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Letter to the Editor
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# May Benzodiazepines Restrict Neural Plasticity? Thoughts on Freud's "Anxiety Signal" and his Contribution for Understanding Crucial Cognitive Development and Adaptation Processes

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## Letter to the Editor

The major clinical advantages of Benzodiazepines (BZD) are known to be their high efficacy, rapid onset of action and relative low toxicity. They are indicated for a broad range of mental conditions: As hypnotics, they are mainly indicated for transient or short term insomnia. As anxiolytics, they should generally be used in conjunction with other measures (psychological treatments, antidepressants, other drugs) although such measures have a slower onset of action. Indications for BZD include acute stress reactions, episodic anxiety, fluctuations in generalized anxiety, and as initial treatment for severe panic and agoraphobia [1]. BZD are not exempt of producing adverse side reactions, among them: dependence, rebound anxiety, memory impairment, and discontinuation syndrome [2].

Despite remarkable clinical recommendations of short-term use, prolonged treatment with benzodiazepines is a common practice: Benzodiazepines are used by approximately 4% of the general population, with increased prevalence in psychiatric populations and the elderly [3]. After long-term use it is often difficult to discontinue benzodiazepines due to psychological and physiological dependence. Moreover, a recent investigation conducted in Italy, showed that the most involved drugs in abuse were "Benzodiazepines and derivatives" [4].

In trying to help people to mitigate their symptoms and suffering, it is clear that the indication of benzodiazepines might be considered appropriate under a variety of circumstances. However, Sigmund Freud warned that certain anxiety levels could be beneficial for patients, promoting changes that were part of the necessary mental development. He conceptualized the "anxiety signal", as an indicator that certain internal cognitive and emotional processes were to be carried on by the individuals to solve internal conflicts. Thus, they could facilitate these processes under introspection to find out the internal factors implied in those conflicts, working through them [5]. For the sake of interpreting and integrating these Freud's concepts with the previously exposed under the light of modern neuroscience a brief reference to neural networks and their possible relationship with BDZ mechanisms of action follows.

In 1943 Warren Mc Culloch and Walter Pitts published a seminal paper in which they communicated their research about the intrinsic logic of Neural Networks (NN) [6]. In particular, they sought to elucidate the theoretical way in which NN organize to solve complex problems and how memories and information can be stored and accessed in an interconnected NN system. From the biophysical point of view it is known today that the transmission of a signal (information) from one neuron to another, through the synaptic scaffolding, is a complex electrochemical process in which, certain neurotransmitter substances are released from the pre-synaptic neuron to the site of reception of the post-synaptic neuron. The effect of this process is to raise or decrease the electrical potential of the cell body of the recipient cell, and along with it, the frequency of production of action potentials. Now, taking into account the mechanism of action of benzodiazepines:

The GABA Receptor Complex and Benzodiazepines Receptors: γ-Aminobutyric acid is the major inhibitory neurotransmitter in the mammalian central nervous system, eliciting its physiological effects through interaction with several distinct classes of cell-surface receptors: GABAA, GABAB, and GABAC receptors. The GABAA receptor is the most abundant and is a member of the super family of ligand-gated ion channels. The interaction of GABA with this

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receptor determines the opening of the intrinsic chloride ion selective channel, which is followed by an increase in chloride flux, with the result of a hyperpolarization of the neuronal cell membrane and a concomitant decrease in neuronal transmission [7].

This means that under BDZ action neural networks are, in general, less responsive. At this point, we think that this fact implies not only a reduction in the mental performance of the individual, which is understandable due the known effects of these drugs, but that there may be also restrictions for the development of the network itself for adapting to new life challenges. The ability for neural networks and systems to re-configure their internal connectivity in order to modify its performance is known as neural plasticity [8].

Now we may wonder: What is the neurobiological nature of anxiety? Why is it a conserved evolutive trait in humans, despite the discomfort and displeasure it elicits? We, as individuals who were born with certain instinctive abilities that not sufficed in relation to lifelong challenges, we needed to develop more and major capacities, most of which should we incorporate across the whole life. The brains of individuals who are confronted with new situations are required to develop new connections between neurons, possibly growing new axons' projections and processes up, recruiting more neurons to carry certain duties on. No new neurons are to be produced in the short time, but new connections may be well elicited and produced in relative short terms.

Thus, it might be possible that anxiety symptoms were manifestations of crucial processes that are occurring at a neural level and that we have to permit to be accomplished, providing the anxiety levels do not lead to any irreversible damage. Our hypothesis, that links all the previously mentioned, is that anxiety, and its related discomfort, might be originated by neural axons' and dendrites' growth themselves, to a certain extent. Are there temporal and chemical relationships between the secreted neurotransmitters under anxiety and neural growth factors? We consider all these matters persuade us to be more cautious when considering the indication of benzodiazepines and suggest directions for future investigations.

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