ARTIGOS (FLUXO CONTÍNUO)

"INVOLVEMENT OF THE BRAIN REWARD SYSTEM IN HARMFUL SITUATIONS: PLEASURE IN SUFFERING"

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Involvement of the brain reward system in harmful situations: pleasure in suffering.

Participação do sistema de recompensa cerebral em situações nocivas; prazer no sofrer

Participación del sistema de recompensa cerebral en situaciones perjudiciales; placer en el sufrimiento

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RESUMO
Introdução: Este estudo representa uma revisão de literatura sobre a participação do sistema de recompensa cerebral em situações prejudiciais. Objetivo: O estudo foi norteado pelo objetivo de analisar e verificar a literatura científica a respeito da participação do sistema de recompensa em comportamentos que geram um sofrimento, destacando as influências neurobiológicas no processo e identificando as estruturas cerebrais as quais a dopamina faz parte. Método: Trata-se de uma revisão narrativa de literatura de caráter exploratório realizada através do cruzamento dos descritores: Neurochemistry AND Motivation; Neuroquímica AND Motivação; Neuroanatomy AND Motivation, aplicados nas bases de dados Bvs e PubMed. Resultados: Com base nos estudos considerados podemos observar que existem influências neurológicas significativas no processo motivacional, foram destacados as regiões do cérebro com maior participação: o Núcleo accumbes seguidas pelas regiões da concha do núcleo accumbens, amígdala basolateral, córtex pré frontal e hipotálamo, e também outras áreas como mesencéfalo, córtex cingulado anterior, estriado ventral, amígdala e área tegmental ventral. Além disso, também foi possível encontrar substâncias neuroquímicas que estão envolvidas no processo da motivação, dando destaque ao glutamato, dopamina e a dopamina mesolímbica. Conclusão: Foi possível observar através dos artigos presentes na amostra que a dopamina e o sistema de recompensa tem participação nos comportamentos de sofrimento ou nocivos quando relacionados com atingimento de metas. Ou seja, há a manutenção desses

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comportamentos, mesmo que nocivos, quando existe a interpretação de que em algum grau e intensidade ocorrerá um ganho futuro, levando assim a hipótese inicial do artigo para uma possível confirmação.

Palavras-chave: Neuroquímica; Motivação; Neuroanatomia.

ABSTRACT

Introduction: This study represents a literature review on the participation of the brain reward system in harmful situations. Objective: The study aimed to analyze and examine the scientific literature regarding the involvement of the reward system in behaviors that generate suffering, highlighting the neurobiological influences in the process and identifying the brain structures in which dopamine plays a part. Method: This is a descriptive and qualitative literature narrative review conducted by cross-referencing the following descriptors: Neurochemistry AND Motivation; Neuroquímica AND Motivação; Neuroanatomy AND Motivation, applied in the Bvs and PubMed databases. Results: Based on the considered studies, significant neurological influences in the motivational process were observed. The brain regions with the highest involvement were identified as the nucleus accumbens followed by the shell regions of the nucleus accumbens, basolateral amygdala, prefrontal cortex, and hypothalamus, along with other areas such as the mesencephalon, anterior cingulate cortex, ventral striatum, amygdala, and ventral tegmental area. Furthermore, neurochemical substances involved in the motivation process were found, with emphasis on glutamate, dopamine, and mesolimbic dopamine. Conclusion: Through the articles included in the sample, it was observed that dopamine and the reward system play a role in behaviors of suffering or harm when associated with goal attainment. In other words, these behaviors are maintained, even if harmful, when there is an interpretation that there will be future gain to some degree and intensity. This finding supports the initial hypothesis of the article for possible confirmation.

Keywords: Neurochemistry; Motivation; Neuroanatomy.

RESUMEN

Introducción: Este estudio representa una revisión de la literatura sobre la participación del sistema de recompensa cerebral en situaciones dañinas. Objetivo: El estudio fue guiado por el objetivo de analizar y verificar la literatura científica sobre la participación del sistema de recompensa en comportamientos que generan sufrimiento, destacando las influencias neurobiológicas en el proceso e identificando las estructuras cerebrales en las que la dopamina forma parte. Método: Se trata de una revisión narrativa de la literatura de carácter exploratorio realizada a través del cruce de los descriptores: Neuroquímica Y Motivación; Neuroquímica Y Motivación; Neuroanatomía Y Motivación, aplicados en las bases de datos Bvs y PubMed. Resultados: Basándonos en los estudios considerados, podemos observar que existen influencias neurológicas significativas en el proceso motivacional, se destacaron las regiones del cerebro con mayor participación: el Núcleo accumbens seguido por las regiones de la concha del núcleo accumbens, amígdala basolateral, córtex prefrontal e hipotálamo, y también otras áreas como mesencéfalo, córtex cingulado anterior, estriado ventral, amígdala y área tegmental ventral. Además, también fue posible encontrar

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sustancias neuroquímicas involucradas en el proceso de motivación, destacando el glutamato, la dopamina y la dopamina mesolímbica. Conclusión: Fue posible observar a través de los artículos presentes en la muestra que la dopamina y el sistema de recompensa tienen participación en comportamientos de sufrimiento o nocivos cuando están relacionados con el logro de metas. Es decir, se mantiene estos comportamientos, incluso si son nocivos, cuando existe la interpretación de que en algún grado e intensidad ocurrirá una ganancia futura, llevando así la hipótesis inicial del artículo a una posible confirmación.

Palabras clave: Neuroquímica; Motivación; Neuroanatomía.

Introduction

This study, a literature review on the participation of the brain reward system in harmful situations, was guided by the need to understand the neurobiological mechanisms and substrates that permeate pleasure situations correlated by suffering.

To this end, we considered Linda Davidoff's (2004) statements about "motivation" that "refers to an internal state that can result from a necessity", so motivation is the driver of satisfaction of primary necessities (which guarantee our survival) and emotions generated by the socio-cultural interaction of the individual. Thus, the incentive model of motivation is fundamental for achieving homeostasis, because through this concept it is possible to understand the process of modeling basic impulses, which begins with experience and results in cognitive and emotional changes, generating goal-oriented behaviors, which also modify cognition and emotion, and may increase or decrease motivation. (Davidoff, 2004).

The author provides subsidies for us to understand that everything starts with motivation, which impels us to think about the subject in a more critical way and, thus, pertinent questions were raised about the subject, especially when we want to relate motivation to neurobiology themes. Thus, the questions "why do we do what we do?" and "what leads someone to continue in a situation of suffering?" were formed in our thoughts and generated concerns that led us to produce this study.

The motivation, this basic psychological process, is what governs behaviors.

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To illustrate, imagine for a moment an individual goal and how this goal to be achieved generates a sensation that we call motivation, with this image we believe it becomes clearer why this phenomenon is the engine, or at least the fuel of our actions.

There are various concepts of suffering in scientific literature, but in this study we consider suffering as the exposure and permanence of the subject to negative or harmful stimuli that are conscious or unconscious in nature, and may be from a physical or emotional perspective. As an example, we can cite the undertaking of seeking a degree through undergraduate courses, where the subject maintains motivated behavior for years in pursuit of future fulfillment (graduation), despite adversities, problems of different natures, sacrifice of social life and other characteristically negative events, but which are faced for later success.

At first, the hypothesis raised to understand such concerns, that there is activation of the reward system during unpleasant situations, starts from this concept, motivation, which is widely known, but unfortunately somewhat undervalued by academic research. (Robbins, Judge, Sobral 2010).

It is then derived from the desire to understand more clearly about the motivation construct that arises from the desire to investigate neurological processing and answer the question that guides this study "does the reward system permeate unpleasant or suffering situations?".

To do so, it was necessary to deepen anatomofunctional and neurophysiological studies of the brain in order to elucidate brain functioning during processes conceived as metaphysical, such as motivation. Even though it is a complex investigation regarding a subjective theme, there are evidences of interaction between different levels of neuronal connections and information processes in distinct areas of the brain constituting several systems such as Reward and Motivational (Fluentes, Malloy-Diniz, Camargo and Cosenza 2014) supported by neurotransmitters known as dopaminergic related tirelessly to pleasure despite different firing patterns that generate reward sensation." (Suárez 2018 p. 3).

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Suárez (2018) has pointed out and confirmed that there is dopamine release in certain areas of the brain in pleasure situations. Thus, we hypothesize that dopamine also permeates situations understood as negative for future pleasure attainment, since the period of goal attainment may be permeated by suffering.

Method

This is a brief narrative review of the literature, with a chronological cut of 10 years (2012/2022) of descriptive feature and qualitative nature guided by the desire to verify the participation of the reward system in behaviors that generate suffering.

The choice of method was due to its breadth of reference capture, based on a qualitative synthesis, allowing more space to describe and discuss development under a certain theme, being subject to updating. (Rother, 2007).

For data collection, the descriptors were submitted and verified in the Health Sciences Descriptor (DeCS) database and thus selected: Neurochemistry, Neurochemistry, Motivation, Motivation, Neuroanatomy, Neuroanatomy; then the crossings were carried out: Neurochemistry AND Motivation; Neurochemistry AND motivation; Neuroanatomy AND Motivation. After defining the descriptors and crossings, searches were made in the PubMed/Medline and BVS/LILACS databases in vernacular and English languages.

To keep the study oriented, establishing a focus for production, the following guiding question was delimited: "Does the reward system permeate unpleasant or suffering situations?"

Inclusion criteria: articles should objectively address the theme in question, even if indirectly (review articles, clinical trials, without language restriction) and exclusion criteria: articles that did not address the theme clearly (experience reports, monographs, theses, dissertations, intervention articles, articles without methodological clarity). The selection was first made by titles and then by abstracts.

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Once the search was completed, the articles were divided among the authors and each was asked to read them in full highlighting which areas of the brain would influence motivation, findings on neuroanatomy, neurochemical influences and other important findings that related to the proposed.

Although this is not an experimental study here, the Ethics in Research norms of resolution 466/2012 were observed with regard to consideration regarding "the progress of science and technology which must imply current and potential benefits for human beings".

During the data collection stage using the aforementioned descriptors a filter was applied by year and selection was made by titles collecting 17 articles for the next stage. The second stage of sample selection took place with reading of abstracts and full reading of articles leaving 10 articles for the final sample, the selection process is better exemplified in flowchart (figure 1).

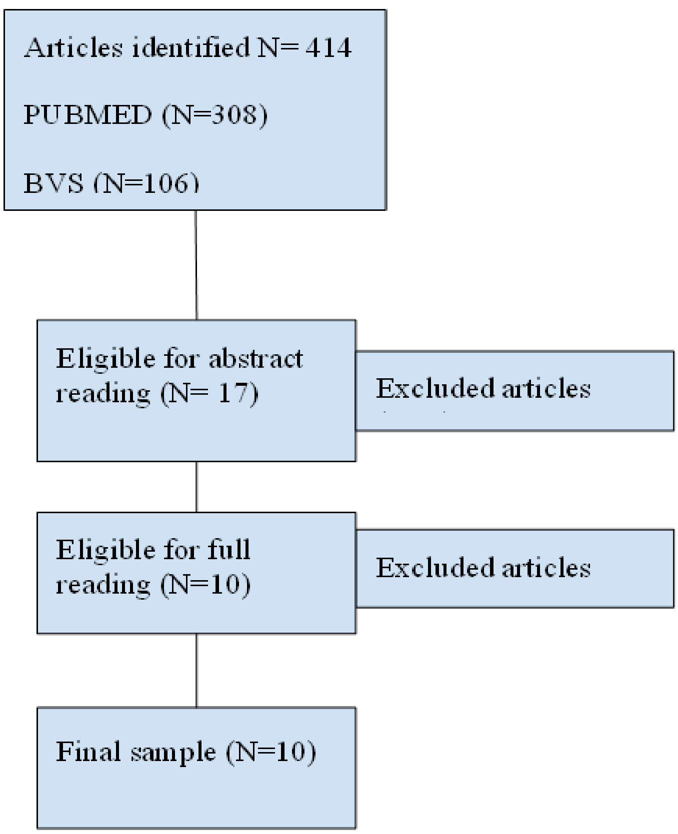

Figure 1: Selection flowchart

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Results and discussions

After the data collection stage, using the aforementioned descriptors, the filter was applied by year and the selection was made by titles, collecting 17 articles for the next selection stage. The second stage of sample selection took place with the reading of the abstracts and full reading of the articles, leaving 10 articles for the final sample.

For a detailed organization of the analyzed works, table 1 was produced containing the name of the authors, the title of each article, the year, the journal and database where it is located and its objective. Each article corresponds to a specific numbering that will serve as a guide for the next tables and charts containing other results extracted from this research.

Frame 1

Sample of articles

N°	AUTHORS	TITLE	OBJECTIVES	INDEX	JOURNAL	YEAR
1	Galtress, Tiffany; Marshall, Andrew T; Kirkpatrick, Kimberly.	Motivation and timing: clues for modeling the reward system	Present some new evidence with more manipulations of the reward value during training versus testing in a peak procedure.	BVS	Behav Processes	2012
2	Baldo, Brian A; Pratt, Wayne E; Will, Matthew J; Hanlon, Erin C; Bakshi, Vaishali P; Cador,	Principles of motivation revealed by the diverse functions of neuropharma cological and neuroanatom ical	Identify distinguishable actions of striatal opioid peptide modulation and dopamine transmission in subcomponent	BVS	Neurosci Biobehav Rev	2013

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N°	AUTHORS	TITLE	OBJECTIVES	INDEX	JOURNAL	YEAR
	Martine.	substrates underlying feeding behavior.	s of reward processing			
3	Zorrilla, Eric P; Koob, George F.	Amygdalostriatal projections in the neurocircuitry for motivation: a neuroanatomical thread through the career of Ann Kelley.	Influentially show that amygdalo-striatal projections are much more extensive than previously thought. Highlight that amygdala projections to the rostral ventromedial striatum converged with projections from the ventral tegmental area and cingulate cortex, forming a "limbic striatum".	BVS	Neurosci Biobehav Rev	2013
4	Kate M Wassum 1, Paul E M Phillips	Probing the neurochemical correlates of motivation and decision making	We discuss paths for future technological development, as well as the need for increasingly sophisticated and interdisciplinary behavioral analyses.	PUBMED	ACS Chem Neurosci	2015
5	Ken T Wakabayashi, Stephanie E Myal,	Fluctuations in nucleus accumbens extracellular glutamate	Examine second-scale fluctuations in extracellular levels of these	PUBMED	J Neurochem	2015

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N°	AUTHORS	TITLE	OBJECTIVES	INDEX	JOURNAL	YEAR
	Eugene A Kiyatkin	and glucose during motivated glucose-drinking behavior: dissecting the neurochemistry of reward	substances in the nucleus accumbens during glucose ingestion behavior in trained rats.			
6	I Morales, L Font, P J Currie, R Pastor	Involvement of opioid signaling in food preference and motivation: Studies in laboratory animals	Elaborate on the potential role of opioid system manipulations in disorders associated with overeating and obesity	PUBMED	Prog Brain Res.	2016
7	Morgane Milienne-Petiot, James P Kesby, Mary Graves, Jordy van Enkhuizen, Svetlana Semenova, Arpi Minassian, Athina Markou, Mark A Geyer, Jared W Young	The effects of reduced dopamine transporter function and chronic lithium on motivation, probabilistic learning, and neurochemistry in mice: Modeling bipolar mania	Investigate putative mechanisms underlying cognition and reward-seeking/motivational changes relevant to patients with manic BD using two validated mouse models and neurochemical analyses.	PUBMED	Neuropharmacology	2017
8	John D Salamone, Mercè Correa , Sarah Ferrigno , Jen-Hau Yang	The Psychopharmacology of Effort-Related Decision Making: Dopamine,	Discuss the pharmacology of effort-related decision-making and focus on the use of these tasks for the	PUBMED	Rev Pharmacol	2018

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N°	AUTHORS	TITLE	OBJECTIVES	INDEX	JOURNAL	YEAR
	, Renée A Rotolo , Rose E Presby	Adenosine, and Insights into the Neurochemistry of Motivation	development of drug treatments for motivational dysfunction.			
9	Marianne O Klein, Daniella S Battagello, Ariel R Cardoso, David N Hauser, Jackson C Bittencourt, Ricardo G Correa	Dopamine: Functions, Signaling, and Association with Neurological Diseases	Describe the potential involvement of these signaling pathways in evoking the onset and progression of some nervous system diseases, such as Parkinson's, Schizophrenia, Huntington's, Attention Deficit Hyperactivity Disorder, and Addiction.	PUBMED	Cell Mol Neurobiol.	2018
10	Jesper Vestlund, Filip Bergquist, V alentina Licheri, Louise Adermark, Elisabet Jerlhag	Activation of glucagon-like peptide-1 receptors and skilled reach foraging	Investigate the effects of repeated Ex4, liraglutide, or dulaglutide on motivation and learning of complex motor tasks, such as skilled reaching foraging in the Montoya staircase test.	PUBMED	Addict Biol.	2020

Source: The authors

Starting the analysis of table 1, we can see the data regarding the concentration of productions per year, with evidence of the years (2013), (2015) and

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(2018) as the ones with the highest production regarding the theme, representing each period 20% of the total sample of articles.

The studied articles allowed us to verify the brain areas most implicated in motivated behavior as follows in table 2.

Table 2

Neuroanatomical influences of motivation

Área envolvida	**N° do artigo**
Nucleus accumbens shell	5; 10.
Nucleus accumbens	1; 2; 4; 7; 5; 9.
Basolateral amygdala	4; 2.
Ventral tegmental area	9
Prefrontal cortex	7; 9.
Hypothalamus	9; 6
Amygdala	3.
Ventral striatum	1;
Anterior cingulate cortex	1;
Midbrain	1;

Source: The authors

After analyzing table 2, it is noted that the Nucleus accumbens area is the one that appears most influenced by the motivational process, representing 60% of the findings, followed by the ensuing regions: shell of the nucleus accumbens, basolateral amygdala, prefrontal cortex and hypothalamus. which appears in 20% of the findings. Finally, the areas found less frequently were mesencephalon, anterior

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cingulate cortex, ventral striatum, amygdala and ventral tegmental area all representing 10% of the findings.

The observation of the influence of the nucleus accumbens on motivation is an encouraging direction to establish possible relationships between the activation of reward pathways and motivation itself, given that this region is considered part of this circuit. (Zorrilla and Koob, 2013)

Next, we compiled data on neurochemical substances involved in the motivational process using table 3 to present the systematization of neurochemical substances cited in the sample of articles.

Table 3

Neurochemical substances involved in motivation

Glucagon-like peptide-1 (GLP-1)	10;
GLP-1R agonists	10;
Glutamate	4; 5;
Dopamine	4; 3;
Midbrain dopamine	1;
Mesolimbic dopamine	8; 9
Striatal acetylcholine	2
Striatal dopamine	7;
Opioid peptides	6
Opioid agonists	2

Source: The authors

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It can be seen that glutamate, dopamine and mesolimbic dopamine are the substances that appear most in the findings, representing 20% of the sample, while the other substances contained in table 3 represent only 10% of the final sample.

In tables 2 and 3 we observe a curious finding: that of greater mention of dopamine and mesolimbic dopamine, since they are substances with direct influence on reward pathways in the cortex indicating a possible relationship between motivational process and activation of these dopaminergic pathways so that subjects remain in unpleasant situations.

The study of motivation can be understood as a representation of the search to unveil what awakens behaviors, and part of this understanding, leads us inevitably to the study of neurology, since understanding such a process proposes a reflection on psychic or, broadly speaking, "mental" instances (Davidoff, 2004). Therefore the hypothesis that motivational processes are related to possible activation of reward circuits is quite coherent when we compare the results presented by Zorrilla and Koob (2013) and those by Milienne-Petiot et al. (2017).

Zorrilla and Koob (2013) point out that amygdala is mainly responsible for emotional circuitry bringing that "amygdala influences emotional behavior by encoding sensory representation of a stimulus with value." Milienne-Petiot et al. (2017) state that high levels of dopamine in the brain, specifically in nucleus accumbens, increases activation of reward and motivation circuit.

It is noted that both amygdala and nucleus accumbens are related to motivational process and both structures are part of motivational circuit as demonstrated by (Zorrilla and Koob 2013) showing logical congruence in presented hypothesis.

Still paying attention to nucleus accumbens, Wakabayashi Myal and Kiyatkin (2015) bring in their findings an extremely important milestone for neurological understanding of motivational process giving neurochemical and neurophysiological explanation to Skinnerian conditioning. In their experiment with rodents, authors discovered an elevation in levels of glutamate concentration in nucleus accumbens

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when individuals are exposed to reinforcing stimulus (cup with glucose), thus indicating motivation process driven by the necessity to obtain presented food.

It is curious to note that such findings can be correlated with those by Vestlund Bergquist Licheri Adermark and Jerlhag (2020) since they also verified the influence of Nucleus Accumbens on motivational process. In their experiment, also with rodents, researchers recorded action of glucagon-like peptide-1 (GLP-1) showing that its action within Nucleus Accumbens models motivation of rats' foraging behavior.

Based solely on these authors it is already evident importance of Nucleus accumbens in this motivation process, but there are still several other authors who converge in their findings, for example Wassum and phillips (2014) bring very directly important information about reward-seeking process which is directly linked to motivation and its neurological correlates agreeing with findings by Vestlund et al. (2020) and Wakabayashi et al. (2015) when they talk once again about influence of Nucleus accumbens.

The same authors, Wassum and phillips (2014) also talk about the relationship between glutamate in basolateral amygdala and dopamine in nucleus accumbens, and how release of these neurotransmitters in these specific regions has an impact on reward-seeking which can be understood as next part after motivational process.

High levels of dopamine in the brain, specifically in the nucleus accumbens, increase the activation of the reward and motivation circuit (Milienne-Petiot et al. 2017) who observed that "reduced motivation is observed during periods of depression in patients compared to healthy individuals, and may result from reduced levels of striatal dopamine," thus behaviors with low dopaminergic neurochemical percentage generate deficits in motivation.

In addition, Milienne-Petiot et al. (2017) state that "Such associative reward behaviors may be important for cognitive training in psychiatric patients and may be mediated by dopamine D1 receptors in the nucleus accumbens," thus it is

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understood that to boost the reward circuit higher doses of dopamine are needed in the nucleus accumbens area.

Other neurotransmitters permeate the motivational process as verified by Wakabayashi et al. (2015) in studies carried out with rodents, as previously explained, which allowed the authors to verify that maintenance of search behavior is mediated by glutamate while pleasure attainment is mediated by dopamine. With this we see how the motivation process is self-fed with neurochemical releases to initiate search and reinforce it, and that glutamate has an expressive participation in persistence behaviors for goal achievement.

Klein et al., 2019 were able to verify dopamine release in mesolimbic dopaminergic system during aversive stimuli and stress claiming that this release is responsible for motivating search for safety behavior. This finding corroborates our premise showing that there is indeed dopamine in suffering situations and not only pleasure leading to interpretation of motivation concepts existing in unpleasant situations.

Prior to this Ikemoto and Panksepp (1999) corroborate Klein with their findings of dopamine in aversive situations and how this neurotransmitter facilitates stress-stimulated behaviors, being essential for behavioral incentives and brain representations. Thus stimulating the environment can trigger avoidance responses which consequently generate motivation of this behavior, which may be directed towards search for safety.

After all construction of this work an old question resurfaced, motivation as an internal state that can result from a necessity, Davidoff (2004) consists of a cognitive process following cognitive cycle pattern proposed by (Beck 2013) in which a thought leads to a feeling and a behavior? or is motivation only a conditioned behavioral response to social variables?

The first proposition would be justified if some study demonstrated that modification of thoughts can alter an individual's motivation, making him withdraw from what we call in this article "situations of suffering" thus, if alteration of thought

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could exert such consequence we could understand motivation as part of a cognitive process and therefore can be rational.

However if modification of thought is not sufficient to alter a subject's behavior such finding could point evidence towards understanding what we call "motivation" being only another response to environment, which in this case would be society in general reinforcing behavior pattern "remain in unpleasant situation" since it would lead subject to some kind of final recognition.

To avoid unfounded discussions and so that we can actually answer this question new studies will be needed, especially experimental ones investigating in detail all components that make up this spectrum that is motivation.

Conclusion

After conducting this study, it is possible to affirm that dopamine and the reward system permeate suffering or harmful behaviors for goal attainment, that is, behaviors are maintained, even if harmful, when there is some degree and intensity of pleasure or future comfort, thus positively our initial hypothesis.

We also observed the main neurotransmitters involved in mediating motivated behaviors, being dopamine, mesolimbic dopamine and glutamate, as well as the clear and expressive participation of amygdala and nucleus accumbens.

We can affirm that our objectives were achieved in the sense that we were able to verify what we initially proposed in this study answering the question that guided this study.

However, we need to state here that we do not intend to be definitive in our statements, since it is a literature review, and thus it is possible that studies with another methodological profile may make findings divergent from those researched here.

Therefore it is important to emphasize that other studies on the subject, under

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different conditions and from different perspectives, should happen for better understanding of neurochemical and neuroanatomical mechanisms and substrates of motivated behaviors permeated by suffering.

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