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MESTRADO INTEGRADO EM MEDICINA

Francisco José Correia Graça Almeida

The structure of non-human animal cognitive neuroscience: an epistemological critique

Estrutura da neurociência cognitiva animal: uma crítica epistemológica

março, 2019

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Mestrado Integrado em Medicina

Área: Neurociências Básicas

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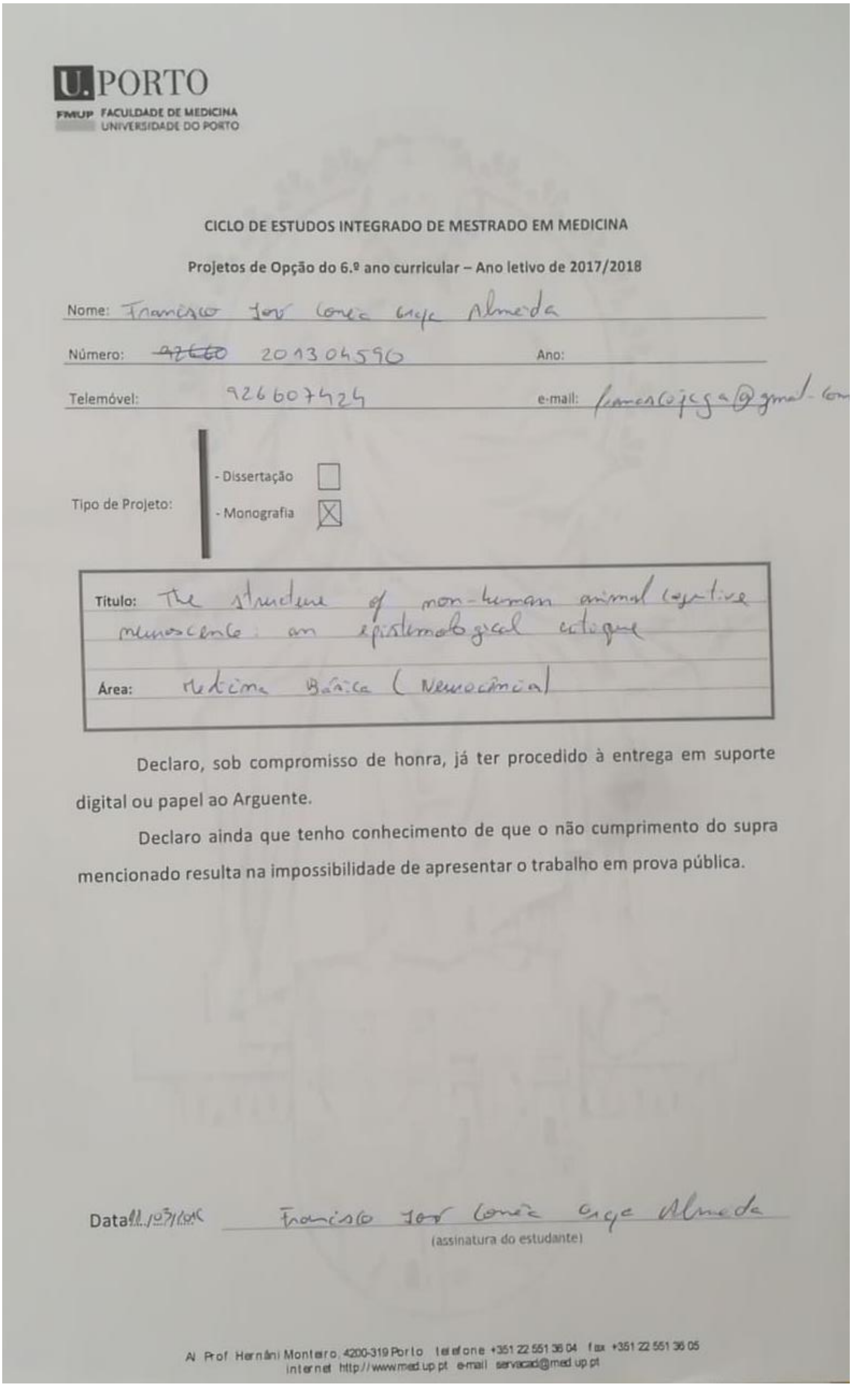

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CICLO DE ESTUDOS INTEGRADO DE MESTRADO EM MEDICINA

Projetos de Opção do 6.º ano curricular – Ano letivo de 2017/2018

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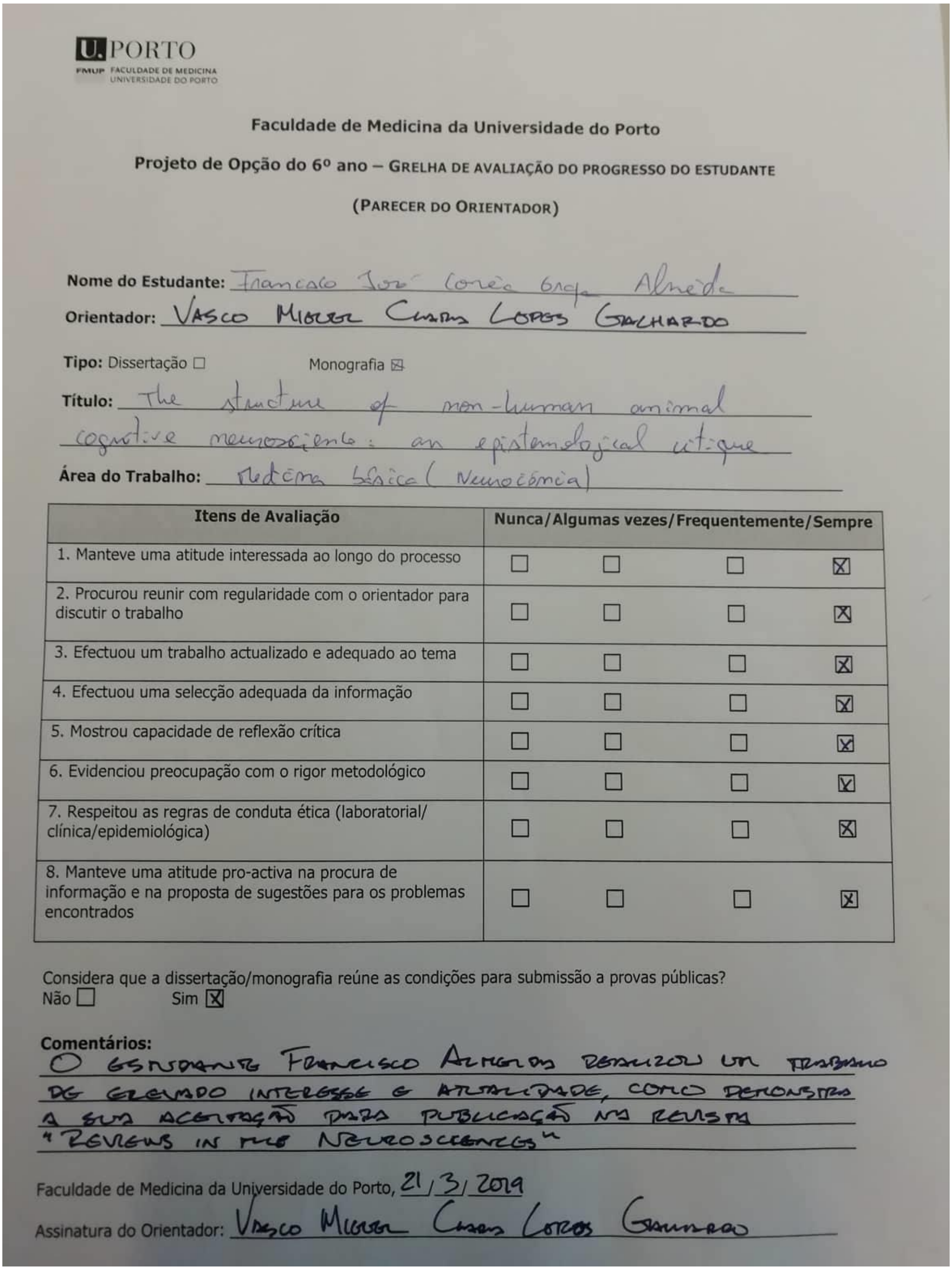

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Nome do Estudante: Francisco José Correia Braga Almeida

Orientador: VASCO MIGUEL CLARA LOPES GALHARDO

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Título: The structure of non-human animal cognitive neuroscience: an epistemological critique

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Itens de Avaliação	Nunca/Algumas vezes/Frequentemente/Sempre			
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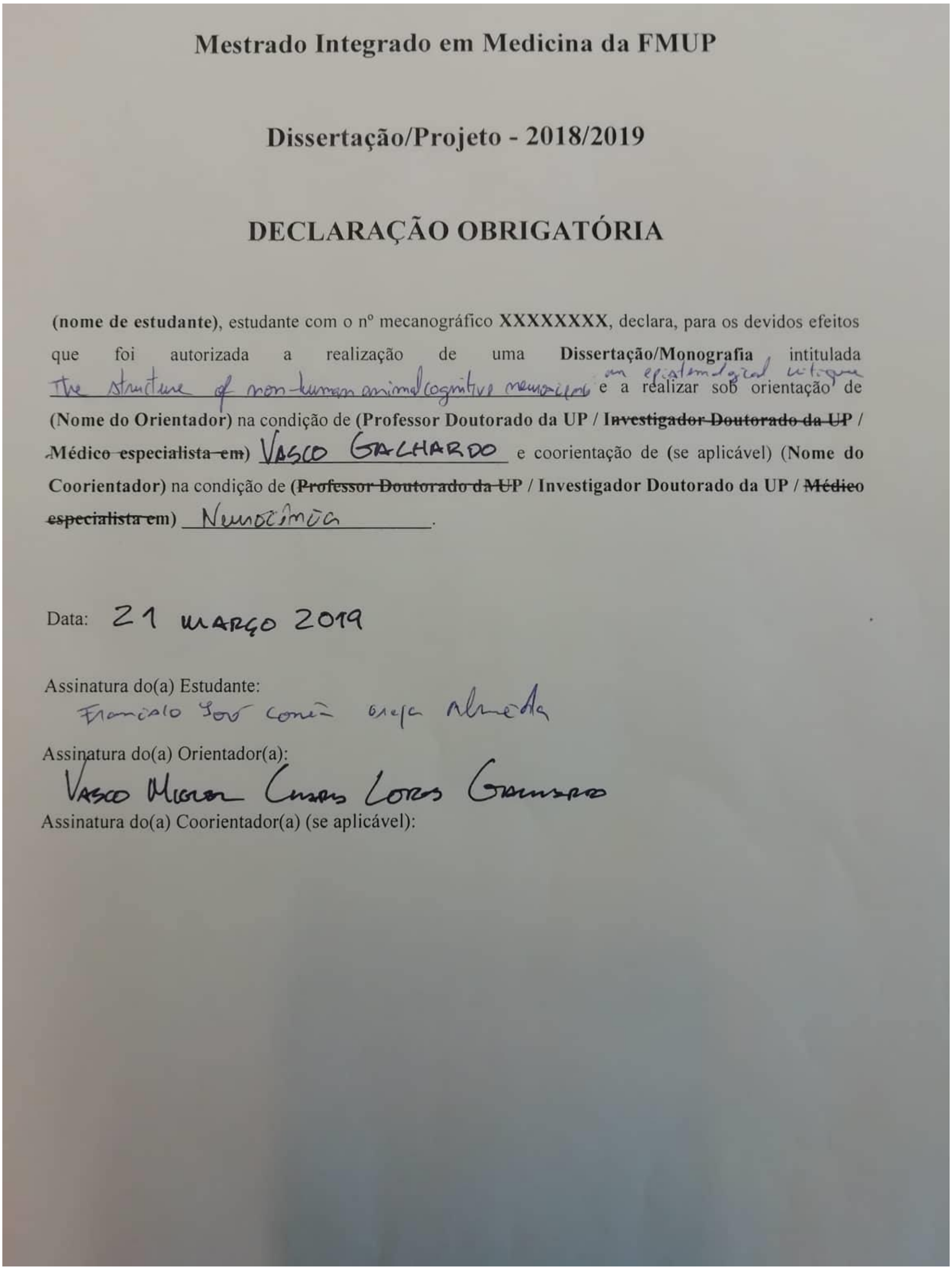

Mestrado Integrado em Medicina da FMUP

Dissertação/Projeto - 2018/2019

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The structure of non-human cognitive neuroscience: an epistemological critique

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Abstract

Every scientific practice rests on implicit unrevised theoretical assumptions. Neuroscience, in particular, focuses on a very controversial object of study- the brain- and is therefore prone to tacitly embrace philosophical positions in its everyday workings. It is thus of the utmost importance to develop a critique of the structure of neuroscientific investigation so as to understand what the uncovered pillars of the field are, what pitfalls they may implicate and how we can correct them. In this paper, I gather the first critiques in animal cognitive neuroscience and hope to establish the first step in a continuous process of revision. By applying a conceptual division of neuroscience into cognitive, behavioural and neurobiological theories, I point out the main problems in articulating the three, based on actual scientific practice rather than purely theoretical reasoning. I conclude by proposing developments on behavioural theory and set an initial critique on assumptions on both cognitive and neurobiological theories.

Keywords

behaviour; reductionism; cognitive; neurobiology; epistemology

Introduction

A critical analysis of the fundamental assumptions and workings of a scientific field is necessary to understand its limitations and how we can tackle them. This entails coming out of the everyday working paradigm and question it from an objective standpoint. What do we actually do when we perform an experiment in cognitive neuroscience? What is its meaning and how does it relate to the real world? In essence, advances within the field, be them technological or in understanding, must be accompanied by an epistemological critique to guarantee their validity and usefulness.

Cognitive neuroscience is an intersection of cognitive theory, behavioural theory and neurobiological theory. By the first, we mean the psychological processes we think are processed in the brain and are somewhat transversally present in all species of study within cognitive neuroscience. The second refers the range of behaviours specific to each species and what these behaviours mean in terms of their life goals. Lastly, neurobiological theory is the body of knowledge about the biology of neurons and how they interact, from circuits to genes. Each of them has specific problems worthy of a dedicated analysis. Perhaps due to the technical and ethical constraints on human cognitive neuroscience research, analysing the relationships between these three fields has been more common than in non-human studies. For this reason, I will focus in non-human research.

Cognitive theory presupposes what has been coined as "cognitive ontologies"(R. A. Poldrack et al., 2016), the cognitive elements at work in the brain, be it fear, memory, etc. Each of them is important for our way of thinking as scientists as well to the hypotheses that can be generated(J. E. LeDoux 2017). Therefore, we must analyse if they provide appropriate concepts and if they have any correlation with what is actually going on in the brain. They also have a relationship with behavioural theory, in as much as behaviours are determined by internal cognitive states. How this relationship is established in practice is an important point for consideration. Moreover, behavioural tasks in the laboratory must be subject to an analysis both in terms of their comparison to natural behaviour, as studied by ethology, and as what concerns their design and which cognitive processes they reflect. Finally, behaviour is correlated with neural evidence, which must itself be analysed in terms of the causal status of interventionist techniques and the statistical treatment of acquired data.

In this article I seek to pinpoint the major challenges in articulating these theories. However, rather than studying their interaction from a purely theoretical point view, I will focus on how actual experimental practice interlinks them in the laboratory.

Behaviour and meaning in non-human cognitive neuroscience experiments

The brain is an ever-changing, dynamic, always active object. For researchers to make sense of it, restrictions have to be made in order to create a space of relevance and significance for the observed behaviours, neural activities and manipulations. This is usually done by confining an animal to a behavioural task, that is, a stereotyped environment where an animal is expected to perform a determined behaviour. This task is designed according to a behavioural theory, a description of what the animal will do in these circumstances. This is then linked to a cognitive theory, that is, the description of which psychological process is in use during this task. While this division of labour between these two fields is clear in theory, we should note that, in experimental practice, we take a certain task to be synonymous with a certain process, e.g., fear learning or reward behaviour. Finally, neurobiological theory joins in by being linked, in accordance with the experimental results, to this chain from behaviour to cognition.

Reductionism is a philosophical theory which amounts to assuming that we can reduce psychological constructs to their neural correlates up to the most fundamental level of molecular biology(John Bickle 2006). While this is a matter of intense philosophical discussion, we rarely see it in the scientific setting. Alternative ways of interpreting the neuroscientific process have been put forward, such as the mechanistic explanation(Carl F. Craver 2009). However, this theory of explanation also fails to give an account of the thinking process underlying actual experimental conditions, namely at the level of behaviour.

Indeed, neuronal changes of whatever level, in circuitry or genetics, only gain meaning within the observed behavioural alterations(J. W. Krakauer et al., 2017). Behaviour is the ultimate meaning-providing test. While information can be decoded from the activation of a neuronal population, e.g. time in the hippocampus (W. Mau et al., 2018), and this undoubtedly provides important knowledge, it cannot be inferred that time is in itself being used in a biologically relevant way, unless it is shown that elapsed time, as a cognitive element, is used by the animal. This requires a task where information about time becomes the central aspect of behaviour, as in recent studies(T. S. Gouvea et al., 2015; G. B. Mello et al., 2015; S. Soares et al., 2016). In fact, what a "neural code" actually refers to, that is, how and what information is represented in it, is a crucial part to build a theory of the brain (for interesting discussion see (R. Brette 2019)).

Thus, the role we assign to a certain biological process will depend on observed behaviour, which in itself, will depend on our ideological assumptions, that is, on the conjunction between our behavioural and cognitive theories. This is a problem of special relevance for neuroimaging, put forward by Russell Poldrack in the following way:

"Although few today would hold that 19th century faculty psychology is an accurate description of the structure of the mind, we can likely all agree that if the phrenologists had created task manipulations to isolate their proposed faculties using fMRI, something would have ''lit up.''"(R. A. Poldrack 2010)

The same problem applies to non-human neuroscience research. Our cognitive ontologies, i.e. what brain processes we think exist, are determinant to the meaning of our investigations. While these ontologies are given by cognitive theory, they are linked with behavioural theory in the behavioural task. Thus, we manage to know if a cognitive process is affected by some experimental condition when we observe the performance of the animals in a certain task.

Its design, then, is of special relevance since it determines which behaviours are possible and what cognitive ontologies are putatively at work (C. R. Fetsch 2016).

An epistemology of behaviour and cognitive processes in their interaction with mechanistic explanation and neural manipulation techniques is in need. First of all, we must provide an analysis of laboratory behaviour in comparison with natural settings and, secondly, we must analyse how, and if, behaviour, as expressed in a behavioural task, reflects the cognitive ontologies we think are at work. Next, I intend to set an initial ground in analysing each of these challenges.

The components of a behavioural task

Recent technological advances allow us to probe deeper into the brain but are not accompanied by a concomitant development in behavioural theory, creating an asymmetry which can pose problems for advancing research(J. W. Krakauer et al., 2017). Behavioural tasks are designed to isolate a specific behaviour, simplifying environments and holding the same conditions for control groups and intervention groups. This implies restricting the options of the animal, forcing it to behave in a certain way. This is fundamental to make our interpretation possible and guarantee internal validity of the experiment. However, simultaneously, it reduces behaviour to an artificial simplicity. An analysis of the task is therefore relevant and it can be dissected, in an initial analysis, into the following components:

.Temporal component: includes the duration of a task, the duration of trials, their number and for how long behaviour and neural activity is followed; also includes timing and duration of discrete stimuli;

.Architectural component: divided into a static component (the architecture of the arena) and a dynamic component (levers, etc);

.Sensory component: electric shocks, lights, sounds, olfactory cues, etc.

.Cognitive component: e.g. through cognitive subtraction

In essence, a spatiotemporal complex (temporal and architectural), a sensorial component and a cognitive component. The decomposition of the task into these elements is relevant insofar as our analysis will correlate neural activity to them and, from this, different meanings may stem. For instance, we can correlate neural activity to the specific spatial location of the animal (place cells), to elapsed time (time cells), to discrete sensory cues (auditory fear conditioning) and to cognitive components, e.g. evidence accumulation (C. D. Brody et al., 2016) or through cognitive subtraction (see below). Further, and importantly, the relations between these components, their temporal and spatial organization determine the behaviour of the animal, but also the cognitive meaning of the task for the researchers. In fact, the very concepts of space and time have been criticized as being human preconceptions which we project onto brain activity(G. Buzsaki et al., 2017). In the same way, a square arena with an auditory cue followed by an electric shock, which causes a particular response in rodents, are the basis of classical pavlovian learning and is understood as causing fear (cognitive ontology) in the animal. Cognitive theory and behavioural theory is therefore linked in our interpretation of the task, with the possible bias in assigning human, all too human cognitive elements to the brain.

Behavioural theory must therefore be strengthened to generate behavioural tests which could prove a certain cognitive element to be at work.

In human neuroimaging, task design is a very important focus of discussion in this respect. One of the most common methods is cognitive subtraction, whereby different tasks are designed to differ only in respect to one cognitive component. While critical assessments of this method have been made for fMRI(K. J. Friston et al., 1996; R. Poldrack 2010), it has not been critiqued for non-human studies. Differences in neural activity between tasks are hypothesised to correspond to the cognitive element which differentiates them. However, cognitive components may not be additive, and may, in fact, interact. Moreover, while subtraction may work at a psychological level of explanation, at the neurobiological level it is not necessarily true that subtraction can isolate neural activity corresponding to the targeted cognitive element. The behavioural tasks which serve as a comparison must be proven to differ only in respect to the cognitive operation under study (see "Phenomenal decomposition and binary assessments of behaviour" below). Detailed behavioural and psychological theories are thus important to allow effective subtraction of cognitive elements, allowing correlation and manipulation of neural activity correlated to a single cognitive construct. Pure behaviourism can therefore paradoxically be avoided also by developing behavioural theory.

Biological realism

Given the artificial conditions of behavioural lab tasks, the need arose of approximating laboratory behaviour to ethology, the study of animal behaviour under natural conditions, and it has been emphasised under the term: biological realism(D. Mobbs et al., 2018). This intention has come out of different lines of research, from decision-making to learning and memory (H. Arakawa et al., 2018; A. L. Juavinett et al., 2018; J. J. Kim et al., 2018; D. Mobbs et al., 2015;

D. Mobbs et al., 2018). Controlled laboratory paradigms allow us to dissect behaviour into quantifiable variables at the expense of its similitude to natural contexts (even though some aspects of behaviour are naturally maintained and may have no difference between natural or lab settings, e.g., huddling behaviour). On the other hand, an ecological understanding of behaviour brings into account evolutionary explanations and the dynamics of the environment, but represents a challenge of conceptualization and quantification in laboratorial settings. Such an abyss between both biological practices and theories must be overcome by searching for more realistic solutions in the lab. This is a complex challenge, but a necessary one. Laboratorial behavioural tasks isolate a specific behaviour, but in nature, animals are constantly choosing between multiple alternatives. This approximation to real life situations is therefore crucial for translational validity, beyond its importance in explanation itself.

If the simplification of behavioural tasks poses a problem regarding its external validity for natural behaviours, it also raises questions in its relation with neurobiological theory. Technological discoveries have provided the opportunity to deeply probe and manipulate the brain, with a level of detail which far surmounts the specificity of behavioural analysis. This imbalance may generate mapping problems between neuronal activity and behaviour(J. W. Krakauer et al., 2017). Indeed, it is still unknown to us what level of analysis is relevant for explaining behaviour, from cell biology to network activation. Moreover, multiple realization, that is, the ability of various circuits to engage the same behaviour, confounds our clear-cut associations, while at the same time, the same circuit can be activated in different behaviours. Since this is also something we should bear in mind when thinking about the validity of neuroscientific experiments, we extend the concept of biological realism to include not only the ethological approximation, but also the need to test the same circuits for different behaviours.

How can we improve biological realism?

So far, the discussion points towards a deeper understanding of behaviour as a solution for this question. The proposal of semi-realistic contexts for the laboratory is not new(D. Mobbs et al., 2015), but a clear approximation has not been possible as far as we know. Next, I will review two examples which provide a practical direction towards this problem. They were selected due to their capacity to illustrate the point, not due to a special relevance within neuroscience. Finally, I will review the promise of computational approaches to behaviour.

The role of the amygdala in fear and reward: insights within a task

Most studies of amygdala function in fear recur to behavioural tasks where a conditioned stimulus(CS), e.g. an auditory cue, is paired concomitantly with an unconditioned stimulus (US), such as a footshock. Animals learn this association and respond to it with freezing or escaping the room where the shock is given. While this is the most common paradigm in neuroscience, it represents “snapshot information”, in opposition to the “panoramic view” provided by ethology(D. Mobbs et al., 2015).

On the other hand, in reward studies, instead of a shock, animals are given some pleasurable substance, inducing them to approach the place where it happened. Tasks would therefore separate positive and negative valence stimuli and give the animal only one choice of behaviour, defensive (sometimes only freezing is possible) or approaching. Amygdala function is consequently seen in reference only to one of these behaviours separately. We know that in real contexts, the possibility of reward usually comes with a cost: the presence of predators, the effort needed to get it, among others.

Thus, in a recent study, by designing a new task, where reward and aversion are present, researchers were able to see that lasting assumptions of basolateral amygdala neurons encoding valence could be overly simplistic, instead revealing multidimensional coding(P. Kyriazi et al., 2018). Previous tasks led to an over-representation of amygdala neurons in encoding valence and representing sensory responses that automatically and immediately caused a behavioural response. Ranges of behaviours may be latent and hidden if not allowed visibility by the task and, therefore, their computation is also hidden. The space of possible behaviours must therefore be extended and well defined in order to have solid mechanistic hypothesis(M. Jazayeri et al., 2017).

From this we learn that the behavioural task defines both the behaviour of the animal, its possibilities of action, as well as the logic of our analysis of neural activity. It creates the world for the animal, an artificial one, thereby posing restrictions to what our neurobiological theory may develop. In other words, the design of the task reflects the structure of our behavioural and cognitive theories, which will themselves reflect onto the neurobiological evidence.

Naturally, new and contrasting information from neural evidence demands an accommodation in cognitive theory. However, only by designing new tasks will we be able to probe deeper into how the brain works, overcoming the analytical restrictions of a particular behavioural paradigm. Only progressive design of new environments will contribute to understand evermore complex computations. Further, new experimental methods, such as specific reversible manipulations (optogenetics, chemogenetics) and longitudinal imaging of neural activity in freely moving animals (calcium imaging miniscopes) will allow us to correlate and influence neural activity in complex tasks, with multiple behaviours. Developments on techniques must therefore be accompanied by the development of behavioural tasks and theory.

Comparing neural activity in a particular area or circuit with different behaviours is consequently a fundamental goal for today. This can be done inside a particular task, but also across tasks, as we discuss next.

The very short story of dopamine: a case for battery tests

Dopamine was once thought to be the “pleasure molecule”. This was supported, according to Berridge, by the following two reasons:

“ 1- mesolimbic dopamine systems that are activated by many reward-related stimuli, and 2- most so-called pleasure electrodes for deep brain stimulation that supported behavioural self-administration (i.e., animals or people were willing to work to stimulate the electrodes, such as by pressing a button).” (K. C. Berridge et al., 2015)

The deconstruction of this hypothesis came from a decomposition of reward into two putative distinct cognitive ontologies: “wanting” and “liking”. Dopamine depletion does not affect orofacial liking experiments and Parkinson’s disease patients still report normal hedonic feelings (K. C. Berridge et al., 2015). The behavioural observation of this “liking” behaviour allowed a dissection of reward into different components. Studies from reinforcement learning also enabled us to hypothesize the role of dopamine in reward-prediction errors(W. Schultz 2016), rather than in pleasure itself. Thus, what seemingly was inseparable, namely, motivation and hedonism, came to be understood as a rather more complex process. Behavioural testing across different tasks, coupled to new technological methods made it possible. Dopamine has now even even implicated in aversion(C. M. V. Weele et al., 2018). The lesson to draw from here is the fact that for us to understand the mechanisms of the brain, we must see it as working in very different behaviours, with circuit activity overlapping across different cognitive processes and behavioural tasks. Our manipulations may affect a certain behaviour in a certain task, but the reason why it does so remains occult if we do not compare it with other behaviours in other tasks. Thus, battery tests, that is, multiple behavioural tasks should be applied as frequently as possible to study a specific correlation to a certain behaviour. Given that, for pragmatic reasons this is not usually carried out and while it is true that tasks could be compared across studies, it would be important to compare the activity of the same neurons in the same animal across tasks. Indeed, comparing neural activity of the same cells across tasks allows us to study the eventual segregation of neurons due to emotional valence and specificity within a component of a task.

Behavioural Data and Computational Opportunities

Acquisition and analysis of large amounts of behavioural data has opened the possibility to construct computational models of behaviour which may apply to broader contexts than localized tasks, thereby promising a framework for task-neutral behavioural descriptions. Moreover, computational models of behaviour may provide bridging opportunities with computational models of neural activity, thus conjoining brain and behaviour(A. Gomez-Marin et al., 2014). Nonetheless, pure behavioural data has to be given meaning within a theoretical background. A theory of behavioural universals means the ability to extrapolate behaviour of the same species (perhaps even between species) across different contexts. However, scientific explanation is dedicated to phenomena, not data (J. Bogen et al., 1988) and this is especially true to behaviour. This means that computational models must be oriented by a framework in which a functional-analytic decomposition is at work (low-level information is relevant according to the contribution to a higher-order function). Determining the relevant functions, that is, which descriptions of behaviour are appropriate seems to be context-specific and dependent upon cognitive theory and animal goals. Tasks based on ethological approaches would thus enable an explanation of the computational models of behaviour, which work at the level of description.

At this point, it might be interesting to direct the interested reader to a discussion (see (O. Shagrir et al., 2017)) of Marr’s computational level(D. Marr 2010) and Gibson’s theory of affordances(J. J. Gibson 2014). Briefly, in the first one, a computation performed by the brain receives its meaning from the structure of the physical world. On the other hand, to Gibson, behaviour is always relational and relative to the environment and the opportunities it opens, with the computations not being necessarily a representation of the physical world. From this second point of view, ethological explanations may thus enable behavioural generalizations which will support computational models and consequently the study of mechanistic correlates across evolution.

Thus, computational models represent an important opportunity to improve granularity of behavioural descriptions and tighten correlations with brain activity. Convergence of behavioural science, cognitive science and neuroscience will be important to test the possibility of generalized descriptions of behaviour and improve biological realism.

Phenomenal decomposition and binary assessments of behaviour

Until now, we have seen how behavioural tasks can be designed to accommodate more complex behaviours, and therefore, approach a more natural environment, unveiling in the process more complex cognitive ontologies. We also saw how battery tests may be important to pinpoint the cognitive interpretation of a behavioural alteration and how big behavioural data and computational models may open the avenue for a generalized theory of behaviour. Here we retake our analysis of the interaction between behaviour and cognition. How do we relate a cognitive ontology (motivation, reward, learning, fear, anxiety) with a specific behaviour? How many ontologies are present in a behavioural task and which of them is present at any time? Which one is affected by a manipulation?

Phenomenal decomposition is the name given to the division of a certain cognitive process into its components or subtypes(William Bechtel 2008). For instance, memory has been classically divided into various types of memory (short-term, long-term, etc). In our example above, reward was divided into motivation and hedonic pleasure. These subdivisions, which interact with each other, but remain separable, are formed both on psychological grounds and in neural evidence. Behavioural tasks are usually seen as reflecting a very broad cognitive category, e.g. anxiety, without taking into account the processes which might have contributed to the behavioural performance. Let us take an illustrating example.

A commonly used behavioural task to measure anxiety is the novelty-supressed feeding paradigm, where a starved animal is presented with food in an anxiogenic environment and the latency to feed is seen as a measure of anxiety itself. Now, this behaviour is based on a conflict between the motivation to eat and the fear of traversing an open space in order to do it. When this task was first designed, the authors wrote the following:

"Conflict paradigms rely upon eliciting some predictable response by an animal, inhibiting that response by introducing a response contingent aversive component and overcoming the behavioral effects of the aversive component by drug treatment. It has been important to show that anxiolytics do not alter an animal's sensation of aversion (e.g., they have little or no analgesic action which would make animals in- sensitive to pain and the analgesic morphine is without anti- conflict action). It is equally important to demonstrate that the drug effect is not to enhance the reward value of the goal towards which the behaviour is directed. That is, the drug should not alter responses in the absence of the aversive component."(D. R. Britton et al., 1981)

While the authors underline the necessity of controlling for possible alterations in the reward value by the drug, we should note that, especially when this task has been used widely in depression models(E. J. Nestler et al., 2010), we have to be sure about the intact motivation of the animal to search for food. Tasks which are based on the effects of drugs, which are thought to act upon certain cognitive processes, must also show that the drug is quite specific in influencing the cognitive process (anxiety in this case) without affecting others. Therefore, this task, while assuming a cognitive ontology for itself, may not be reflecting a necessary phenomenal decomposition of behaviour, consequently confounding results.

Another important point is how we understand the results of performance in a task. Due to experimental easiness, classically, we usually look at behaviours in a binary way. The animal is either learning or not. It's motivated or not. It's anxious or not. While this facilitates our analysis, we see that the behaviour of the animals is dependent upon a gradation. Indeed, research to establish a mechanistic account of gradual accumulation of evidence for decision-making in rodents is already underway(C. D. Brody et al., 2016). Moreover, even in classical paradigms we see the necessity of this gradual account. For instance, rats with reduced neurogenesis don't learn fear conditioned responses in single-trials, but do in multiple trials(M. R. Drew et al., 2010). Rats with chronic pain reinstate an avoidance behaviour after a pain predictive cue when in conflict with small rewards, but approach for larger ones, their motivation depending on the value of the reward(Neil Schwartz et al., 2017). The ethological approach takes into consideration multiple variables to explain a certain behaviour. From the effort of approaching to the value of the reward, all these ontologies must be taken into consideration as a dynamic interplay.

Thus, behavioural tasks should also take into account the possible variation of behaviour depending upon, for example, the perceived weight of a stimulus. What seemingly could be attributed to an absolute incapacity may turn out to be a redefinition of the motivation to act or of the limitations of learning in a certain condition.

To sum up, detailed analysis of behaviour and its relation to phenomenal decomposition, the complexification of the environment and the comparison of behaviour in battery tests are important challenges for future research and for an epistemological account of neuroscience.

Conclusion

These considerations are important to expand our knowledge of the mechanisms of the brain and what they mean in terms of psychological processes. Explanation of a neuronal mechanism is relevant as pure knowledge, but its practical use, be it for drugs or for understanding human brains must have meaning in our psychological theory. Preclinical studies in the area of cognitive neuroscience do not predict success well in human trials and a number of reasons regarding scientific methodology have been pointed out(K. K. Tsilidis et al., 2013). In fact, human studies and animal models are separated by a methodological abyss. However, a critique directed at the working epistemology of neuroscience is also fundamental. While attempts have been made at providing a framework to optimize and guide research(A. J. Silva et al., 2013), they remained based on reductionist assumptions. Focusing on behaviour in order to bring it closer to biological realism is an essential step to make translation more plausible. Otherwise, all research will be valid only in its specific laboratorial conditions, wasting resources and animal lives with very low usefulness. Analysis of the structure of both these areas and how they may be bridged represents a challenge and a necessity for the future. It should be noted that the challenges herein analysed do not exhaust the problems. Biological realism as here defined is not a panacea, but only the definition of one possible path. Other areas are worth a critique, for example, the analysis of causality in neuroscience and animal models of human diseases.

This paper attempts to lay down first steps in a critique which must be made by neuroscience and philosophy in conjunction. Since it is based on concepts derived from experimental practice, it is limited to an historical and example-based construction. This means that further analysis of emergent and past practices is needed in conjunction with conceptual and theoretical frameworks from philosophy.

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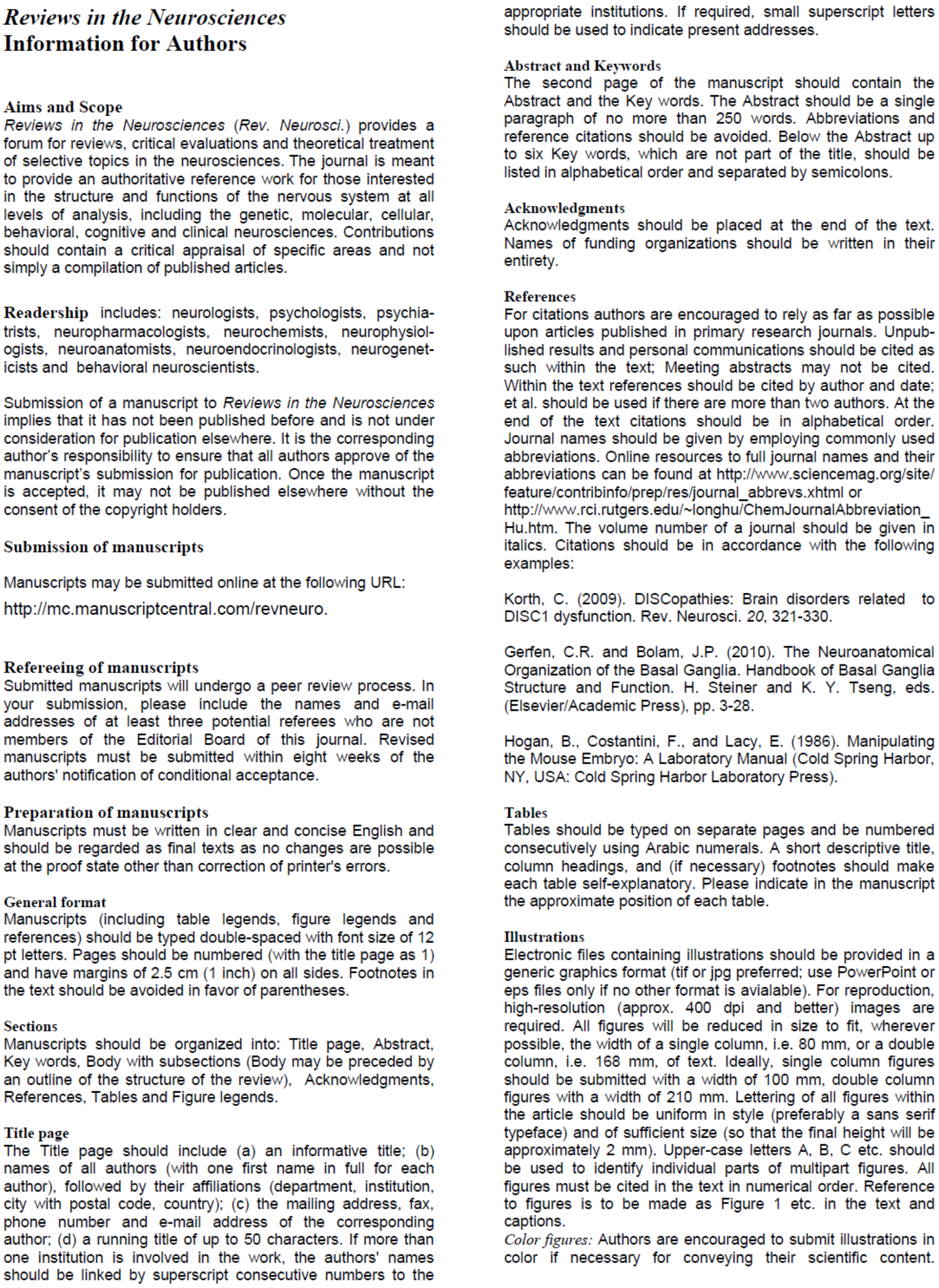
Anexo I



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