PRC 2

Research in Cognitive Neuroscience and Information Technology

Maintenance of sustained attention.
Dopamine and adrenaline regulation through video games
GAMEATTENTION

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1. Title, acronym and scientific summary of the proposal

One of the most worrying issues of our 21st century is the environment with multiple distractions we live into, which is competing with our ability to sustain attention for a long period of time. However, some jobs strongly require this capacity in order, not only to be successful, but to not risk the lives of thousands of human beings. Some of these jobs include air traffic controllers, surgeons or pilots. Sustained attention cannot be maintained during long time slots, and that is what scientists have named “vigilance decrement”: the drop in the cognitive efficiency and hence a decrease in the sustained attention (Al-Shargie et al, 2019). Being able to unravel the causes of vigilance decrement can become a powerful tool to attenuate its inconsistencies. Thanks to that, the aforementioned professions will be successful in their jobs and thousands of lives will be preserved from inattention accidents.

The area that appears to be involved in the vigilance attention system -which will be used as a synonym of “sustained attention” in all of our project- is the frontal lobe of the brain, and the neurotransmitter -and hormone- implicated is the norepinephrine (NE) (Posner & Petersen, 1990 in Castillo & Paternina, 2006). For this reason, this project will be based in the study of the neurotransmitters involved in sustained attention. Specifically, the project will be focused, firstly, on the dopamine -a norepinephrine precursor-. Moreover, to understand the whole pathway, the project will also study the influence of adrenaline, which is the hormone released after norepinephrine, through the mesolimbic pathway dopamine-norepinephrine-adrenaline.

The project will be carried out in three phases: the study of the dopamine, the study of the adrenaline and the intervention with video games. First of all, the levels of dopamine needed for the brain to deploy sound sustained attention will be measured. We will also measure how long dopamine lasts at optimal levels, before vigilance decrement starts to kick in. To estimate dopamine levels, we will apply use Positron Emission Tomography (PET) Magnetic Resonance Spectroscopy (MRI) dopamine measurement. The levels of adrenaline needed for the brain to be in a state of sound sustained attention will be measured, as well as for how long adrenaline lasts at optimal levels. These levels will be measured with a urine test (Sander & Hesse, 2018).

When these two parameters have been measured, a video game based intervention will be developed. The aim of the intervention will be to find the proper video game which reaches the levels of dopamine and adrenaline at the level which has been found to be the proper one when sustained attention is adequately enacted. Once tested and validated, the video game will become a solid tool to monitor sustained attention for large periods of time. The most efficient intervention would be to let professionals in high-risk professions to play with these video games. The frequency in which they should play would be determined by the time dopamine and adrenaline can last at optimal levels, characterized before. While these professionals are forced to sustain attention without any extra motivation, being able to play video games regularly in their jobs could provide a great means to their reduce their vigilance decrement, so that they continue their working day with levels of dopamine and adrenaline necessary for sound sustained attention.

2. Summary for a non-specialist public of the proposal

Sustained attention -or vigilance- is defined as the ability to remain alert to a particular stimulus over a prolonged period of time (Al-Shargie et al, 2019). However, this century is causing a decrease on our ability to execute sustained attention, due to the multiple stimuli which we live surrounded by. Some professions are strongly vulnerable to this situation, since a decrement on their attention could cause a big impact on thousands of lives: for instance, professions such as air traffic controllers, surgeons or pilots.

In the sustained attention, the neurotransmitter dopamine and the hormone adrenaline are the principal substances involved. In our project, therefore, we aim to estimate the levels of dopamine and adrenaline which are released when sustained attention is taking place. Moreover, we also aim

to unravel how long these two substances are able to last at optimal levels, before sustained attention decreases. When having measured these parameters, we will test some video games in these high-risk professionals, in order to understand which of all of the video games gives them the parameters needed to enact sustained attention. Once having selected the correct video game and knowing the amount of time dopamine and adrenaline can last at optimal levels, we will implement an intervention with the professionals mentioned above. The intervention will consist on letting them play with these video games in the frequency which has been calculated that sustained attention can last. When vigilance decrement is occurring, playing these video games will rise their levels of dopamine and adrenaline again, up to the point where sustained attention is activated again.

3. Context, conceptual framework and state of knowledge

Sustained attention

Sustained attention -or vigilance, which is being used as a synonym in this project- is defined as the ability to remain alert to a particular stimulus, location or task over a prolonged period of time. Multiple professions are required to maintain vigilance, sometimes due to their high cognitive workload or, on other occasions, because they need to maintain their cognitive efficiency for a long period of time (Al-Shargie et al, 2019).

However, sustained attention has seen its decrement rapidly during this 21st century. There are two reasons which might have caused this decrement. First of all, the massive increase of the stimuli we live surrounded by, as well as the multiple multitasking operations which we carry out nowadays have led into vigilance decrement and a loss of cognitive efficiency. On the other hand, monotony has been found as the second reason for vigilance decrement, discovering that target detection performance decreases by 15% in 30 minutes during a monotonous task. Indeed, many of the professions mentioned above -air traffic controllers, surgeons or pilots- which are precisely those that need sustained attention the most, are also normally professions which are very monotonous (Al-Shargie et al, 2019).

When taking a look at the anatomy of sustained attention, it has been spotted that the frontal lobe of the brain is the main area involved (Jodar et al, 2019). That has been demonstrated with Positron Emission Tomography (PET), since the bloodstream rises in this area when the subject is in sustained attention status (Castillo & Paternina, 2006). Indeed, one of the main functions of the frontal lobe is the cognitive control of the body, associated with memory, planning and focusing attention (Miller & Cummings, 2018). For this reason, it makes actual sense that vigilance is taking place right in this region of the brain.

In an attempt to organise the concepts, Posner and Petersen proposed a theoretical structure in order to categorise the attentional system: the rear attention system, the previous attention system and the vigilance attention system. The one which concerns us is the last one, which takes place when the subject needs to be alert to the appearance of a possible stimulus (Castillo & Paternina, 2006). As it has been mentioned above, the vigilance attention system takes place at the frontal lobe. The most important neurotransmitter which is activated during the sustained attention has been found to be the norepinephrine (NE). That has been demonstrated with studies where this neurotransmitter was blocked -by the administration of clonidine or guanfacine, which decrease the NE release- and thus, a vigilance decrement was found (Petersen and Posner, 2012). More specifically, strong evidence relates the locus coeruleus-norepinephrine pathway as one of the starring in alertness and attention (Oken et al, 2010).

The neurotransmitter involved: dopamine

Norepinephrine, however, follows a pathway that must be examined: the mesolimbic pathway. This pathway follows the route dopamine-norepinephrine-adrenaline. The reason why we want to study this pathway in such a detail is because the short-term objective in our project is to investigate

dopamine, the precursor of epinephrine -the main neurotransmitter related with sustained attention- (Anstrom et al, 2009).

When taking a closer look at dopamine, this is a neurotransmitter capable of activating five different types of cellular receptors, from D1 to D5. A neurotransmitter is a chemical messenger which, through chemical synapse, transmits signals from one neuron to another. Therefore, neurotransmitters play an important role in shaping our life and our functions, because they transmit the information that our body needs to operate. Moreover, dopamine is the only neurotransmitter in the mesolimbic pathway which does not act as a hormone and which does not cross the blood-brain barrier. On the other hand, dopamine is related with reward, motivation, arousal, memory and attention; therefore, as stated below, it becomes an essential substance in our study (Maechler, 2010).

The hormone involved: adrenaline

We also have to take into account, however, that the hormone adrenaline is released when the mesolimbic pathway is activated, during sustained attention. As Oken et al (1010) state, is important to understand vigilance on a unidimensional continuum, that is to say, that when we study these activation states, we should try to control and report on as many parameters as possible. For this reason and taking into account that we will create an intervention based on video games -which will probably release adrenaline- we believe that measuring adrenaline, the main hormone involved in this process becomes imperative.

Adrenaline is a hormone which has in its main functions the increase of the heart rate, the contraction of the blood vessels and the dilatation of the airways. It becomes, therefore an important hormone in the regulation of stress and escape, and also probably a hormone which will be released when playing video games (Sakai & Sunada, 2017).

Current status

There are some studies related to our project that we will summarise, in order to have a more accurate state of the knowledge. The first thing we are analysing in our study is the relationship between dopamine and sustained attention. In this sense, a study made by Marshall et al (2019), confirmed that the selective activation of dopamine D3 receptors enhances sustained attention. From their study, it is also interesting to note another finding: methylphenidate blocks dopamine and norepinephrine reuptake and is the leading choice for attention treatment. Even though we have not assured that more dopamine means more sustained attention -we want to measure the quantity of dopamine that enables a correct sustained attention status-, this study implies that dopamine is closely linked with vigilance. That is, if the presynaptic neuron is blocked from reuptake, more dopamine will be released and, consequently, sustained attention will take place. In our study we will use a hybrid technique using Positron Emission Tomography (PET) Magnetic Resonance Spectroscopy (MRI), where we aim to understand more precisely the exact amount of dopamine released in the state of sound sustained attention.

On the other hand, it is important to note that many intervention techniques have been carried out in order to enhance sustained attention. Some of them have been mental training, meditation, yoga, sports, exercise, caffeine, chewing gum or diet and herbal extracts. There are even other unconventional means of enhancement which have included drugs, neural implants or brain-computer interface (Al-Shargie et al, 2019). In our study, however, we aim to introduce a new intervention technique based on video games.

Related to that, our study correlates the intervention of video games with sustained attention. In this sense, two studies are noteworthy. First of all, a study with video games was carried out with patients with brain injury in order to improve their cognitive abilities and their sustained attention. The findings were that there is no evidence to support the usefulness of video games in improving cognitive abilities (Malec et al, 1984). Although this may seem a bit disappointing, it is important to note that it is quite an old study and it has been performed with patients with brain injury, while our participants

will be healthy. On the other hand, taking a look at more recent studies, a study made by Weerdmeester et al (2016) found out that a full body movement video game -called Dragon- enhanced the cognitive abilities of children with Attention Deficit Hyperactivity Disorder (ADHD). This video game improved several cognitive areas of the children with only a short amount of game play, and the satisfaction of the game was high. For this reason, it seems important that we try out all different types of video games -full body video games, calm video games and action video games- when developing intervention, to see which one reaches best the levels of dopamine needed for sustained attention. As mentioned before, it is important to try out not only action sitting games, but rather games where the full body is used, since they have been successful previously.

4. General long-term and short-term objectives

The long-term goal of this project is to improve the performance at work among high-risk professionals, by testing an intervention that prevents their vigilance decrements

Jobs and activities such as air traffic controllers, surgeons or pilots need the ability to maintain sustained attention -or vigilance- during large periods of time. A decrement on their attention could cause the death or injury of thousands of people, who are under their responsibility. However, our 21st century is competing with our ability to maintain sustained attention; therefore, these professionals might have a hard time when developing their jobs.

Sustained attention has been related to the frontal lobe of the brain, with dopamine, norepinephrine and adrenaline as the main substances associated to it. Consequently, our project aims to measure the optimal levels of these parameters, in order to develop a video game intervention that can be used to enhance vigilance. If the professionals can use the video games in order to set their levels of dopamine and adrenaline to activate sustained attention, the risk of failure in their jobs could be prevented. Thanks to the current research project and application, we aim that high-risk professionals are able to pursue their jobs at a high level of performance and low levels of anxiety or stress, which will, ultimately, preserve thousands of lives.

The short-term goal of this project is to quantify levels of dopamine and adrenaline that occur in vigilance to use such information to develop a video game based intervention to enhance vigilance

Sustained attention has been related to the frontal lobe of the brain. The main neurotransmitter in this process implicated is the norepinephrine, which follows the pathway dopamine-norepinephrine-adrenaline. Hence, this project aims to study the optimal levels of dopamine -for being the precursor neurotransmitter- and the optimal levels of adrenaline -for being the hormone released- that occur when the brain is in sustained attention and the time they can last at optimal levels.

After having measured these parameters, the project aims to develop an intervention with video games for the high-risk professionals above mentioned. This intervention will consist in finding the adequate video game which sets the levels of dopamine and adrenaline into the optimal levels previously found, from a possibility of three video games: full-body video game, calm and relaxing video game, and action video game. After having found the satisfactory video game, the professionals will be able to play it when their vigilance is starting to decrease, which will have been found previously as well. Consequently, playing this video game will help them regain the correct levels of sustained attention, and therefore reduce their decrement.

5. Specific objectives of the proposal

Specific aim 1. We will determine the optimal levels of dopamine enabling the activation of sustained attention

We will determine the levels of dopamine which occur during the process of vigilance. We will recruit 60 participants, n=20 from each one of the jobs mentioned above -air traffic controllers, surgeons and pilots-. Then we will separate the participants in 2 groups. From the participants, n=30 will be from the control group and n=30 will be from the sustained attention group. The n=30 first participants will have their dopamine levels measured at resting stage, while the other n=30 will have this done while they carry out a task requiring sustained attention. Measures will be conducted for 1.5 hours, during 5 different sessions. We will also measure how long dopamine is able to last at optimal levels, before sustained attention decreases. Once all measures have been taken, we will average them out. We hypothesize that dopamine levels will be different depending if the participant is in sustained attention mode or not. Moreover, we aim to quantify the exact level of dopamine which takes place in vigilance status and for how long it lasts. As mentioned before, to measure dopamine we will use PET MRI dopamine measurements. The introduction of hybrid, simultaneous PET/MRI systems will allow us to see the dynamics of the neuroreceptor dopamine signal transmission on the brain (Sander & Hesse, 2018).

Sustained attention will be activated thanks to the Sustained Attention to Response Test (SART). This test is designed to form a simple, controlled and replicable measure of such lapses. In the test, participants view a computer monitor on which a random series of single digits are presented at the regular rate of 1 per 1.15 seconds. The task, therefore, is to press a single response key following each presentation with the exception of a nominated no-go digit, to which no response should be made (Manly & Robertson, 2005).

Specific aim 2. We will determine the optimal levels of adrenaline enabling the activation of sustained attention

In this aim, we want to determine the levels of adrenaline which occur during the process of vigilance. The same 60 participants measured in specific aim 1 will be separated again in two groups: n=30 will be from the control group and n=30 will be from the sustained attention group. The 30 first participants will have measured their adrenaline in resting stage, while the other 30 will have it measured while they carry out a task which requires sustained attention. Measures will be performed during 5 different sessions. We will also determine for how long this substance is able to last at optimal levels, before sustained attention decreases. We hypothesize that the levels of adrenaline will be different depending if the participant is in sustained attention mode or not. Moreover, we aim to quantify the exact level of adrenaline which takes place in vigilance status and for how long it lasts. Since adrenaline is a hormone, it will be measured with a urine test, with the units of measure ng/ml from the International System.

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Specific aim 3. We will determine the type of video game able to induce dopamine and adrenaline release at similar levels as those found previously to enable sustained attention

This experiment will be executed, again, with the same n=60 previous participants of specific aims 1 and 2. Participants will be separated in 3 teams (n=20), each of them playing a different video game: body video game, calm and relaxing video game, and active video game. These video games will be developed by the video game developers of our project. We aim to isolate the following video game properties: movement and action. Therefore, we have chosen one video game which includes full body movement and two which do not include it. Moreover, we have chosen a calm and relaxing video game versus an active one, to understand if the action at the game also plays a role in sustained attention.

6. Materials and methods

Regarding general inclusion criteria for patient recruitment, we will take a group of n=60 participants, n=20 from one of the jobs mentioned above -air traffic controllers, surgeons and pilots-. They will all be between 19 and 75 years old, with an equal representation of women and men -50 per cent of each- and the same representation in all age groups -19 to 37, 38 to 56 and 57 to 75-.

The type of sampling used will be stratified sampling. That is so because the population will be separated by distinct categories or strata -control group and sustained attention group, gender and age group- but in each category, the members will be randomly selected. We have decided to keep a balance both in gender and age because sustained attention is a phenomenon which affects genders and ages similarly; consequently, we want to keep a representation of all categories when analysing the results.

With respect to the first measure -dopamine levels-, this will be carried out with a PET MRI dopamine measurement. This is a technique which introduces hybrid, simultaneous PET/MRI systems, allowing to see *in vivo* the imaging of the dynamics of the neuroreceptor signal transmission of the brain -in our case, dopamine signal transmission-. The PET MRI technique enables both the real time assessment of the dopamine binding to receptors, but also receptor-specific neurotransmission. In it important to note that both PET and MRI are non-invasive techniques, which means that they do not penetrate any parts of the body. The measures will be conducted for 1.5 hours, during 5 different sessions (Sander & Hesse, 2018).

Regarding the specific radiolabelled tracer for the PET/MRI measurement, fluorine-18 PET tracer has been found as a successful tracer when measuring dopamine transporter, serotonin transporter and norepinephrine transporter. For what concerns us -dopamine measurement-, marking with fluorine-18 tracer will be an adequate way to measure the dopamine levels we are willing to quantify (Stehouwer & Goodman, 2009).

Regarding the measure of the adrenaline, since it is a hormone, it will be measured with a urine test, with the units of measure ng/ml from the International System. A urinalysis test is a simple test, which is performed by collecting a urine sample from the patient in a specimen cup. Usually, only small amounts (around 30-60 ml) are required for urinalysis testing. The urine sample can be either analysed in the medical clinic or sent to a laboratory to perform the tests. In the case of this project, a urine catecholamine test will be pursued, which is a test that measures the level of catecholamines or catecholamine metabolites in the urine. Catecholamines are a group of hormones such as dopamine, epinephrine, adrenaline, norepinephrine, amongst others, which can be measured on a urine test. It is important to bear in mind that the normal values of adrenaline on the urinalysis are 5,000 to 20,000 ng after 24 hours of the urine recollection. Again, these measures will be conducted during 5 different sessions (UCLA Health, 2018).

Concerning the video game experiment, the game properties that we want to measure are movement and action. The reason for this choice is that previous studies have demonstrated that full body movement video games can foster the attention of ADHD children. On the other hand, we also aim to understand if action -related with adrenaline levels- plays a role in sustained attention. The video games will be developed by the video game developers participating in the project -in the following pages an explanation about that can be found-. However, these developers shall bear in mind that each video game must have the following characteristics: one body video game, one calm and relaxing video game, and one active video game.

Finally, regarding the SART test, that is a test which will activate the sustained attention of the participants; therefore, we will be able to measure their dopamine and adrenaline levels at the time they are pursuing the test. In the test, participants view a computer monitor on which a random series of single digits are presented at the regular rate of 1 per 1.15 seconds. The task is to press a single response key following each presentation with the exception of a nominated no-go digit, to which no response should be made (Manly & Robertson, 2005).

7. Materials and methods detailed by specific objectives

In the first objective, we aim to determine the optimal levels of dopamine enabling the activation of sustained attention. To do so, we first will choose our 60 participants. The participants chosen will be selected from three professions: air traffic controllers, surgeons and pilots (n=20 from each group). Therefore, we will contact El Prat Airport and the Clinic Hospital in Barcelona, as explained further in the project. Once contacted these associations and randomly selected n=20 people from each profession, we will divide our population into strata -control group and sustained attention group- and assign n=30 participants to each of these groups. The type of sampling will be stratified sampling, and that is so because the population will be separated by distinct categories or strata -control group and sustained attention group- but in each category, the members will be randomly selected. Therefore, the participants will be randomly assigned to each group -control group or sustained attention group-.

With respect to the specific aim 1 of the study, the hypothesis is that dopamine levels will be different depending if the participant is in sustained attention mode or not. Therefore, we aim to quantify the exact level of dopamine which takes place in vigilance status and for how long it lasts. As mentioned before, to measure dopamine levels we will use PET MRI dopamine measurements, using the fluorine-18 PET tracer. The PET/MRI is a hybrid mechanism which allows to see the dynamics of the neuroreceptor signal transmission of the brain. By combining the specificity of PET radiotracers -in our case, fluorine-18 tracer- to neuroreceptors with the MRI signal as a functional readout, we will be able to locate the connections of the brain activity (Sander & Hesse, 2018).

We have decided to study dopamine because it is the only neurotransmitter in the mesolimbic pathway -which we are studying- that does not act as a hormone and that does not cross the blood-brain barrier. Therefore, the study of its action in the brain will be easier, following the techniques we mentioned above (Maechler, 2010).

The tasks carried out will be the following: measuring the dopamine levels on patients which are on resting stage and measuring the dopamine levels on patients which are pursuing the SART test to activate sustained attention. Apart from that, we will measure the time these levels last in the sustained attention participants. These measures will be conducted for 1.5 hours, during 5 different sessions. In other words, we will measure the dopamine levels for 1.5 hours, while one group is only in resting stage and the other one is pursuing the SART test. These measures will be conducted in 5 different sessions, in order to lately cross the data obtained in all the sessions. After having measured both the dopamine levels in resting stage and in sustained attention, we will sum all of them to get an average. Later on, we will compare both of them and determine if the difference is significative. After this process, we will have the result of the levels of dopamine which take place in vigilance status and for how long they last.

With respect to the specific aim 2 of the study, the hypothesis is that the levels of adrenaline will be different depending if the participant is in sustained attention mode or not. Therefore, we aim to quantify the exact level of adrenaline which takes place in vigilance status and for how long it lasts. As mentioned before, we will measure the levels of adrenaline with a urine test, keeping in mind that the normal parameters for adrenaline on urine are 5,000 to 20,000 ng after 24 hours of the urine recollection (UCLA Health, 2018).

The tasks carried out will be the following: measuring the adrenaline levels on patients which are on resting stage and measuring the adrenaline levels on patients which are pursuing the SART test to activate sustained attention. Apart from that, we will measure the time these levels last in the sustained attention. These measures will be conducted during 5 different sessions. After each session of resting stage and SART test, we will take a urine test to the participants. Also, in order to measure the time adrenaline lasts at optimal levels, we will take the urine test right after the session, 30 minutes later and 1 hour later. After having measured both the adrenaline levels in resting stage and in sustained attention and also at different time lapses, we will sum all of them to get an average. Later on, we will compare both of them and determine if the difference is significative, and at what

time adrenaline starts to decrease. Therefore, we will have the result of the levels of adrenaline which take place in vigilance status and for how long they last.

It is important to note that there is a possibility that the video games which will be explained later on, reach dopamine and adrenaline levels to a point where sustained attention is suboptimal. Therefore, it is extremely important to quantify, in the specific aim 2, the optimal and suboptimal levels of dopamine and adrenaline. If we know which are the suboptimal levels, we will be able to determine which levels we should surely not allow dopamine and adrenaline to be at when we decide which video game is the most suitable. Moreover, there is the possibility that one of the video games designed releases both neurotransmitters but in different ratios. In this case, we will try to find the specific video game which activates both neurotransmitters at their optimal levels, even if they are different. The aim is to find a video game which can reach the optimal levels for both dopamine and adrenaline, even if they are different.

Furthermore, it is relevant to note that in both the specific aim 1 and 2 of the project, we will use the SART test to activate the participant's sustained attention. As explained before, in this test the participants view a computer monitor on which a random series of single digits are presented at the regular rate of 1 per 1.15 seconds, where they have to press a single response, with the exception of a nominated no-go digit, to which no response should be made. Because of the structure of this test, individuals must remain sufficiently attentive to their responses so that, at the appearance of a target, they can induce a motor response; therefore, it becomes a very powerful tool to enhance sustained attention (Manly & Robertson, 2005).

Finally, in regard to the specific aim 3, we aim to understand which is the video game which best activates the levels of dopamine and adrenaline needed to maintain sustained attention. The game developers of our project will develop three different video games: one full body video game, one calm and relaxing video game, and one active video game. That is because our aim is to isolate the game properties of movement and action.

In order to avoid biases, we will rotate the teams three times, so that all the participants will play out the 3 video games in counterbalanced order in blocks of 30 minutes each. We will monitor their levels of dopamine and adrenaline after having played 30 minutes of the video game each time. Finally, we will analyse all these outcomes to conclude which is the video game which best reaches the dopamine and adrenaline levels required for sustained attention.

To carry out this last procedure, we will randomly separate our participants in three groups. Each group will rotate 3 times, so that all the participants get to play the 3 video games in counterbalanced order. They will play these video games in blocks of 30 minutes each. While they play, we will monitor their levels of dopamine and adrenaline, with the same measures mentioned before. Finally, we will analyse all these outcomes to conclude which is the video game which best reaches the dopamine and adrenaline levels required for sustained attention.

The characteristics of the video games will be the following. The first video game will be a body video game, which involves a full movement of the body. For instance, a game similar to Wii Sport could be a very suitable one. In this game, the players have to move their body in order to play the five sports which are included in the game: tennis, baseball, bowling, golf, and boxing. Since we want to isolate the property "movement" to see if it has an impact in the dopamine and adrenaline levels, we have chosen a video game that involves a full-body movement.

The second video game will be a calm and relaxing video game. For instance, one similar to Flower video game could be a really suitable one. The aim of this game is to awaken calm emotions, while participants propel a flower petal into the air using control moves. Since we want to isolate the property "movement", we have chosen a video game which includes very few movements to be able to compare it with the previous one. Also, since we want to isolate the property "action" we have chosen one which does not include a lot of action, to compare it with the third video game.

Finally, the third video game will be an active video game, but which does not include full-body movement. One possible video game could be one similar to Xenowerk, where the participants have to play against the clock to stop a plague that is taking over the world. That is because we also want to isolate the property “action”, which needs to be compared with the second video game, and this video game includes a big amount of it.

The video game developers will extract the most relevant properties of each of the three previously mentioned games to create games that have similar properties to the aforementioned ones: playing a sport through interaction with the whole body, playing a quiet game with few stimuli and playing a game that requires speed but no body movement. After the experiment, one of the three video games will be selected as the successful one, and the one which can increase dopamine and adrenaline to their suitable levels. The examples of the three video games can be found at the annex.

It is also important to note that we have chosen that participants play video games because they increase the levels of dopamine and adrenaline. Dopamine gets activated when pleasure is being experienced. Through the route dopamine-norepinephrine-adrenaline, both dopamine and adrenaline get release (Bressan & Crippa, 2005). Video games are a pleasant experience for people, because they let them engage with the world around them and they bring lots of challenges and rewards. Moreover, since adrenaline is also released when stress levels are increased, we expect that it will also be released, due to the stress that video games cause, bringing people to overcome the challenges that they offer. Therefore, it is expectable that video games will activate the aforementioned pathway of dopamine-norepinephrine-adrenaline (Gee, 2005). In the annex, two figures regarding the topics we just stated can be found. The first one explains the pleasure pathway, which activates dopamine, and the second one explains the stress pathway, which activates adrenaline.

The objective of the video games will be to generate the correct levels of dopamine and adrenaline for a period of time long enough so that the workers can maintain the sustained attention until the next work break comes. The goal is, therefore, to find the video game that is able to maintain sustained attention for the time -observed in the specific aim 1 and 2- that dopamine and adrenaline can be maintained at optimal levels. For instance, if dopamine can be maintained at optimal levels for an hour, then participants should play the video game until they have activated dopamine and adrenaline at its optimal levels, and then they will be able to maintain these levels for one hour. That means that workers will need a work break every hour, where they play again the suitable video game, so that they can get back to work with the needed sustained attention levels again.

8. Possible project’s breakthroughs

I have identified four possible bottlenecks which might occur in this project: one methodological, one experimental and two logistic. Considering the methodological one, it might happen that sampling does not occur as random as we want it to. For instance, if we advertise the study only in specific sectors of the Clinic Hospital in Barcelona, we might only get participants who work in a specific speciality -for instance, only cardiothoracic surgeons or neurosurgeons-. To solve it, we will allocate a large part of our budget to marketing campaigns, and we will spread them throughout all the hospital, to make sure that all the sectors we are willing to obtain are covered.

In reference to experimental difficulties, some people might not feel comfortable with urine test, or may be having urethra difficulties. In order to solve it, we will have an alternative measured as a back-up, which will be launched if a participant asks for another measurement or is not responding well to the urine test. To measure the adrenaline -which is a hormone-, we can also use a blood test.

Finally, we find two possible logistic issues. Firstly, the relationship with the hospital where we will execute the study. It is possible, for instance, that the equipment we need in a specific day is

occupied, or that we are not provided with all our necessary material. To solve that, I believe that the relationship with the hospital is crucial. From a beginning, we will set the list of our material and the hours in which we will occupy it. We will also ensure a good relationship with them by having weekly meetings, where we can comment on issues, make demands and listen to their queries. Secondly, we might encounter a number of dropouts while the study lasts. Sometimes patients may get tired of the study, change residence or lose interest. To prevent that from happening, on the one hand we will make participants sign an agreement at the beginning of the study, and we will explain to the importance of participating during the 30 months that the study will last. However, it is possible that dropouts still occur. Therefore, on the other hand we will hold a waiting list, so we can incorporate more people in case there is a withdrawal.

9. Calendar distribution of phases and milestones by specific goals

TASK ID	TASK TITLE	START DATE	DUE DATE	DURATION	% OF TASK	MONTH 1-5					MONTH 5-10					MONTH 10-15					MONTH 15-20					MONTH 20-25					MONTH 25-30					MONTHS 30-36						
						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
1	Prepare the study conditions																																								
1.1	Hospital where study is developed	01-01-21	01-02-21	31																																						
1.2	Design of the stratified sampling methodology	01-02-21	15-02-21	14																																						
1.3	Advertisements to collect participants	15-02-21	15-03-21	28																																						
1.4	Participants' selection and information	15-03-21	15-05-21	61																																						
1.5	Guidelines	15-05-21	30-05-21	15																																						
1.6	Project initiation	30-05-21	30-06-21	31																																						
2	Determine optimal levels of dopamine when vigilance																																								
2.1	Preparation electrodes and measurements	30-06-21	15-08-21	46																																						
2.2	Measurement participants control group	15-08-21	15-10-21	61																																						
2.3	Measurement participants sustained attention group	15-10-21	15-12-21	61																																						
2.4	Determinatio optimal levels of dopamine	15-12-21	01-02-22	48																																						
2.5	Determination duration of dopamine in optimal levels	01-02-22	15-04-22	73																																						
3	Determine optimal levels of adrenaline when vigilance																																								
3.1	Preparation urethra tests and measurements	15-04-22	01-06-22	47																																						
3.2	Measurement participants control group	01-06-22	01-08-22	61																																						
3.3	Measurement participants sustained attention group	01-08-22	01-10-22	61																																						
3.4	Determinatio optimal levels of adrenaline	01-10-22	01-11-22	31																																						
2.5	Determination duration of adrenaline in optimal levels	01-11-22	01-12-22	30																																						
3.6	Algorithm optimal dopamine and adrenaline vigilance	01-12-22	01-01-23	31																																						
4	Intervention to determine the optimal video game																																								
4.1	Testing of the first video game	01-01-23	01-02-23	31																																						
4.2	Testing of the second video game	01-02-23	01-03-23	28																																						
4.3	Testing of the third video game	01-03-23	01-04-23	31																																						
4.4	Algorithm: optimal video game for vigilance	01-04-23	01-08-23	122																																						
4.5	Results and distribution	01-08-23	30-12-23	151																																						

10. Potential scientific, clinical, social and technological impact of the proposal

This project has great scientific, clinical and social potential. In reference to the scientific and clinical, the proposal will determine the optimal levels of dopamine and adrenaline in order to activate sustained attention. The concept of sustained attention has become such an important issue in this 21st century, since it is something which is decreasing rapidly due to multitasking and the multiple stimuli we live around with. Therefore, I believe that understanding more about it, as well as comprehending the key features to activate it, can be crucial in order to enhance it and to help people not to diminish it.

On the other hand, the project has a big impact on the social level. As it was mentioned before, the inability to maintain sustained attention is competing with the capacity to perform well in plenty of jobs, especially in these such as air traffic controllers, surgeons or pilots. Not being able to accomplish these jobs with excellence can cause a big impact in people's lives, leading to serious injuries or even deaths. The possibility to increase sustained attention in these professionals can be a strong release of stress for them, who will also be able to perform much better as well as not risk lives of thousands of people.

Furthermore, it is interesting to combine an innovative solution -video games- with the clinical research in this project. Even though a myriad of solutions have been proposed to increase sustained attention -meditation, yoga, sports, exercise, caffeine, etc-, I believe it is interesting that this project proposes a video-gaming one. I believe the project has an interesting impact because of its interdisciplinary approach, since it combines scientific, clinical, video-gaming and social disciplines to give a solution to one problem. In the 21st century, it has been claimed that knowledge and solutions will necessarily need to integrate a wide array of fields and people from different backgrounds working together. It is for this reason that this project stands as indispensable. Working with interdisciplinary teams can lead to much more creative results, hence it is possible that, when the project is developed in reality, solutions which we have not contemplated in this proposal or synergies which we have not foreseen might appear.

11. Justification of the team of researchers and institutions involved

Regarding the institutions chosen for the project, we need to take into account three different kinds of institutions: hospitals, the research team and entities to collect participants. To do so, we will follow two guidelines which will help us decide: proximity and professionalism.

Concerning the hospital chosen, after having studied some of the most important Spanish hospitals, the Clinic Hospital in Barcelona has been selected. This hospital appears as the first institution in Catalonia rankings, thanks to its seriousness, experienced personnel and great deal of machines. For this reason, we believe that a wide array of equipment will be found there, as well as large rooms to work, qualified professionals with whom to interact with, and maturity and excellence when handling our project.

Regarding the research team, we will need doctors -preferably neurologists-, statisticians and video game developers. As for the doctors, we will contact a strong team of neurologists. Following our first guidelines -proximity and professionalism-, we have decided that we will contact the Neurology Service of the Clinic Hospital in Barcelona. That is one of the pioneer services in the country, created in 1972 and nowadays forming part of the Clinical Institute of Neurosciences, from Spain. Their webpage is the following: https://www.clinicbarcelona.org/servicio/neurologia. The team is formed by an efficient and qualified team who carry out plenty of services, such as investigation, teaching and training. Before starting our project, we will contact them in order to meet, create network and expose our project. If the project sounds appealing to them, we will be able to count on some of the researchers to work with us in our project. They which will be in charge the medical and clinical aspects of it.

In reference to statisticians, we have followed the same guidelines as before, thus found the GRBIO, the Biostatistics and Bioinformatics Research Group from the University Politècnica of Catalonia (Barcelona), with the following webpage: https://www.eio.upc.edu/en/recerca-en/research-groups/grbio-research-group-in-biostatistics-and-bioinformatics. Their main goal is to promote joint research in biostatistics and bioinformatics in both applications and development of new methodologies. Therefore, they address complex interdisciplinary issues and make relevant scientific contributions on health and biology, which are areas where closer collaboration is needed to promote future development and welfare of the society. Moreover, they also carry out clinical trials and develop statistical and computer tools for the exploitation of the results of biomedical research. Following the same procedure outlined before, we will contact them in order to meet, create network and expose our project. If the project sounds appealing to them, we will hire some of its statisticians to work in our project, since we will need a strong team analysing the data results obtained from the studies we have carried out with the participants.

Concerning the video game developers, we have been lucky to discover that Catalonia leads the video game industry, which is growing by 23% every year (Ayén, 2019). Along these lines, the company Social Point has been found as one of the leading edges on this sector. Their webpage can be checked out here: https://www.socialpoint.es/. Along their vision, they work fast and

embracing change in the gaming industry, while they cooperate and work in cross-functional teams. Since we really value professionalism and they define themselves with the values “proactivity, accountability and ownership”, we believe they could be a great fit in our project. As usual, and following the same procedure outlined before, we will contact them in order to meet, create network and expose our project. If the project sounds appealing to them, we will hire some of its game developers to work in our project, which will be in charge of proposing and developing the three most suitable video games to play, following our three categories: body video game, calm and relaxing video game, and active video game.

Finally, concerning the participants, we need 60 types of participants, 30 from each group: air traffic controllers, surgeons and pilots. In order to find the air traffic controllers and the pilots, we will contact the only airport which is available in our area: El Prat Airport. In order to find the surgeons, we will contact the ones in the Clinic Hospital in Barcelona, since they will be extremely close to where we are doing our project, and therefore, they follow the criteria we established at the beginning. These two enterprises will have the task to get in contact with the participants who will be randomly selected to participate in our study.

12. Approximate budget and justification of items

13. List of tasks	Items and number	Price item	Number months	Total
Salaries				**336,000€**
	2 doctors	2,000€/month	36 months	144,000€
	2 statisticians	2,000€/month	36 months	144,000€
	2 video game developers	2,000€/month	12 months	48,000€
Material rented from the hospital				**7,800€**
	PET/MRI	400€/month	18 months	6,000€
	Urine tests	100€/month	18 months	1,800€
Participants				**48,000€**
	60 participants	60€/month/parti.	10 months	36,000€
	Transportation	20€/month	10 months	12,000€
Equipment				**42,300€**
	Computers	400€/month	36 months	14,400€
	Offices’ rent	700 €/month	36 months	25,200€
	Advertisement	300€/month	5 months	1,500€
	Material for video games	400€/month	3 months	1,200€
Others				**5,400€**
	Publications	300€/month	6 months	1,800€
	Contingencies	100€/month	36 months	3,600€
Total				**439,500€**

14. Project's ethical implications

Regarding the ethical implications, we will not find many in our project, since all the procedures used are non-invasive techniques. However, informed consent from all the participants must be obtained, which will consist of an explanation of the study and its phases, so that patients sign off in agreement. It is crucial that patients are aware of the procedures practised on them at all times and it is also important that all the professionals working in the study maintain an open mindset and availability to answer any query that a participant might have.

Concerning data protection, it is important that we follow the newest Data Protection procedures from the European Union (EU) which, without the intention of giving too detailed and tedious information, can be found on the GDPR official website, which is available here: https://europa.eu/youreurope/business/dealing-with-customers/data-protection/data-protection-gdpr/index_en.htm. The GDPR sets out detailed requirements for companies and organisations on collecting, storing and managing personal data, and it applies both to European organisations that process personal data of individuals in the EU as well as to organisations outside the EU that target people living in the EU.

Finally, another ethical issue might arouse, which is the intervention technique that we will use. Some people may argue that playing video games could be a way to cover up our root problem, which is the difficulty of maintaining sustained attention. Therefore, some people may claim that perhaps a more ethical solution is to reduce multitasking or the big quantity of stimuli we live around with. To counteract this argument, on the one hand we believe that it is very difficult to eliminate the number of stimuli we live with, since that would be a battle against the whole structure of the society. On the other hand, if there are people that, while the study is being conducted, consider that video games are not a good tool for them and, in addition, they feel that video games are being counterproductive in their wellbeing, it will be accepted that they withdraw from the study, while we would look for substitution.

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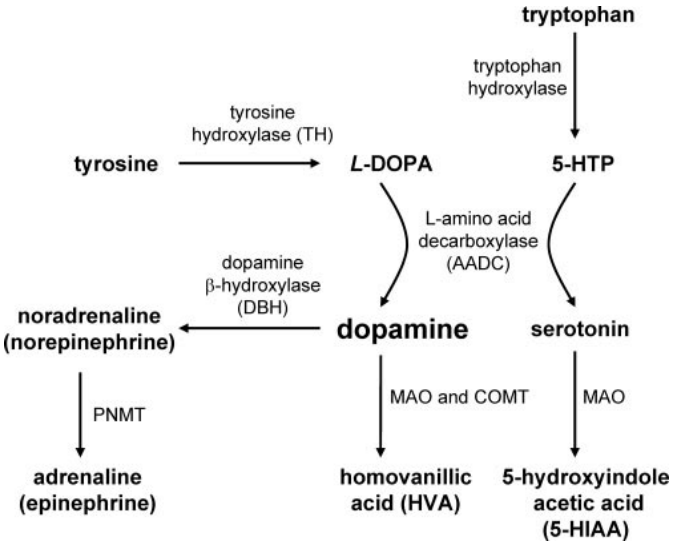
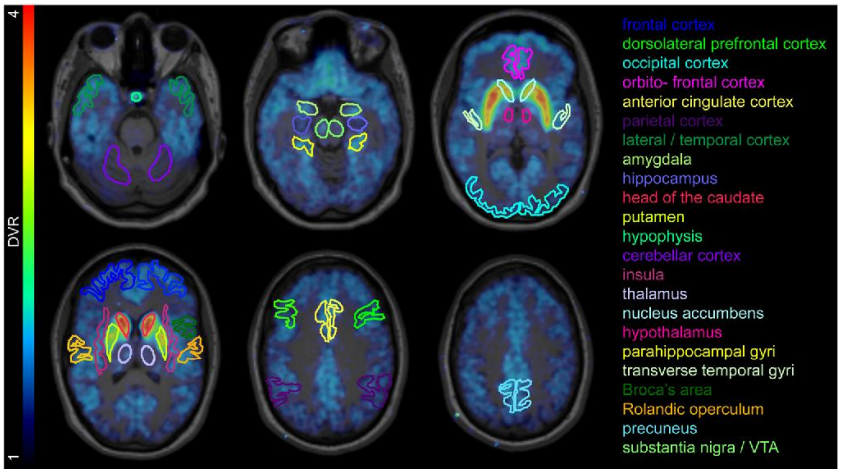
16. Annex

Epinephrine synthesis



Source: Rubí, Blanca & Maechler, Pierre. (2010). Minireview: New Roles for Peripheral Dopamine on Metabolic Control and Tumor Growth: Let's Seek the Balance. Endocrinology. 151. 5570-81. 10.1210/en.2010-0745.

Dopamine measurements using PET/MRI imaging



Source: Kaller, S., Rullmann, M., Patt, M., Becker, G., Luthardt, J., Girbardt, J., Meyer, P.M., Werner, P., Barthel, H., Bresch, A., Fritz, T.H., Hesse, S., & Sabri, O. (2017). Test-retest measurements of dopamine D1-type receptors using simultaneous PET/MRI imaging. European Journal of Nuclear Medicine and Molecular Imaging, 44, 1025-1032.

First game proposed: full-body video game: Wii Sports

Source: Rhodes, Marc (2020). The 25 Greatest Sports Video Games of All-Time. https://newarena.com/other-sports/ranked-the-25-greatest-sports-video-games-of-all-time/

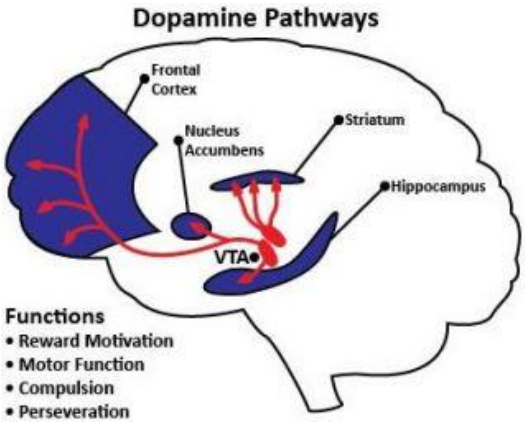
Second game proposed: calm video game: Flower

Source: Geoff (2012). Flower Review. http://4pgames.net/1776/reviews/flower

Third game proposed: action video game: Xenowerk

Source: Pixelbite Games (2019). Xenowerk Tactics. https://www.youtube.com/watch?v=IVXqyk3S6SY

Dopamine activation: pleasure releases dopamine



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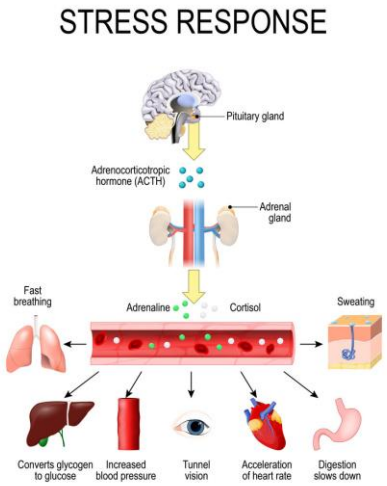
Stress activation: stress releases adrenaline



Source: Vector Stock (2016). Activation of the stress system. https://www.vectorstock.com/royalty-free-vector/activation-of-the-stress-system-vector-23522600