Editorial for the Special Issue 'Why behavior matters to brain science'

TITLE: Placing behaviour at the forefront of brain science

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The 2020 FENS forum in Glasgow witnessed four international societies (EBBS, EBPS, EMCCS, and IBANGS) come together to sponsor a mini-conference entitled 'Behavioural Neuroscience for the next decade: why behaviour matters to brain science'. This special issue of Neuroscience and Biobehavioral Reviews arises from that mini-conference and emphasises the revived interest in behavioural sciences and the central role they play in neuroscience.

In recent decades, neuroscience research has benefited from significant technological advances, which have allowed thoroughly focused investigations of the neural mechanisms of brain function. These technological advances allow us to target single cells or single genes in order to study the molecular components of brain function. However, quite unexpectedly given these tremendous technological advancements, the gap between basic science and the translation to clinically effective treatments has grown even larger (e.g. Seyhan, 2019), particularly so for neuroscience (e.g. Davies et al., 2020). Rightly so, the field must now seriously question the basic assumptions of its preclinical models, as well as addressing reliability, reproducibility, and the statistical tools used. Even more importantly, it has to evaluate whether the right questions are being asked.

Behaviour should (to our mind) be a critical component of this self-evaluation within the field. Within behavioural neuroscience, behaviour is used as a tool to both infer cognitive processes and model human disease. However, whilst the tools used to study neural processes have developed and spread rapidly throughout the field in recent years, behaviour is often the poor relation in behavioural neuroscience studies. Single behavioural tasks are often used to assert relevance of an animal model to complex cognitive processes. In addition, behavioural tasks in animals are often interpreted at a general level, at the expense of specific aspects of behaviour that reflect specific cognitive processes in a complex task.

Take, as an example, the lack of significant advance in treatment for the memory loss in Alzheimer's disease (AD), despite very significant investment over many years (e.g. Cummings et al, 2014). The nature of memory loss in Alzheimer's disease is very complex. Issues are apparent across many different types of memory, even though some types of memory impairment (such as episodic memory) seem to occur early in the disease, and perhaps even prior to diagnosis (e.g. Brent et al, 2008). The reality is, then, that memory loss in a disease such as Alzheimer's is complex, multi-faceted, and highly interacting. Nonetheless, much published work on AD models in behavioural neuroscience focuses on a small number of memory tasks (e.g. Morris Water Maze, or Spontaneous Object Recognition), and rarely considers different types of memory, using different types of tasks in a single study. Whilst these same studies have responded to the failure to translate to the clinic by focusing on ever more precise neurobiological and genetic models of AD, a generic approach to behavioural measures of memory remains.

Some have argued for a more targeted approach through a better understanding of behaviour. Whether it's exploring the nuances of a behavioural task to extract more relevant information (e.g. Ameen-Ali, 2015), or the need to understand the entire behavioural response of an animal (e.g. Castellucci, 2008) the message regularly appears that behaviour has to matter more in behavioural neuroscience, and yet the field continues to advance the neuroscience tools whilst maintaining a limited repertoire of behavioural tools.

One possibility is that the importance of behaviour is misunderstood in much behavioural neuroscience. Much is made of the relevance of a biological model, whilst little is made of the relevance of the behaviour to assess these models. This raises the concern that there is a failure to remember in all cases that behaviour in animal studies is itself a model. Take a highly complex condition like Autism Spectrum Disorder (ASD). Within humans, ASD is not a single behavioural change, or even a reliable group of changes. Instead, a range of characteristic criteria are used, with diagnosis arising from the co-occurrence of a number of these possible criteria (e.g. Hodges et al, 2020). Therefore, in humans there is no single behavioural phenotype, and yet animal models of ASD often assess specific aspects of behaviour, relating these to specific criteria for ASD, failing to consider the full range of possible expressions of the disorder. Modelling a complex condition such as ASD in animals must rely on better behavioural assessments, and the field is starting to consider such approaches (Silverman et al, 2022). In the meantime, a better understanding of behaviour allows us to more precisely say that a particular model is relevant to a specific category of behaviour (e.g. social play) without making inappropriate generalisations.

Another critical aspect that needs to be highlighted is whether - independently from the (animal) model we use - we are asking the right questions in brain science. Studying individual molecules and processes, so far, has not brought us closer to understanding the functioning of the brain (Krakauer, 2017). One important example is the case of the roundworm (*Caenorhabditis elegans*) which has been studied thoroughly at the molecular level as the cells, the genome, and the connectome are all well-known. Despite this relevant knowledge it is still not completely defined how the known structure can be related to the worm's - relatively limited - behavioural repertoire. This case well exemplifies the notion that describing neural activity and connections between nerve cells does not equal knowing what they do to cause behaviour. One of the main problems we envision here is that neuroscience has switched much of its focus from asking fundamental questions, having to do with proximate causation, ontogeny and phylogeny (Tinbergen, 1963), to the development of technologies and approaches that are mainly focused on dealing with the massive amount of data generated by recent technological advancements (Krakauer et al. 2017).

In order to develop conceptual frameworks that allow us to relate behaviours to neural circuits we need to use hypothesis-driven approaches. The interaction between the individual and the environment can be key to properly address questions that have to do with causation, ontogeny and phylogeny (Tinbergen, 1963). Indeed, adaptive and goal-directed behaviours have been sculpted by evolutionary history and by the environmental constraints that a selected species has encountered. Placing behaviour at the interface between the brain and environment can thus allow us to frame meaningful questions to start unravelling the complexity of the brain (Branchi, 2022). Behaviour can be seen as a unique and privileged level of control and orchestration of brain structure and activity, as external challenges have selected specific behavioral responses that, in turn, have constrained and shaped brain activity (Branchi, 2022).

Nonetheless, outstanding understanding of behaviour exists in the field. Many researchers are still developing strong models where specific behaviours are understood to relate to specific elements of cognition and/or disorders (Puscian et al. 2022). These models of behaviour continue to develop all the time, and their application combined with the most advanced neuroscience techniques for behaviour tracking (Lauer et al. 2022) can provide exceptionally strong approaches when informed by an evolutionary approach.

The aim of this special issue is to reflect on some of the key issues that are preventing the field from being more fertile for translatable approaches. We believe it wise to remember that "behavioral work provides understanding, while neural interventions can test causality" (Krakauer et al. 2017). We believe the papers in this special issue emphasise the centrality of behaviour to behavioural neuroscience and encourage all researchers to develop strong theoretical frameworks that can lead to new behavioural tools and approaches that will certainly move the field forward.

REFERENCES

Ameen-Ali KE, Easton A, Eacott MJ. (2015) Moving beyond standard procedures to assess spontaneous recognition memory. Neurosci Biobehav Rev. 53:37-51

Branchi I. Recentering neuroscience on behavior: The interface between brain and environment is a privileged level of control of neural activity. Neurosci Biobehav Rev. 2022 Jul;138:104678. doi: 10.1016/j.neubiorev.2022.104678. Epub 2022 Apr 26. PMID: 35487322.

Brent J. Small, Stuart W.S. MacDonald, Lindsay Iser, Lars Bäckman (2008) Memory and cognitive performance in preclinical Alzheimer's disease and preclinical vascular disease. In Handbook of Behavioral Neuroscience, Eds: Ekrem Dere, Alexander Easton, Lynn Nadel, Joseph P. Huston

Castellucci, V.F. (2008) Animal models and behaviour: Their importance for the study of memory. Progress in Brain Research 169: 269-275

Cummings, J.L., Morstorf, T. & Zhong, K. (2014) Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alz Res Therapy* 6, 37. https://doi.org/10.1186/alzrt269

Davies, C., Hamilton, O.K.L., Hooley, M., Ritakari, T.E., Stevenson, A.J., & Wheater, E.N.W. (2020) Translational neuroscience: the state of a nation (a PhD student perspective). *Brain Communications* 2: fcaa038

Hodges H, Fealko C, Soares N. (2020) Autism spectrum disorder: definition, epidemiology, causes, and clinical evaluation. Transl Pediatr. 9(Suppl 1):S55-S65.

Krakauer JW, Ghazanfar AA, Gomez-Marin A, MacIver MA, Poeppel D. Neuroscience Needs Behavior: Correcting a Reductionist Bias. Neuron. 2017 Feb 8;93(3):480-490. doi: 10.1016/j.neuron.2016.12.041. PMID: 28182904.

Lauer J, Zhou M, Ye S, Menegas W, Schneider S, Nath T, Rahman MM, Di Santo V, Soberanes D, Feng G, Murthy VN, Lauder G, Dulac C, Mathis MW, Mathis A. Multi-animal pose estimation, identification and tracking with DeepLabCut. Nat Methods. 2022 Apr;19(4):496-504. doi: 10.1038/s41592-022-01443-0. Epub 2022 Apr 12. PMID: 35414125; PMCID: PMC9007739.

Puścian, A., Bryksa, A., Kondrakiewicz, L., Kostecki, M., Winiarski, M., Knapska, E., 2022. Ability to share emotions of others as a foundation of social learning. Neurosci. Biobehav. Rev. 132, 23–36. https://doi.org/10.1016/j.neubiorev.2021.11.022

Seyhan, A.A. (2019) Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles. *Translational Medicine Communications* 4: 18

Tinbergen, N. (1963). "On aims and methods of ethology." Zeitschrift für Tierpsychologie 20:410-433.

Silverman, J.L., Thurm, A, Ethridge, S.B., Soller, M.M., Petkova, S.P., Abel, T., Bauman, M.D., Brodkin, E.S., Harony-Nicolas, H., Wöhr, M, & Halladay, A. (2022) Reconsidering animal models used to study autism spectrum disorder: Current state and optimizing future. Genes, Brain & Behavior 21: e12803