonly occurs for cardiac pulsations and respiration time courses). These results may suggest that cardiac rate variations induce their effects in ways that are not mediated by motion or susceptibility-change effects and should be considered when one wants to significantly take into account the ANS effects on the fluctuations of the BOLD signal.

4. The role of ANS indicants in cortical activity

While the above-reviewed studies aim to characterize the variance explained by various physiological quantities and remove their effect from the BOLD data, another body of work has approached the analysis of ANS indices from a completely different approach, treating these as meaningful signals. This line of work has focused on the neural and behavioral correlates of autonomic indicants in order to understand which brain regions are involved in triggering, modulating or monitoring ANS functions. From the perspective of such studies, the BOLD variance explained by physiological signal is a potentially meaningful component whose properties should be examined.

The idea that bodily states are monitored by the brain and processed at different levels of conscious experience has an established history in the study of psychology and cognitive neuroscience. Both cortical and subcortical structures are known to monitor physiological states such as breathing rate and cardiac responses [42]. These monitoring and control operations occur largely on an unconscious level. However, different lines of theoretical and experimental work have also developed the notion that ongoing experience is partly determined by a person's awareness or monitoring of his or her bodily states. One of the earliest and stronger forms of this approach postulated that the emotional aspect of human experience is actually generated as a result of monitoring visceral responses (see, for example, Ref. [43]). This strong form of the hypothesis was later strongly criticized on various grounds [44], including the fact that severing connections from internal organs (viscera) to the nervous system still allows the experience of emotions and that

visceral responses may be triggered after an emotion is experienced. Recent lesion-based dissociations support this line of criticism, suggesting that the emotion-experience and autonomic responses evoked by emotional stimulus are associated with different systems and are independent of each other [45].

Nonetheless, the notion that bodily states, including those triggered by the ANS, play a functional role in human experience at different levels has been continuously influential in the cognitive neurosciences. The somatic marker hypothesis developed by Bechara et al. [46] is a theory of human decision making that holds that decisions are "influenced by marker signals that arise in bioregulatory processes, including those that express themselves in emotions and feelings." This approach conjointly holds that bioregulatory processes affect or "color" ongoing experience, as well as decision-making processes. This hypothesis is based on several types of empirical studies, most generally those suggesting that risky-decision making has not only cognitive components but also emotional ones. For instance, whereas nonclinical participants generate skin conductance responses before making an uncertain choice, patients with ventromedial damage do not generate this response. This line of work does not directly address the issue of directionality — i.e., is the relation between ventromedial activity and the ANS response due to an afferent track by which the ventromedial cortex drives ANS activity or to an efferent track by which the region monitors the ANS state? In addition, given the heterogeneity of this frontal region, it is possible that it is involved in both generation and monitoring of ANS responses.

Subsequent work has documented that instances of conflict resolution, such as those evoked by conflict states (e.g., a Stroop task), similarly induce changes in skin conductance, suggesting that cognitive conflict is associated with ANS changes [47]. This has also been documented for cognitive conflict occurring during high-level mental processes such as reasoning, which was shown to induce changes in ANS activity [48]. These findings are particularly important given the well-established association between one particular ventromedial region [the anterior cingulate cortex (ACC)] and cognitive conflict. To the extent that the ACC is involved in monitoring of somatic states or their generation, such findings could pose an interesting explanation for some ACC activation patterns during conflict.

Consistent with this body of theoretical and experimental work, a body of neuroimaging work to date has attempted to identify neural structures that drive or monitor ANS responses, with particular interest in cortical structures. An important body of work in the area was pioneered in several papers by Critchley et al. whose work examines the links between ANS measures and neural function. This work merges classical emotional theories (see, e.g., Ref. [49]) with physiological and neuroanatomical concepts (see, e.g., Ref. [50]). In a recent work [49], cortical correlates of emotional feelings were studied, using fMRI and gastric electrogastrogram acquisitions. Participants were instructed to watch and judge videos where several kinds of feelings of disgust were elicited. Changes in ANS indicants were reflected in the activity of the insula: this area showed correlated activity with increased high-frequency heart power. This suggests that the insula could be involved in the representation of afferent information from the ANS towards the cortex (see also Ref. [51]). Brain activity increases in the insula and in the inferior parietal lobule were shown to be related to the accuracy in counting heart beats [52], suggesting the area mediates attention to one's own arousal.

Other support for high-level modulation of the relationship between brain function and ANS was examined in a study by Metz-Lutz et al. [53]. In that study, fMRI and ECG were acquired to explore human adhesion during movie watching (the belief that what is shown is real). They studied changes in heart rate variability using a lagged-autocorrelation index (correlation coefficient in Poincarè plots) to explore at what points do heart rate changes occur. They found that decreases in heart rate variability occurred at the same time as the activation of several brain regions, including Brodmann areas 21/22 and 37/39. From a physiological perspective, this exemplifies how naturally occurring emotions during movie viewing are associated with ANS indicants such as heart rate variability. From a technical viewpoint, such a finding highlights the importance of considering this relation during data analysis, since the link between this ANS measure and cognitive activity implies that procedures that remove the effect of heart rate variability from the BOLD signal could well remove meaningful components of the BOLD signal as well.

The relationship between ANS indicants and BOLD has also been examined outside the domain of high-level cognitive function. In an early study [54], PET data were collected while individuals' blood pressure (mean arterial pressure) and heart rate were monitored. Participants in that study were instructed to perform either effortless or effortful variants of two tasks: an isometric (squeezing a bulb) exercise or a mental arithmetic (serial subtraction) stressor task. Conjunction analyses were performed to explore areas common to both tasks, revealing activity in subcortical structures including the cerebellar vermis and brainstem, but also in the right ACC. These same regions and the right insula were shown to covary on a group level with mean arterial pressure. Finally, activity in the pons, cerebellum and right insula was associated with heart rate in the same way.

Follow-up work used fMRI and electrocardiographic acquisitions [55]. In this study, cardiac time courses were processed to separate low- (0.05–0.15 Hz) and high-frequency (0.15–0.50 Hz) components that refer, respectively, to sympathetic and para-sympathetic neural influences on heart rate [56]. The tasks utilized were similar to those used by Critchley et al. [54]. The study found a significant correlation between the low-frequency cardiac component and ACC activity. The authors interpreted this

finding as showing an involvement of the ACC in the modulation of cardiac function. Importantly, the same study demonstrated that patients with a lesion in the ACC performed well on both tasks but did not show the same sort of ANS modulation. Instead, they showed relatively reduced cardiovascular responses to effortful cognitive tasks. This was taken to suggest that that the ACC plays an important role in the regulation of bodily states of arousal, to meet concurrent behavioral demands.

The study of the relationship between brain activity and ANS indicants could be performed by modeling their relation to brain activity as mediated by high-level cognitive functions. Wager et al. [57] demonstrated that social evaluative threat was correlated with cardiovascular responses. In that study, they combined fMRI and physiological monitoring and presented participants with stimuli eliciting this kind of threat in a block-design study. A conjunction analysis identifying regions correlating with both the stimulus and heart rate identified a set of brain regions including the pregenual ACC, orbitofrontal cortices and the putamen. An analysis of the information pathways between these three areas using mediation analysis showed that they play independent roles in regulating the relationship between activity patterns related to a task's cognitive demand and those activity patterns related to ANS indicants such as heart rate. The nonartifactual nature of these findings was supported by the strong spatial localization of the effect, which stands in contrast to the more widespread correlates of physiological fluctuations. Based on the same data, another work [58] underlined the importance of prefrontal and subcortical systems as well: ventromedial prefrontal cortex and rostral ACC were shown to be involved in the relationship between brain function and heart rate, through the mediation of periaqueductal gray.

Another study [59] explored the interrelations between ANS and neural activity using sensorial mechanisms. In that fMRI study, several autonomic measures were acquired during the scan: electrocardiogram (ECG), heart rate and mean arterial pressure data. Participants were instructed to wait for slight nonpainful electrical shocks. These shocks were given either synchronously with or delayed with respect to the cardiac peaks (R wave, dominant peak in ECG cycle). This particular experimental setup was designed to examine whether stimulus processing would depend on a person's ongoing visceral state. Analyzing ANS indicants, they found that mean arterial pressure increases when shocks were given synchronously with the ECG R wave. BOLD signal was analyzed using regressors constructed by convolving the timing of synchronized and unsynchronized shocks with an HRF. It was shown that the anterior insula, amygdala and brainstem showed different responses to synchronous and delayed shocks. Specifically, the left (and, statistically less significant, the right) anterior insula and the mid pons showed greater activity for synchronous shocks, and the right amygdala showed weaker activity. This suggests that there exist a set of brain regions that support the integration of somatosensory information with cardiovascular feedback to control autonomic arousal.

The spatial localization of the effects we previously described could be referred to the cortical back-ends of the interoceptive information pathways on the cortex (see Ref. [51] for a useful schema). The afferent information from the peripheral nervous system towards the central nervous system [50] passes through thalamic nuclei and then towards several cortical areas — the insula, the ACC, the orbitofrontal cortices — and terminates in the right anterior insula [51,60]. The relationship between ANS and brain function emerges as a crucial factor in the BOLD fluctuations in these areas.

5. Summary

In this work, we have presented two views of the functional role of ANS indices in the context of fMRI BOLD analysis. On the one hand, these indicants are sometimes treated purely as physiological noise. When treated in this way, the aim of researchers is to remove the effect of these indices from the BOLD signal. As reviewed, a number of covariates have been explored in this context, including the original cardiac and respiratory recordings, their harmonic expansions, undersampled derivatives matched to the temporal resolution of the TR, and more complex derivatives capturing heart rate variance and respiration variance over time. Given the relation of such measures to purely nuisance variables such as head motion, cardiac-induced tissue motion and changes in CO_2 concentration, this approach is clearly justified.

However, the importance of work showing the interesting functional relation between ANS indices and activity in both cortical and subcortical regions should be considered as well. From this perspective, brain regions that play a meaningful functional role in driving or monitoring ANS activity will show activation patterns that correlate with the BOLD signal. For this reason, technical procedures that aim to remove the effect of ANS indices from the BOLD signal will also remove a meaningful variance component not only when studying processes associated with these regions, but also when studying any process in which there might be a confound between cognitive processing and ANS states. The impact of "physiological cleaning" can therefore be particularly detrimental in various experimental contexts. These may include, e.g., (a) manipulations of cognitive conflict that are associated with ANS activity, (b) studies that explicitly use emotional stimuli, (c) studies of decision making under uncertainty, (d) naturalistic viewing of engaging ecological stimuli such as movies that induce fluctuations in ANS activity over time and (e) studies evoking startle or surprise responses. Furthermore, as we have outlined, the study of the relation between ANS and cortical function is an important topic being currently developed, and describing the frequencies driving such connectivity, the pathways of information and the way in

which the link between ANS activity and cortical activity can be manipulated is a central question in this domain. Clearly, none of these questions can be answered if ANS indicants were removed from the signal.

Addressing the role of ACC and its function during rest is related to both these viewpoints. On the one hand, the ACC is a central node in the "default mode network," which is considered to be one of the dominant resting state networks [61]. Functional connectivity studies examining this region have treated ANS indicants as external factors that represent physiologically confounding data. On the other hand, the literature we reviewed suggests that the ACC is one of the most important brain mediators between sympathetic information and brain activity, as was shown from studies of clinical and nonclinical populations. For this reason, it could be that the ACC mediates unique functions not shared with the rest of the default mode network. If so, removing variance attributed by physiological measurements from this region could result in removing a unique component of variance, thus leading to an incomplete theoretical description of the ACC's role. For instance, it could be that the ACC is partly related to other regions mediating ANS functions, and this relation will not be found after the removal of ANS correlates.

On the basis of these considerations, we suggest that researchers carefully evaluate whether their particular research question unambiguously justifies the removal of ANS indicants from the signal. While it could be that in the near future methods will be available that will allow limiting the correction for ANS fluctuations to particular brain regions, to our knowledge such procedures have not been validated as of yet. Consequently, if the theoretical question being examined may have a functional link to ANS activity, it may be pertinent to analyze the data with or without the removal of ANS effects. In our opinion, increased synergy between research examining cortical systems mediating ANS function and technical work aiming to identify ANS-BOLD correlates holds the potential to advance research in both domains.

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