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Translating the hemodynamic response: why focused interdisciplinary integration should matter for the future of the functional neuroimaging

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The amount of information acquired with functional neuroimaging techniques, particularly fNIRS and fMRI, is rapidly growing and has enormous potential studying human brain functioning. As follows, many scientists focus on solving computational neuroimaging and Big Data issues to advance the discipline. However, the main obstacle - the accurate translation of the hemodynamic response (HR), by the investigation of a physiological phenomenon called neurovascular coupling (NVC),- is still not fully overcome and more importantly often overlooked in this context. This article provides a brief and critical overview of significant findings from cellular biology and in vivo brain physiology with a focus on advancing existing HR modelling paradigms. A brief historical timeline of these disciplines of neuroscience is presented for readers to grasp the concept better, and some possible solutions for further scientific discussion are provided.

1 **Translating the hemodynamic response: why focused** 2 **interdisciplinary integration should matter for the future of** 3 **the functional neuroimaging**

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7 **Abstract.** The amount of information acquired with functional neuroimaging techniques,
8 particularly fNIRS and fMRI, is rapidly growing and has enormous potential studying human
9 brain functioning. As follows, many scientists focus on solving computational neuroimaging and
10 Big Data issues to advance the discipline. However, the main obstacle - the accurate translation
11 of the hemodynamic response (HR), by the investigation of a physiological phenomenon called
12 neurovascular coupling (NVC),- is still not fully overcome and more importantly often
13 overlooked in this context. This article provides a brief and critical overview of significant
14 findings from cellular biology and in vivo brain physiology with a focus on advancing existing
15 HR modelling paradigms. A brief historical timeline of these disciplines of neuroscience is
16 presented for readers to grasp the concept better, and some possible solutions for further
17 scientific discussion are provided.

18 **Keywords:** brain; brain physiology; cerebrovascular regulation; computational modelling; cellular
19 biology; functional magnetic resonance imaging; functional near-infrared spectroscopy; healthcare;
20 hemodynamic response; neuroscience; neurovascular coupling.

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23 **INTRODUCTION**

24 Modern functional neuroimaging methods cover broad spatial and temporal scales (Pouratian,
25 Sheth, Martin, & Toga, 2003) and facilitate the important exploration of the functional
26 organisation of the human brain in health and disease (Liu et al., 2015). Numerous statistical or
27 methodological challenges are addressed with this complexity. However, some threats arise from

28 fundamental conceptual challenges that remain widely underappreciated within the clinical and
29 neuroimaging communities (Poldrack & Yarkoni, 2016). Current trends in neuroimaging and
30 computational neuroscience promote the advanced mathematical modelling of human brain
31 function based on neuroimaging, and the implications associated with the use of Big Data
32 (Hansen, Miron-Shatz, Lau, & Paton, 2014) in scientific research and healthcare innovations.
33 These multidisciplinary interactions between different branches of science are vital for overall
34 scientific progress. However, some main conceptual challenges may remain shadowed by
35 massive trends and become a barrier to progress. For example, the ability to assess neural
36 activity in a noninvasive way by measuring the brain's circulation of blood has revolutionised
37 neuroscience. As a result, we are witnesses to enormous growth in the field of human brain
38 research (Raichle, 2009; Toga, 2015). Each of the functional neuroimaging techniques used
39 today, such as functional near-infrared spectroscopy (fNIRS), functional magnetic resonance
40 imaging (fMRI), positron emission tomography (PET) or single photon emission computed
41 tomography (SPECT) to explore different metabolic or particular physiological events, but all
42 are based on the physiological principles of neurovascular coupling (NVC). Neurovascular
43 coupling is the process by which active brain regions induce a local increase in blood flow to
44 match their energy demands via the dilation of capillaries and arterioles through various cellular
45 signalling paths (Mishra et al., 2016). Capillary dilation generates a significant portion of the
46 blood flow increase, evoked by neuronal activity (Hall et al., 2014), and is expected to contribute
47 substantially to the observed hemodynamic response (Lindauer et al., 2010). Nevertheless, our
48 understanding of NVC in humans despite its importance is still incomplete due to a lack of
49 appropriate and consistent analysis strategies and stimulation paradigms (Hillman, 2014;
50 Phillips, Chan, Zheng, Krassioukov, & Ainslie, 2016). Despite their technological differences,
51 widely used functional neuroimaging techniques, such as functional magnetic resonance imaging
52 (fMRI) and less known but prominent functional near-infrared spectroscopy (fNIRS), are mainly
53 based on the common underlying phenomenon of NVC (Hillman, 2014; Huneau, Benali, &
54 Chabriat, 2015; Iadecola, 2017; Phillips et al., 2016). It makes some results of current
55 experimental methods ambiguous compared to the more in-depth fundamental perspective
56 (Lindauer et al., 2010; Phillips et al., 2016; Sotero & Trujillo-Barreto, 2007).

57 The scientific knowledge is always limited to some extent and arguably with each new finding.
58 However, the real concerns occur summarising that at the moment, a big part of scientific and

59 clinical research production is based on sophisticated mathematical manipulations of
60 neuroimaging data which was derived from the observations of NVC, referred to as a
61 hemodynamic response (HR). A generalisation like this, emphasise the need of tighter and
62 focused interdisciplinary integration within particular neuroscience fields to improve the
63 translation of physiological signal into neuroimaging data, which later is processed with
64 sophisticated mathematical and statistical methods. The goal of this article was to fill the gap
65 between the critical and brief overviews of one of the under-appreciated neuroimaging challenge:
66 accurate translation of the hemodynamic response to scientific and clinical findings. The next
67 objective was to provide the scientific reader with a summary of key aspects and analyse why
68 this problem is relevant to those that are interested in or directly involved in human cognition
69 and behaviour neuroscience or clinical research. To serve this purpose, this article conceptualises
70 the current knowledge of neurovascular coupling from several perspectives, mainly cellular and
71 molecular neuroscience, and functional neuroimaging (particularly fNIRS and fMRI as they are
72 closely related).

73 **SURVEY METHODOLOGY**

74 The review was designed with a focus on the existing scientific paradigm in human brain
75 functional neuroimaging research, mainly addressing the absence of necessary interactions
76 between different multidisciplinary branches of neuroscience such as cellular biology, human
77 brain physiology and computational modelling. The articles that were reviewed in this paper
78 were identified in databases (e.g., Google Scholar, PubMed, ScienceDirect) and subject-specific
79 professional journal and websites (e.g., PLOS, PeerJ, Frontiers, JCBFM). The literature review
80 was assured to be unbiased and comprehensive by narrowing down the exploration by searching
81 for original research articles and reviews that discuss i) cerebrovascular regulation; functional
82 hyperaemia; NVC; astroglial network; the origin of the hemodynamic response signal in fNIRS;
83 the origin of the blood-oxygen-level-dependent (BOLD) signal in fMRI; or ii) the biophysical
84 model of fNIRS and fMRI signals; the computational modelling methods used in fNIRS and
85 fMRI; and iii) studies that compare both methods or combine them in humans. The author also
86 searched for articles in cellular and molecular biology, animal studies, subsequently regarding
87 studies in health and disease. However, it was done only in combination with the previously
88 mentioned search criteria to identify only relevant publications. The other inclusion criteria for

89 selected articles required that articles would be directly related to the topic and would not
90 exhaustively cover unrelated material such as other neuroscience methods if the results were not
91 directly comparable with functional neuroimaging.

92 **WHAT IS A HEMODYNAMIC RESPONSE?**

93 The human brain represents only 2% of the total body mass. About 25% of the oxygen and from
94 20 to 70% of the glucose consumed by the human body is dedicated to cerebral functions
95 (Herculano-Houzel, 2011). The maintenance and restoration of the ion gradients dissipated by
96 signalling processes such as post-synaptic and action potentials, as well as the uptake and
97 recycling of neurotransmitters are the primary processes contributing to the high brain's energy
98 needs (Attwell et al., 2010). The brain blood circulation system actively regulates the constant
99 demand and supply. However, active brain regions are often provided more than they require.
100 One of the researchers poetically illustrated it as 'watering the garden for the sake of a single
101 thirsty flower' (Malonek & Grinvald, 1996). This overcompensation or functional hyperaemia is
102 a fundamental phenomenon in normal brain function. It was first confirmed by (Roy &
103 Sherrington, 1890) and defines the dilation of arterioles and capillaries of a brain region in
104 response to a local episode of high neuronal activity. Functional hyperaemia is a generalised
105 term for the outcome of a complex cerebrovascular regulation mechanism which will be briefly
106 discussed in this section. At this point, the term hemodynamic response (HR) is associated with
107 the quantitative measures of functional hyperaemia using fNIRS and fMRI. In fMRI, it is better
108 known as the hemodynamic response function (HRF) to imply its mathematical properties.
109 Further, in the text, only the hemodynamic response (HR) term will be used, as it describes an
110 observation of a physiological NVC event common for both techniques.

111 Functional magnetic resonance imaging and functional near-infrared spectroscopy have different
112 capacities to explore human brain functions. As was introduced, both methods, despite their data
113 acquisition differences, are based on a common underlying phenomenon termed NVC. However,
114 fMRI is more common in general, due to its broad application possibilities and historical
115 background, especially in clinical practice (Glover, 2011), while fNIRS was primarily used for
116 the bedside monitoring of infants, and other fields where fMRI were not applicable. Thus only
117 quite recently with technical progress fNIRS became an equivalent method for investigating
118 human cognitive brain functions (Boas, Elwell, Ferrari, & Taga, 2014). Despite common

119 underlying phenomenon (Hillman, 2014; Huneau et al., 2015; Iadecola, 2017; Phillips et al.,
120 2016) both methods have their own strengths and limitations associated with biophysical and
121 physiological signal origins (Kim & Ogawa, 2012; Scarapicchia, Brown, Mayo, & Gawryluk,
122 2017). A comparison of how the same physiological process of NVC originates as a
123 hemodynamic response measured using fNIRS (A) and hemodynamic response function
124 measured using fMRI (B) can be found in Figure 1. The example of hemodynamic response (A),
125 is based on measuring the composition of the total cerebral blood volume in the particular brain
126 area. These measures can be directly done *in vivo*, and both oxygenated haemoglobin $\Delta[\text{HbO}_2]$
127 and deoxygenated haemoglobin $\Delta[\text{Hb}]$ concentration changes are observed simultaneously. In
128 contrast, the BOLD signal in fMRI is based on the paramagnetic deoxyhemoglobin decrease in
129 T_2^* contrast, relative to the situation with diamagnetic oxyhemoglobin (Bandettini & Wong,
130 1995; Chavhan, Babyn, Thomas, Shroff, & Haacke, 2009). Thus, the $\Delta[\text{Hb}]$ curve in Figure 1.A.
131 could be seen as a BOLD signal representation, even though it is not straightforward due to other
132 physiological contributors captured in the BOLD response (such as regional cerebral blood flow
133 and volume),(Arthurs & Boniface, 2002; Kim & Ogawa, 2012).

134 *Figure 1. Examples of canonical hemodynamic response (A), and hemodynamic response function (B). A neural*
135 *activity from 0 to 5 seconds (grey bar) causes neurometabolic and later neurovascular coupling, which can be seen*
136 *as a delay of response (around 2 seconds). Box in hemodynamic response (A) indicates a small inflow of $\Delta[\text{HbO}_2]$,*
137 *when the total blood volume is still relatively unchanged (due to increased cerebral blood flow), and later b)*
138 *$\Delta[\text{HbO}_2]$ increases rapidly due to functional hyperemia caused by vasodilatation. The small increase of $\Delta[\text{Hb}]$*
139 *occurs due to insufficient washout when the cellular oxygen demand exceeds current supply in a tissue. The*
140 *canonical example of a hemodynamic response is based on measuring the composition of cerebral blood volume via*
141 *chromophore concentration changes (oxy-Hb and deoxy-Hb). fNIRS studies can directly measure both oxy-Hb and*
142 *deoxy-Hb),(Venclove, Daktariunas, & Ruksenas, 2015). In contrast, the canonical hemodynamic response function*
143 *(HRF) from the Blood Oxygenation Level Dependent (BOLD) method represents the magnetic field change in*
144 *response to the $\Delta[\text{Hb}]$ curve (B) and is relative to the baseline.*

145 With technological progress, the number of combined functional fMRI-fNIRS studies has begun
146 to increase slowly. According to the PubMed database search for the terms “fMRI” and “fNIRS”
147 in the title/abstract field and restricted to the results of the articles and review papers published
148 between 1977/01/01 and 2018/06/06, a total of 752 documents with human participants were
149 identified. After additional restriction to search for these terms only in the title field, a total of 11
150 documents remained (Anwar et al., 2013; Cui, Bray, Bryant, Glover, & Reiss, 2011; Frederick,

151 Nickerson, & Tong, 2012; Gagnon et al., 2012; Maggioni et al., 2013; Okamoto et al., 2004;
152 Sasai et al., 2012; Sato et al., 2013; Strangman, Culver, Thompson, & Boas, 2002; Tong &
153 Frederick, 2010; Toyoda et al., 2008). A few of them were comparisons, which have been
154 conducted for a variety of cognitive tasks to illustrate similarities and differences between fNIRS
155 and fMRI capabilities (Cui et al., 2011; Steinbrink et al., 2006). To wrap it up, the described
156 PubMed search serves as an illustrative example for two points: a) number of multimodal, cross-
157 validation, or comparison studies within even closely related techniques such as fMRI, and
158 fNIRS is still insufficient; and b) that integration of more distinct branches of neuroscience might
159 be even more daring, but as will be discussed in further section, might also add compelling value
160 to the field of functional human brain research.

161 **Hemodynamic response and classical approach in neuroimaging**

162 The fundamentals of coupling between brain electrical activity, metabolism, and the observed
163 HR are incredibly complex. Classical functional neuroimaging approaches for simplicity assume
164 that the vascular response induced by neural activity is a nearly linear function of blood volume
165 increase. This approach is convenient to model and reconstruct the possible neural activity from
166 the HR but is not entirely accurate. Nonlinearities are believed to arise from both nonlinearities
167 in the vascular response and neuronal activity, as several studies have demonstrated (Birn et al.,
168 2013; Birn & Bandettini, 2005; Hillman, 2014; Wager, Vazquez, Hernandez, & Noll, 2005).
169 Many more studies may be discussed depending on the reader's point of view, but the two
170 following studies were chosen subjectively to provide a reader with references to short
171 illustrative introduction to this topic for non-experts. Wager and colleagues published in 2005 an
172 empirical study with fMRI (Wager et al., 2005), where they attempt to characterise nonlinear
173 effects in visual and motor cortex in twelve human participants and presents finding that these
174 nonlinear effects are relatively consistent throughout the all tested brain areas. Additionally, a
175 more recent and exciting multimodal study by Fabiani and colleagues published in 2014 is
176 recommended (Fabiani et al., 2014). In this multimodal study nineteen young and forty-four
177 older healthy adults were examined to address physical fitness and age effects on neurovascular
178 coupling in the primary visual cortex and show the quadratic relationship between neural activity
179 and blood flow. The overall results indicate, that nonlinearity in neurovascular coupling has

180 more than one aspect to be considered, and the classical neuroimaging approach is not sufficient
181 to explain it.

182 What is the classical explanation of the origin of the hemodynamic response? Over a decade, the
183 understanding of NVC initiation and its overall role for HR formation dramatically changed
184 (Attwell et al., 2010). From a cellular and molecular neuroscience perspective, for a long time,
185 researchers favoured the idea that blood flow is locally controlled by a passive negative-feedback
186 system, where neural activity leads to a local substrate demand. It was thought that the metabolic
187 signal inducing HR could be a lack of O₂ or glucose, or the local rise of CO₂, ADP, or lactate.
188 However, this negative-feedback hypothesis failed to adequately explain the experimental
189 findings of NVC in animal models (Attwell et al., 2010; Walsh, 2016). Manipulations of O₂ and
190 glucose did not regulate blood flow as expected, and CO₂, ADP together with lactate showed
191 only partial effects (Attwell et al., 2010). More novel, feed-forward neurotransmitter-mediated
192 mechanisms suggest active control of the vascular energy supply in the brain (Attwell et al.,
193 2010). In this process, the neurons either signal or activate astrocytes to release vasoactive
194 messengers onto vessels. According to this hypothesis, astrocytes are anatomical intermediaries
195 between neurons and blood vessels (Attwell et al., 2010; Petzold & Murthy, 2011). However, is
196 it all about astrocytes or other glial cells are involved as well? Recent studies have begun to
197 challenge the astrocytes role of the main drivers of NVC due to inconsistencies between
198 spatiotemporal properties of vasodilatation, and the structure-functional properties and
199 distribution of astrocytes in the cortical volume (Iadecola, 2017; McCaslin, Chen, Radosevich,
200 Cauli, & Hillman, 2011). In the following sub-section the three examples of recent *in vivo*
201 experiments will be discussed, to better illustrate the importance of non-neuronal HR origin.

202 **What induces a hemodynamic response and why it matters?**

203 From a historical perspective one hundred and fifty years ago the neuroglial was thought to be
204 only a connective material in the brain and was given an entirely passive supportive role
205 (Kettenmann & Verkhratsky, 2008). Since then, a substantial amount of research has been
206 published supporting the idea that the previous “neuron-centric” perspective of neuroscience is
207 not accurate. Today it is evident that glial cells are integral to the development and maintenance
208 of the healthy central nervous system and play a vital role in the pathogenesis of many brain
209 disorders (Liddelow & Barres, 2017).

210 The particular scientific focus was first given on astrocytes, as they are the most abundant
211 population of glia in the mammalian brain (Azevedo et al., 2009; Liddelw & Barres, 2017; von
212 Bartheld, Bahney, & Herculano-Houzel, 2016). It was proved that astrocytes are not only
213 responsible for physical brain structuring but also are a) critical homeostatic cellular elements
214 that are capable of gluconeogenesis, provide neurons with lactate, and control overall glucose
215 levels (Bélanger, Allaman, & Magistretti, 2011; Brooks, 2009; Magistretti, 2006); b) form a
216 tripartite synapse with neurons and modulate synaptic activity via ion and neurotransmitters
217 concentrations in the extracellular space (Allen & Eroglu, 2017; Haydon & Carmignoto, 2006;
218 Krencik, van Asperen, & Ullian, 2017; Perea & Araque, 2005; Perea, Navarrete, & Araque,
219 2009); c) they are responsible for some immune activity, promote neuronal survival and enable
220 re-myelination within the brain (Ayaz, Allen, Platek, & Onaral, 2008; Liddelw & Barres, 2017;
221 Rommy von Bernha, 2016); and d) act as direct and indirect modulators of cerebrovascular tone
222 (Ayata & Lauritzen, 2015; Bazargani & Attwell, 2016; Filosa, Morrison, Iddings, Du, & Kim,
223 2016; Gratton, Chiarelli, & Fabiani, 2017; Iadecola, 2017; Mishra, 2017). Moreover, they form
224 equivalent to neurons astroglial network (Attwell et al., 2010; Giaume, Koulakoff, Roux,
225 Holcman, & Rouach, 2010; Scemes & Spray, 2003).

226 After all, one may ask how these new cellular findings translate into functional neuroimaging.
227 For example, the study of *in vivo* animal models (cat and rat) for a single-vessel hemodynamic
228 demonstrated that pial surface arteries in cat's visual cortex (as well as neurons) show orientation
229 responsiveness (in contrast to rats, where orientation maps are not shown in general), meaning
230 that propagation of vascular dilation between neighbouring columns in the brain needs to be
231 accounted for when decoding hemodynamic signals (O'Herron et al., 2016).

232 Another *in vivo* study of animal models (rat and mice) show that when the sensory input
233 increases blood flow capillaries dilate before arterioles and are estimated to produce 84% of the
234 blood flow increase (Hall et al., 2014). Previously it was thought that capillaries usually do not
235 significantly contribute. Moreover, the study identifies pericytes as significant regulators of
236 cerebral blood flow as they are the first vascular elements to dilate during neuronal activity, and ,
237 in turn, initiate hyperaemia. It also unexpectedly show that vasodilators released from active
238 neurons, interneurons, and astrocytes (Hamel, 2006; Miller & Halpern, 2014) are not the only
239 essential players in functional imaging. In fact, the role of pericytes in CNS is as diverse as it

240 was previously described with astrocytes: pericytes integrate, coordinate and process signals
241 from their neighbouring cells to generate diverse functional responses that are critical for CNS
242 functions in health and disease, including a) regulation of the blood-brain barrier permeability; b)
243 angiogenesis; c) clearance of toxic metabolites; d) neuroinflammation and stem cell activity; and
244 finally e) initiating capillary hemodynamic responses (Hall et al., 2014; Iadecola, 2017; Kisler et
245 al., 2017; M. D. Sweeney, Ayyadurai, & Zlokovic, 2016).

246 Also, another non-neurons cell type crucial for inducing hemodynamic response was recently
247 identified - vascular endothelium. Several kinds of research demonstrated that vascular
248 endothelium could propagate upstream dilations of cerebral vessels (Andresen, Shafi, & Bryan,
249 2006; Chen, Bouchard, McCaslin, Burgess, & Hillman, 2011; Hannah, Dunn, Bonev, & Nelson,
250 2011; Iadecola, 2017; Rosenblum, 1986). The *in vivo* study by Chen and colleagues, 2014 (Chen,
251 Kozberg, Bouchard, Shaik, & Hillman, 2014) demonstrated that spatially selective endothelial
252 disruption with light-dye treatment in rats somatosensory cortex significantly attenuated the HR
253 by blocking the retrograde dilation. The early stage and the peak of hyperaemia were affected the
254 most, meaning that neurons, astrocytes, pericytes and endothelial cells are all involved in
255 forming HR detected by functional neuroimaging.

256 There are many other scientific sources regarding cellular, molecular biology and NVC that
257 could be discussed. However, even with the given three *in vivo* examples, it is evident that the
258 main drivers of NVC, and temporal properties of HR associated with it, depends on the spatial
259 location along the cerebral vasculature (Iadecola, 2017). These new findings allow re-evaluating,
260 how spatiotemporal specificity may be improved alongside the technological progress of fNIRS
261 and fMRI. Because ultimately, the non-invasive use of HR is one of the most powerful tools at
262 our disposal to explore human cognition in health and disease.

263 **ACCOUNTING FOR THE COMPLEXITY OF CEREBROVASCULAR** 264 **REGULATION**

265 The HR describes the empirical observation of a physiological NVC event. It may be detected as
266 an amplitude changes in light absorption (fNIRS) or as a magnetic signal variation (fMRI). In
267 other words, a HR is a spatiotemporal picture of underlying NVC and cerebrovascular regulation

268 at large. To better understand this picture, some structural and functional properties of
269 cerebrovasculature must be explained.

270 **Neurovascular Unit (NVU)**

271 The concept of the neurovascular unit (NVU) emerged around 2001 (Iadecola, 2017). The whole
272 mechanism of cerebrovascular regulation can generally be decomposed into several stages
273 (Hamel, 2006; Phillips et al., 2016; Walsh, 2016). The most explored cerebral microcirculation is
274 provided by the structural and functional derivative called Neurovascular Unit (NVU),(Attwell et
275 al., 2010; Leybaert, 2005). The neurovascular unit represents the interface between the vascular
276 and neural compartments in the brain and is composed of vascular, glial and neuronal cells such
277 as a neurones, astrocytes, endothelial cells, and pericytes (Hawkins & Davis, 2005; M. D.
278 Sweeney et al., 2016; P. W. Sweeney, Walker-Samuel, & Shipley, 2018). The NVU is an
279 essential structure for several main processes: formation of neurometabolic coupling (NMC),
280 NVC, and formation of the blood-brain barrier (BBB), (Leybaert, 2005; Leybaert, De Bock, Van
281 Moorhem, Decrock, & De Vuyst, 2007; Petzold & Murthy, 2011). NVU may vary in structure
282 and function depending on location in the brain (Iadecola, 2017; Kowiański, Lietzau, Steliga,
283 Waśkow, & Moryś, 2013; Petzold & Murthy, 2011), thus emphasising the complexity of
284 numerous processes that are involved in maintaining adequate blood flow in the healthy human
285 brain. Neuronal activity in the brain causes two cerebrovascular regulation processes:
286 neurometabolic coupling (NMC), which undergoes a substrate exchange between a neurone and
287 an astrocyte and later initiates (but not necessarily) NVC. NVU also supports the Blood-Brain
288 Barrier (BBB) coupling but is believed to be unbundled from the already mentioned NBC and
289 NVC, as it regulates the integrity and functions of the BBB (Leybaert, 2005; M. D. Sweeney et
290 al., 2016). New pieces of evidence suggest that another critical component of the NVU are the
291 interneurons that transduce signals from perivascular nerves (Hamel, 2006; Walsh, 2016). The
292 crucial role of the perivascular nerves is to regulate the cerebrovascular tone influencing the
293 overall brain perfusion. NVC is then determined by the chemical signals released from the
294 activated perivascular nerves and astrocytes, and together alter a vascular tone to adjust local
295 perfusion in accordance to the brain activity (Hamel, 2006; Walsh, 2016).

296 **Signal transduction path in the neurovascular unit**

297 With progress in molecular and cellular biology, a conceptual shift in our understanding of
298 cerebral blood flow occurred where astrocytes, previously believed to be passive supporting
299 cells, has been shown to actively participate in many other physiological processes, as well as
300 creating neural equivalent to the astroglial network, and and directly modulating neural activity
301 (Giaume et al., 2010; Kowiański et al., 2013; Scemes & Spray, 2003). For a while, the idea that
302 elevations of calcium concentration in the astrocytes may release transmitters that regulate
303 neuronal and vascular functions was controversial. This changed when numerous contradictions
304 were reported between different studies and had been resolved (Bazargani & Attwell, 2016).
305 Shortly after the discovery that glutamate triggers an increase of intracellular calcium
306 concentration ($[Ca^{2+}]_i$), it was suggested that there might be a mechanism by which calcium
307 signalling propagates towards astrocytes endfeet and stimulates the release of vasoactive
308 messengers (Attwell et al., 2010). Vasoactive messengers can cause vasodilatation (most of the
309 neurotransmitters; nitric oxide; prostaglandins; epoxyeicosatrienoic acids; lactate; adenosine etc.)
310 or vasoconstriction (norepinephrine; 20-HETE etc.) of arterioles (Giaume et al., 2010;
311 Kowiański et al., 2013; Leybaert, 2005; Petzold & Murthy, 2011; Scemes & Spray, 2003).
312 Current understanding suggests that astrocytes, as well as neurones, should be divided into three
313 spatial compartments, such as processes, soma and endfeet (Bazargani & Attwell, 2016). In this
314 way, the release of specific vasoactive messengers in the endfeet is explained by an overall
315 summation of ($[Ca^{2+}]_i$) in the soma and processes. The response may differ in terms of frequency,
316 kinetics, spatial spreads and interaction with other cellular messengers (Bazargani & Attwell,
317 2016). As was previously discussed, astrocytes are not the only cells that are involved in HR, but
318 they continue to be considered the main drivers of NVC.

319 Because of this, the article proposes the conceptual biophysical scheme of the biological signal
320 transduction path in the neurovascular unit (Figure 2), as a brief adaptation of the classical
321 approach of NVU. Figure 2 summarises how metabolic and physiological events (NMC and
322 NVC accordingly) via calcium concentration elevation cause the hemodynamic response. This,
323 in turn, can be observed with functional neuroimaging. Note that the conceptual biophysical
324 scheme inevitably assumes neural activity-derived NVC. Nonetheless, recent findings show that
325 astroglial metabolic networks may sustain or suppress neuronal activity (Giaume et al., 2010).
326 For simplicity, this article does not account for it or discuss it thoroughly, as more studies have
327 to be done to generalise new findings (Giaume et al., 2010; Walsh, 2016). However, the idea

328 should be kept in mind for the critical evaluation of current functional neuroimaging methods,
329 and the proposed scheme should be used as a tool for a brief explanation how signal transduction
330 for cerebrovascular regulation occurs in NVU. Previously mentioned evidence of spatiotemporal
331 specificity of NVU are not included to avoid unnecessary complexity as information about
332 additional players in coupling is still under investigation.

333 *Figure 2. The conceptual biophysical scheme of biological signal transduction path in the neurovascular unit. A)*
334 *Neurometabolic coupling (NMC); B) Neurovascular coupling (NVC). Both neurones (neurotransmitter release) and*
335 *astrocytes (glucose and oxygen consumption) respond to increased extracellular glutamate, and intracellular*
336 *calcium to transmit direct and indirect vasoactive signals for the appropriate blood delivery and distribution in the*
337 *electrically active brain area.*

338 The same complexity of cerebrovascular regulation raised the developmental of numerous
339 approaches, ranging from purely statistical signal processing to biophysical modelling at various
340 levels of detail. Regional hemodynamic changes measured by fNIRS and fMRI are modelled
341 separately because of different aspects of HR that are captured, and sources of noise that are
342 involved. Regarding fNIRS, the extended version of an existing computational model of cerebral
343 physiology, 'BrainSignals' should be considered as the most prominent (Caldwell et al., 2016). It
344 incorporates components of a) hemodynamic; b) mitochondrial brain metabolism c) brain
345 oxygen consumption; and d) scalp hemodynamic. This model also joins haemoglobin-based and
346 the cytochrome c oxidase redox state based measurements (which are out of scope in this article
347 but are promising branch of optical brain measurements). Moreover, the authors compare their
348 empirical model with real measurements, which give promising results in detecting non-linear
349 confounding effects, which are also extensively highlighted by other authors (Tachtsidis &
350 Scholkmann, 2016).

351 Meanwhile, most models of BOLD response are based solely on cerebral blood flow, cerebral
352 blood volume, and the local metabolic rate of oxygen consumption (Kim & Ogawa, 2012; Toga,
353 2015). These models depict the transient hemodynamic, and oxygenation changes in the
354 activated cerebral areas also mimic some of the physiological mechanisms of functional
355 hyperemia and are extensively discussed by Huneau and colleagues 2015 (Huneau et al., 2015).
356 Authors shortly state, that despite the accumulation of new findings, NVC has surprisingly been
357 forsaken in modelling functional neuroimaging, especially in humans. On the other hand, the
358 field of mathematical modelling of BOLD reached some significant consensus across variables

359 that should be involved in a generative hemodynamic model (using dynamic causal modelling
360 approach), (Havlicek et al., 2015). It involves several different models, such as a) neuronal; b)
361 NVC; c) hemodynamic; and d) BOLD in a joint model. The approach reflects experimental
362 observations of underlying physiological processes and corresponds well with multimodal
363 experimental datasets (Havlicek, Ivanov, Roebroek, & Uludağ, 2017).

364 Meanwhile, technological improvement of neuroimaging techniques allows creating new and
365 more specific models for investigating NVC. For example, novel *in vivo* study combining
366 imaging of cortical microvascular and mural cell architecture together with mathematical
367 modelling of blood flow and oxygen transport provided new insights on seemingly paradoxical
368 observations in the literature around reduced blood velocity in response to arteriolar
369 constrictions, and found that it might be caused by propagation of constrictions to upstream
370 penetrating arterioles (P. W. Sweeney et al., 2018). A similar investigation of CBF regulation
371 would be inaccessible in a conventional experimental context. In this study, results were
372 achieved by using *in vivo* collected information for *in silico* experimentation.

373 **WHY FOCUSED INTERDISCIPLINARY INTEGRATION SHOULD MATTER**

374 How does one determine whether HR under neurological or psychiatric conditions reflects
375 underlying neural activity rather than altered NVC? Does it mean that in many cases additional
376 validation studies linking neuronal activity with NVC might be needed to rely on cognitive
377 inferences derived from functional neuroimaging entirely? A growing body of evidence from
378 animal studies suggests it (Lindauer et al., 2010; O'Herron et al., 2016). Other questions like i)
379 how new findings of non-neural cell interactions change the interpretation of neural activity
380 derived from previous functional neuroimaging, and ii) how to distinguish between neural-
381 activity-derived and only glia-activity-derived hemodynamic events, remain open.

382 Neuroscience is a multidisciplinary branch of biology, and its scope has broadened over time to
383 include a lot of new and different approaches in many aspects of the nervous system. As a result,
384 neuroscience exploded in a number of interdisciplinary fields such as neurophysiology, cognitive
385 and behavioural neuroscience, computational neuroscience and translational neuroscience
386 research. Somehow, common researchers' knowledge assumes that in such a broad community
387 of neuroscientists and clinicians there must be enough professionals dedicating their time and

388 effort to some issues and that necessary integration will occur naturally at the particular
389 threshold. However, some main conceptual challenges may remain unlighted due to an
390 unfocused, one-side-driven interdisciplinary integration. Illustrating it with terms of symbiosis:
391 when relationships and interactions between different branches of neuroscience are based more
392 on commensalism (when part A benefits from part B, but B remain unaffected), rather than
393 mutualism (when part A benefits from part B, and *vice versa*). Of course, interdisciplinary
394 integrations are way more complicated, but some relevant patterns may be observed. For
395 example, a few historical moments of fMRI, fNIRS, and cellular and molecular neuroscience
396 (CMN) are given in a single timeline (Figure 3). As can be seen from Figure 3, some significant
397 milestones, such as a burst of functional neuroimaging studies using fMRI and fNIRS were
398 achieved simultaneously around 1992. While others, conceptually very important, such as the
399 concepts of the tripartite synapse and neurovascular unit, emerged only around 2000. There is no
400 surprise in the different timing between different neuroscience branch achievements in general.
401 However, even after more than a decade following seminal research in 2000, the NVC is still
402 surprisingly overlooked in functional neuroimaging modelling, especially in humans. Meaning
403 that current functional neuroimaging inference guidelines are poorly addressing even already
404 known findings of underlying physiological mechanisms of NVC. This renders further
405 interpretations of the HR based functional neuroimaging results ambiguous and entirely reliable
406 only with support from anatomical and electrophysiological studies. As it is often the case, the
407 primary concern is not the validity of previous and current studies using functional
408 neuroimaging, but advancements and innovation in the existing paradigm. Ultimately, the non-
409 invasive use of HR is one of the most powerful tools at our disposal to explore human cognition
410 in health and disease, and thus the focused interdisciplinary attention on its accuracy should
411 matter to anyone working or interests in the field of human brain research.

412 *Figure 3. A timeline of magnetic resonance imaging (MRI), functional near-infrared spectroscopy (fNIRS), and*
413 *cellular and molecular neuroscience (CMN) milestones.*

414 CONCLUSIONS AND FUTURE PERSPECTIVES

415 The significant part of scientific and clinical research production is based on complex
416 mathematical manipulations of neuroimaging data derived from NVC. To improve the overall
417 quality of this production, a complete interpretation of HR should become a number one concern

418 in the field, as it is the primary information source of underlying human brain neurophysiology.
419 However, the amount of available information is growing exponentially, and due to this
420 information overload, researchers' attention span may be naturally decreased, thus making it a
421 definite obstacle. On the other hand, as was illustrated with the PubMed database search, even
422 within closely related techniques such as fMRI, and fNIRS there is evident lack of close
423 integration. Moreover, significant results from even more distinct branches of neuroscience such
424 as cellular biology and *in vivo* brain physiology are instead offered to be considered than
425 provided for implementing in existing computational modelling of human brain function.

426 One way to overcome it is to stress out the concern and make it easy to perceive for broader
427 scientific communities. In accordance, this article fills the gap of a critical view on HR
428 translation into scientific findings and expresses the need for more similarly focused
429 interdisciplinary reviews, as numerous aspects cannot be thoroughly generalised at once. Also, it
430 addresses the need to integrate neurophysiology and computational neuroscience fields to
431 stimulate innovations in neuroimaging by improving an accurate translation of physiological
432 brain signals. At this point, another possible suggestion would be to implement existing machine
433 learning algorithms for data mining. It would allow meticulously compare the existing data of
434 cellular and molecular neuroscience studies of NVC, and functional neuroimaging.

435 In contrast to existing approaches (which use sophisticated algorithms to perform large-scale
436 medical data analysis to search for patterns and predictions in certain brain diseases), attention
437 could be focused on the problem of translating complex physiological phenomena (NVC) to
438 functional neuroimaging (brain maps of hemodynamic response). This analytical approach in
439 biomedicine is successfully implemented elsewhere (Cao et al., 2018; Ching et al., 2018). In fact,
440 according to latest report of artificial intelligence (AI) use (Shoham et al., 2018), the significant
441 portion of AI-technology-based papers in the USA and Europe tend to be focused on
442 Humanities, and Medical and Health Sciences. Unfortunately, no such attempt was found in the
443 current literature concerning the hemodynamic response. The existing approaches, from previous
444 (Banaji, Mallet, Elwell, Nicholls, & Cooper, 2008; Buxton, Wong, & Frank, 1998; Caldwell et
445 al., 2016; Friston, Mechelli, Turner, & Price, 2000; Huneau et al., 2015; Sotero & Trujillo-
446 Barreto, 2007, 2008), to more recent (Havlicek et al., 2017; P. W. Sweeney et al., 2018) models
447 are exploratory, meaning that they try to determine, whether what is being observed might be

448 explained by a currently existing theory. Meantime, an analytical approach with machine
449 learning algorithms could be used for patterning and prediction in a conceptually different
450 manner. Despite the notable advantages, it is important to note that applying it would be
451 inevitably challenging. Mostly because of data properties, as several different approaches might
452 be needed at once (Cao et al., 2018; Ching et al., 2018). Meanwhile, the author suggests a few
453 general points to discuss, how necessary integration could be initiated:

454 a) Systematic reviews and meta-analyses of previous research studies could be performed
455 selectively on different aspects of NVC and HR (i.e. modality used to investigate, species of a
456 subject, spatial location of interest in the brain volume, goals of research, and used
457 pharmacological agents). The literature search could be expanded with AI algorithms
458 dedicated for the search of relevant scientific content with extensive vocabulary from a
459 different neuroscience fields (to avoid losing information, when publications conceptually are
460 about the same physiological phenomenon, but due to historical context, or other reasons, is
461 described differently (like terms hemodynamic response and hemodynamic response
462 function). This would ensure unbiased (by the investigators' prior knowledge) collection of
463 relevant publications. As an existing equivalent could be considered AI2 system by Allen
464 Institute, called “Semantic Scholar”, dedicated to finding peer-reviewed research from only
465 trusted, verified sources (<https://www.semanticscholar.org>). Another example – Elsevier
466 Fingerprint Engine, - the same systems that were applied to explore previously mentioned AI
467 tendency to focus on healthcare. It used a primary set of about 800 keywords relevant to AI
468 (Shoham et al., 2018). Other engines that are not mentioned in this publication may also be
469 used directly or as a prototype. After the initial search on particular aspects of NCV and HR
470 (mostly to make easier the quality check before further analysis), the data could be combined
471 and sliced by any relevant dimension. With a sufficient quantity of information, several
472 different data mining approaches could be possibly applied.

473 b) The initial collection for systematic reviews and meta-analyses could be reused for creating a
474 database (or a platform with some user interface) and creating a unified template for a new
475 data entry, as a suggestion what metadata file could be associated with a new publication. It
476 would make it easier to import and this in turn would increase its impact and visibility. Some
477 concepts of similar systems could also be borrowed and implemented from already existing

478 projects such as the Human Brain Project (<https://www.humanbrainproject.eu>), or maybe even
479 branch out as a separate compartment of an already existing platform.

480 c) The created database could also serve as an information source for any level of computational
481 insight: computational modelling (CM), deep learning (DL), machine learning (ML), or
482 artificial intelligence (AI). The database could provide some guidelines for the researchers
483 when searching, or preparing training data for their *in silico* experimentation. The purpose of
484 mentioned algorithms may vary from an automated classification of inputs from living cell
485 microarrays (Jonczyk et al., 2016) to sophisticated machine learning algorithms searching for
486 discrepancies across multimodal studies as in previously given examples.

487 To sum up, most of the perspective tools are already available and needs only to be implemented
488 towards a particular problem. A broader and multi-disciplinary appreciation of NVC could
489 further boost basic and clinical neuroscience. Thus, a reason why it is still not in the frontlines of
490 functional neuroimaging remains debatable. On another hand, this gap in neuroscience requires
491 state-of-the-art scientific solutions. Because of this, the author invites scientific researches to
492 respond in comments or with a follow-up publication and propose tools or strategies that
493 according to them could be implemented towards accurate translation of hemodynamic response
494 for the future of the functional neuroimaging.

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Figure 1

Examples of canonical hemodynamic response (A), and hemodynamic response function (B)

A neural activity from 0 to 5 seconds (grey bar) causes neurometabolic and later neurovascular coupling, which can be seen as a delay of response (around 2 seconds). Box in hemodynamic response (A) indicates a) small inflow of $\Delta[\text{HbO}_2]$, when the total blood volume is still relatively unchanged (due to increased cerebral blood flow), and later b) $\Delta[\text{HbO}_2]$ increases rapidly due to functional hyperemia caused by vasodilatation. The small increase of $\Delta[\text{Hb}]$ occurs due to insufficient washout when the cellular oxygen demand exceeds current supply in a tissue. The canonical example of a hemodynamic response is based on measuring the composition of cerebral blood volume via chromophore concentration changes (oxy-Hb and deoxy-Hb). fNIRS studies can directly measure both oxy-Hb and deoxy-Hb (Venclove, Daktariunas, & Ruksenas, 2015). In contrast, the canonical hemodynamic response function (HRF) from the Blood Oxygenation Level Dependent (BOLD) method represents the magnetic field change in response to the $\Delta[\text{Hb}]$ curve (B) and is relative to the baseline.

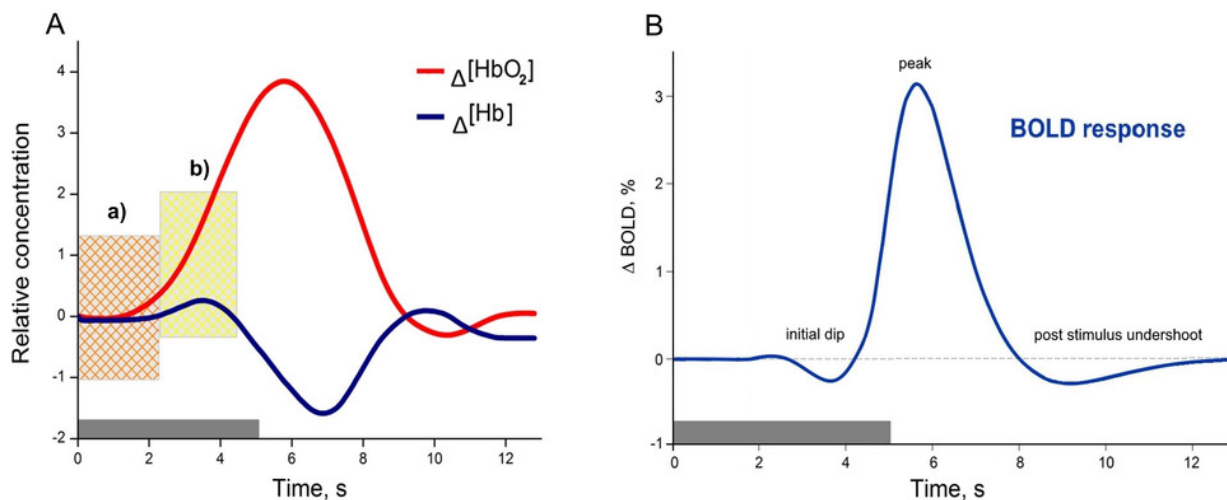


Figure 2

The conceptual biophysical scheme of biological signal transduction path in the neurovascular unit.

A) Neurometabolic coupling (NMC); B) Neurovascular coupling (NVC). Both neurones (neurotransmitter release) and astrocytes (glucose and oxygen consumption) respond to increased extracellular glutamate, and intracellular calcium to transmit direct and indirect vasoactive signals for the appropriate blood delivery and distribution in the electrically active brain area.

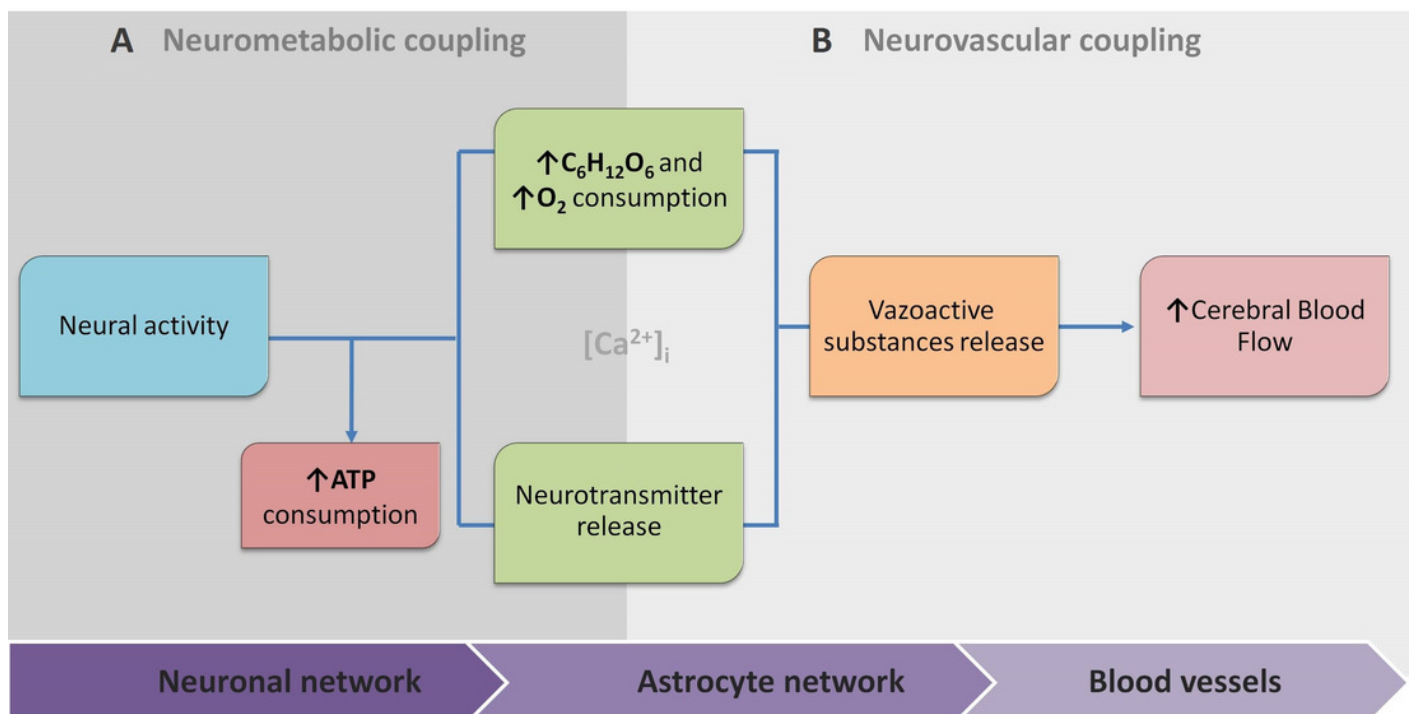


Figure 3

A timeline of magnetic resonance imaging (MRI), functional near-infrared spectroscopy (fNIRS), and cellular and molecular neuroscience (CMN) milestones.

TIMELINE OF MAJOR EVENTS

