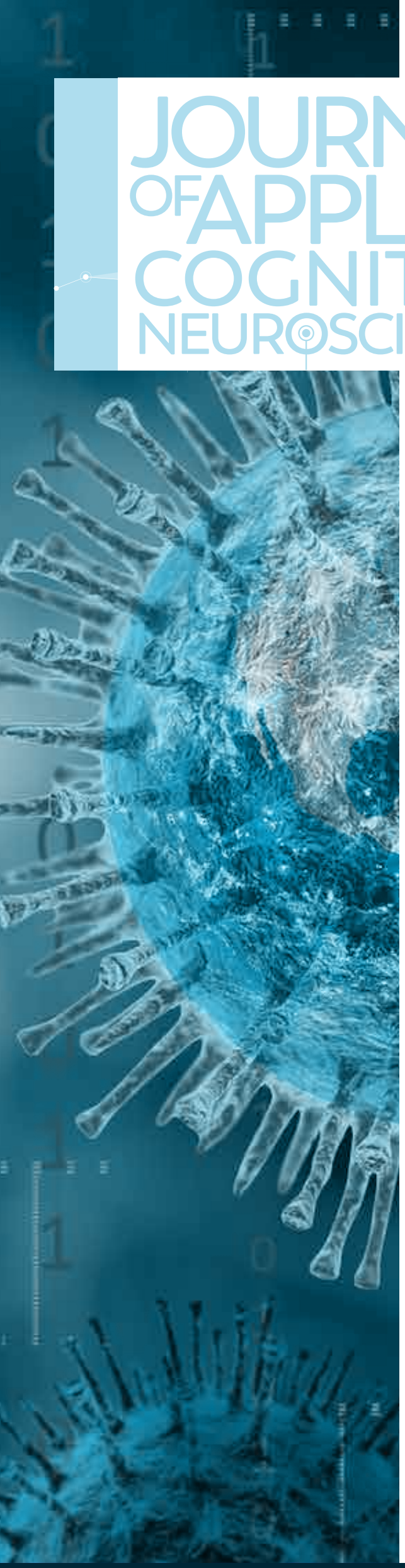

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Editorial

Neurosciences and Neuro post-COVID-19

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COVID-19 pandemic is the world's greatest public health concern, at the same time with various stages depending on the regions. At the moment of this Editorial (01/06/21), 170 million people have been confirmed cases, which represents 2% of the population of the entire planet. World Health Organization-WHO estimates that 20% of the population has been infected and the numbers continue to grow (WHO, s.f.). Currently, three of the five countries with the highest number of cases are in Latin America (Brazil, Argentina, and Colombia) (Johns Hopkins University & Medicine, s.f) (Figure 1).

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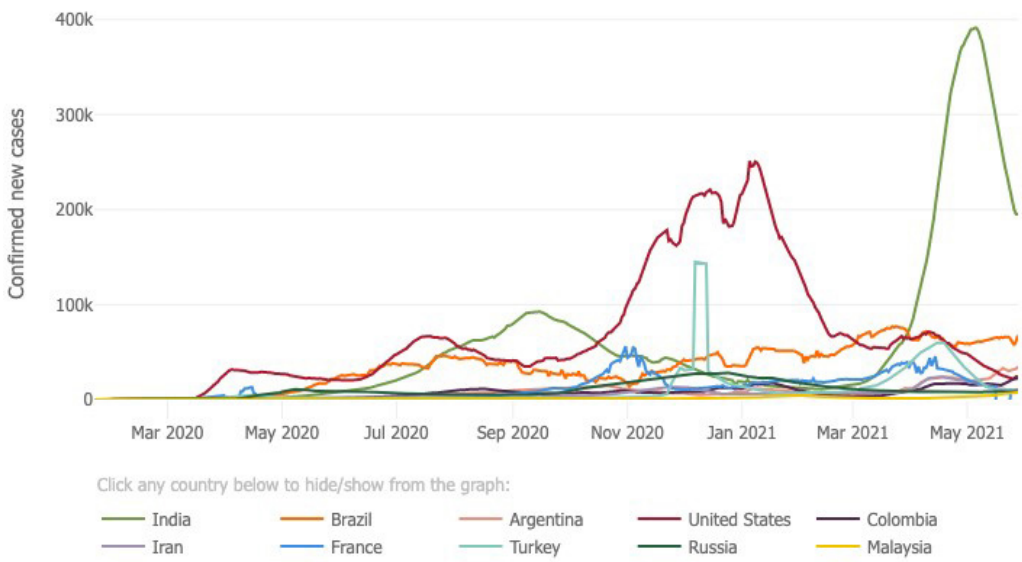

Figure 1. Daily Confirmed New Cases: Outbreak evolution for the current most affected countries (date 01/06/21).
Source: Johns Hopkins University & Medicine (s.f.).

Public health has faced several key problems that this infection generates, on the one hand, the severity of the respiratory syndrome and with it the need for intensive care and the increase in morbidity and mortality; and on the other hand, the contagiousness of the picture that generates a rapid rise in the number of cases saturating the response capacity of the health system. Thus, the known effects of the virus were limited to a respiratory condition of variable severity.

At present, it is recognized that this situation will have an impact on health motivated by the virus itself and the described condition, an impact on the delay of the treatment of acute pathologies due to the saturation of the system (called the second wave of impact), a third impact motivated by the decompensation of chronic pathologies such as Alzheimer's disease or cardiovascular disease (hypertension, diabetes, dyslipidemia, etc.) that have not received the necessary control and a fourth wave due to psychiatric disorders that the catastrophic experience and the emotional impact of certain measures such as lockdown can bring in the long term (Allegri & Sevlever, 2020) (Figure 2).

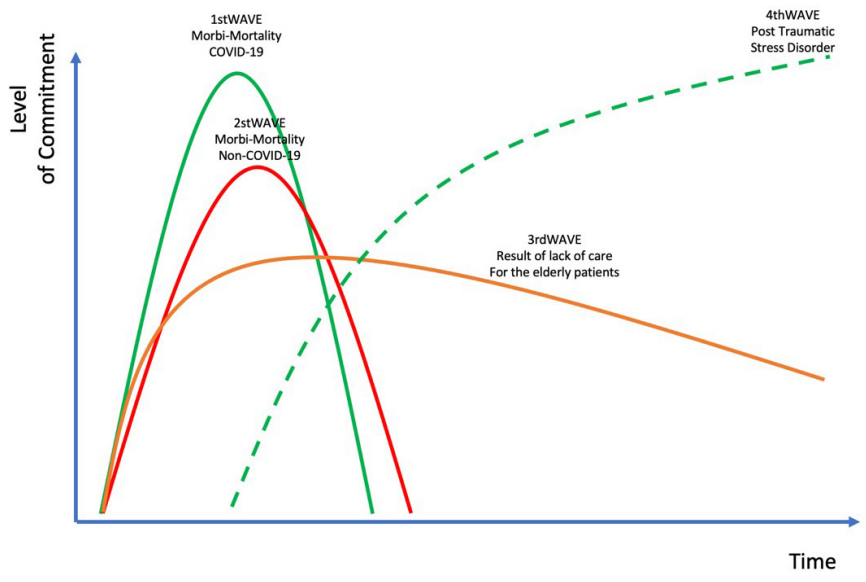

Figure 2. The four issues not to forget in Pandemics.
Source: Authors.

Despite this exhaustive theoretical scenario, the virus is considered a monophasic and acute entity, and its long-term impact on health are estimated based rather on system deficiencies or on the effects of the strategies implemented to reduce the first wave. However, there is no evidence, and it has not been considered in most scenarios, about the possibility that the virus could have a long-term impact, as it could increase the prevalence of certain syndromes and thus affect health general in a kind of five waves.

The absence of this evidence, on the other hand, is not necessarily an indication that these complications do not exist, only that this is a unique moment in the history of medicine where there are no previous experiences to assess it. However, other pandemic experiences in the past showed the possibility that these complications are a real problem and that they occur in the plan of neurological manifestations

A paradigmatic case was the Spanish influenza virus epidemics. Neurological complications as sequelae of influenza infection have been documented for more than a century. Henry, Smeyne, Jang, Miller & Okun (2010) reported in a historical review, a document on Spanish influenza in 1918 where an association between neurological disorders, and the pandemic was established, detailing a temporal relationship between influenza outbreaks and meningitis, poliomyelitis and poliomyelitis encephalitis. Other neurological manifestations such as lethargic encephalitis and post-encephalitic Parkinsonism have been closely associated with the Spanish influenza pandemic.

On the other hand, there is also evidence of neurological complications in other Coronavirus epidemics. During the outbreaks of severe acute respiratory syndrome (SARS) in China (Tsai, Hsieh & Chang, 2005; Xu et al., 2005; Lee et al., 203) and the Middle East Respiratory Syndrome-MERS in Saudi Arabia (Saad et al., 2014; Kim et al., 2017) neurological signs and symptoms were reported both in acute form (encephalitis, polyneuropathy, stroke, seizures, etc.) and subsequent neurological complications (neuropathies, myopathies, fatigue, myalgia, weakness, depression, and cognitive impairment), and varying degrees of evidence linking them directly with the viral infection. These become relevant in the theoretical framework due to the enormous similarity between the genome of both viruses and SARS-CoV-2 (the causal agent of Covid-19), as well as the transmission mechanism and clinical manifestations. This leads to thinking that some of this evidence is "transferable" when thinking about the future scenario of the pandemic by covid-19 (Figure 3).

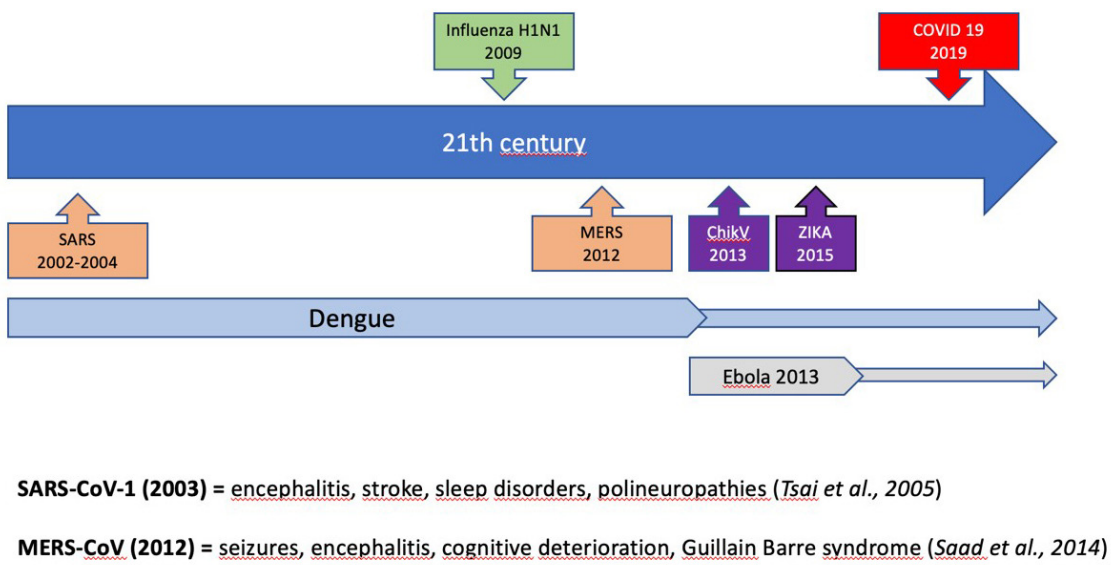

Figure 3. Pandemics in the 21th century.
Source: Authors.

With the previously mentioned results, it is expected to find neurological involvement in patients with covid-19. In the context of a pandemic with a wide population diffusion, it is difficult to determine whether the symptoms detected are causality associated with the virus or simply concomitance; however, it is important to specify the findings that can clarify the neurological effect of the virus.

In this COVID-19 pandemic context, there are 3 types of neurological complications (Table 1):

Table 1.
Neurological Complication due or concomitant to COVID-19 pandemics.

Patients with previous neurological diseases	Dementia, Alzheimer`s Disease, Parkinson's Disease
Neurological complication in the context of acute COVID	
Due to acute COVID	Anosmia, ageusia, stroke, encephalitis, Guillain Barre syndrome, neuropathies etc…
Patients in Critic Care	Stroke, myopathies, neuropathies, etc.
Neuro Post COVID	
Long COVID	Headache, fatigue, anosmia, ageusia, cognitive impairment, sleep disorders, dizziness, motor paresis, neuropathies, etc.
Post COVID	Parkinsonism, Alzheimer, etc.

Source: Authors.

Patients with neurological diseases before the pandemic such as those with dementia in whom there is a greater risk of morbidity and mortality due to Covid-19 infection.

This is because they are elderly patients and in these patients, the general morbidity and mortality of the virus is higher than in young patients (probably explain by the decline immune response or because they are confined in long term care homes or residences for the elderly where the chance of contagion is greater or even due to genetic predisposition as occurs with APOE e4 genotype (for which homozygosity is associated with Alzheimer disease and with severe COVID-19 illness.

Patients with neurological complications in the context of acute Covid.

In this case, the neurological complications may be due to the direct neurotropic effect, or to the indirect secondary impact induced by the virus, in terms of immunity, hypoxia, hypertension, systemic inflammatory reaction and other mechanisms, or to the frequent complications of the critical patient in intensive care units beyond of the causes.

So it can be divide in:

a. Acute Neuro-Covid linked to Covid infection: anosmia, ageusia, cerebrovascular accident, encephalitis, Guillain Barre syndrome, Myopathies, Neuropathies, etc.

b. Acute neurological symptoms not linked to the virus: neurological symptoms or disease related with the Critical Patient: cerebrovascular accidents, fatigue, myopathies, etc.

The clinical complications related to acute COVID-19 involve the central and peripheral nervous systems. Regarding the central nervous system, headache has been reported in various series at a variable frequency between 89 and 98% of cases, sometimes as part of the febrile syndrome but in 22% of cases as the first manifestation of the infection.

One of the most characteristic acute conditions is anosmia. Due to the enormous frequency of this symptom, Li, Bai & Hashikawa (2020) suggested that the viral neurotropism of COVID-19 could cause the invasion of the olfactory nerve, the rhinencephalon and then the brainstem acting as one more cofactor that would explain the typical respiratory failure of COVID-19.

There is sufficient evidence to ensure that COVID-19 may increase the risk of venous and arterial thromboembolism associated with inflammation, hypoxia, immobilization, and diffuse intravascular coagulation (Varga et al., 2020). There are few case series still reported but the evidence seems to suggest that there is an increased risk for a cerebrovascular disease that appears to exceed the aforementioned mechanisms (Li et al., 2020). Microvascular inflammation or increased platelet aggregation determined by alterations in virus-specific inflammation mediators have been suggested as possible causes.

A striking finding is the presence of cortical symptoms in patients infected with COVID-19. Helms et al. (2020), reported 58 patients with severe COVID-19. Neurological findings were found in 84% of patients at ICU admission, including agitation (69%); signs of the corticospinal tract (67%), such as hyperreflexia, clonus, and bilateral extensor plantar responses (Babinski sign); added to delirium in 65% of cases. The presence of any neurological symptom, sign, or disease increases 37% the mortality (Beghi et al., s.f.). In one study, delirium was present in 73% of COVID+ patients with pre-existing dementia (Beghi et al., s.f.) (Figure 4).

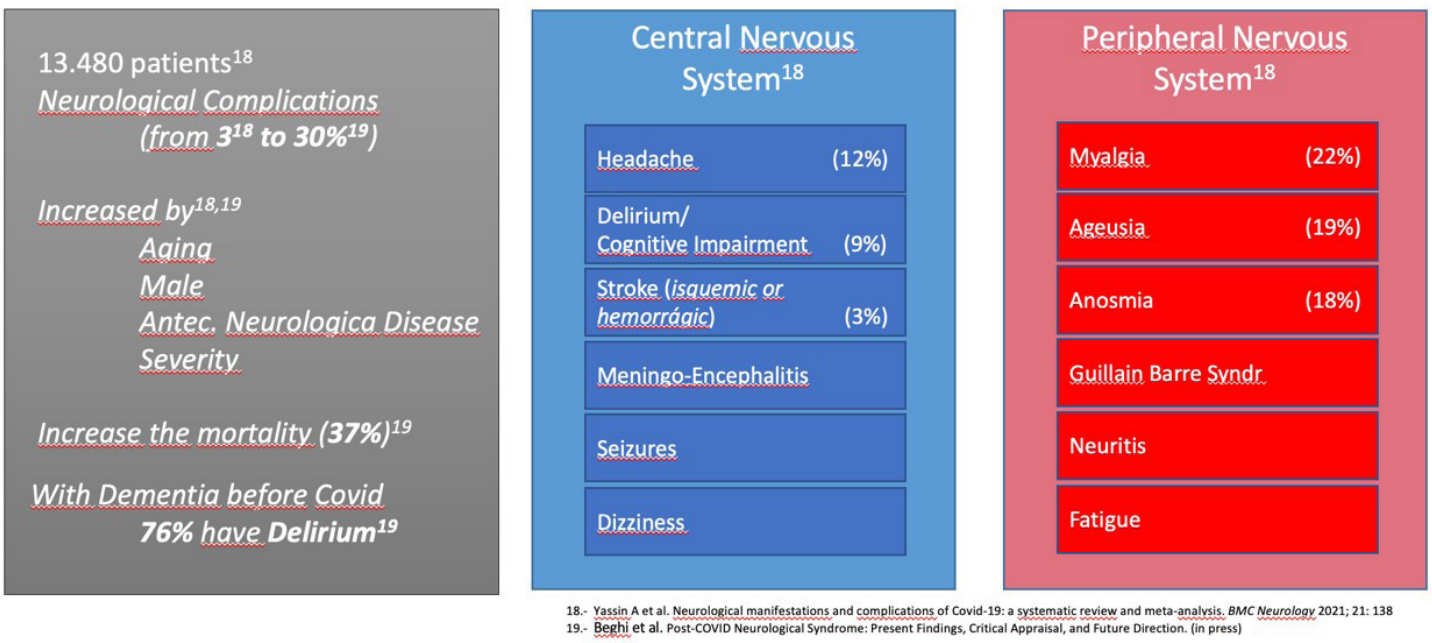

Figure 4. Neurological Findings in Acute COVID-19.
Source: Authors.

Patients with long-term neurological sequels of Covid-19

In recent months, persistence, worsening, or new appearance of neurological symptoms have been described at 3 and 6 months after the acute episode (Taguet et al., 2021; Huang et al., 2021; Nersesjan et al., 2021).

At present, a specific phenotype that would specify a post-COVID (long-COVID) neurological syndrome has not yet been identified. However, registries and other surveillance systems have been activated in several countries, including follow-up visits, and will serve as important sources for the investigation of neurological disorders resulting as sequelae of this viral infection or occurring de-novo once the acute phase has elapsed (Begui et al., s.f.).

Huang et al. (2021) found 20% neurological manifestations at 6 months, with 63% fatigue and muscle weakness, 26% sleep disorders, 24% gait disorders, and 23% anxiety and depression21. Nersesjan et al. (2021) evaluating patients who were hospitalized in intensive care units, 45% had neurological disorders at 3 months, 31% encephalopathy, 28% cognitive impairment, 13% polyneuropathy, 11% gait disorder, 11% tetraparesis.

In the study by Taquet et al. (2021) out of 236, 370 patients at 6 months, the global incidence of neurological and psychiatric pathologies was 33% of those infected with symptoms, in those who were admitted to intensive care units the incidence was 46% and in those who had encephalitis 62%. These authors showed a higher frequency of ACV, nerve, nerve root or plexus disorder, myoneural or muscle disease, dementia, mood, anxiety, or psychotic disorder.

Although the majority of people infected recover within weeks, many people experience persistent symptoms. Persistence of symptoms relating to COVID-19 infection for more than 28 days after diagnosis is Long COVID (Mendelson et al., 2020) and development of new symptoms or impairment of existing symptoms is named Post-COVID. Other authors define Long COVID or post-acute COVID (symptoms beyond 3 weeks) and chronic post-COVID syndrome (beyond 12 weeks) (Halpin, O'Connor & Sivan, 2020).

30% of post-COVID patients have shown poor concentration, cognitive impairment, behavioral changes, and psychological symptoms called "brain fog" (Stefano, Ptacek, Ptackova, Martin & Kream, 2021). They describe cognitive functions that are energy sensitive become functionally disruptive, but we don't know the causes or treatments.

In one COVID-19 pandemic that affects more than 20% of the world population, with an uncertain but significant neurological impact on long-term health, we must ask ourselves what the correct approach to long-term or post-COVID-19 will be. Probably we need a multifaceted approach to tackle the post-COVID, a multidisciplinary team including neurology, psychiatry, neuropsychology, psychology and cognitive rehabilitation. Health systems around the globe needs to develop Post COVID clinics to prevent a future tsunami of chronic neurological disability (Halpin et al., 2020).

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Research

Does caffeine matter for arousal? Affective and autonomic responses induced by caffeine in coffee intake: evidence from a double-blind tasting task

¿Importa la cafeína para la excitación? Respuestas afectivas y autónomas inducidas por la cafeína en la ingesta de café: evidencia de una tarea de degustación doble ciego

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Abstract

Coffee is consumed worldwide, but there are different types of espresso blends, each with its unique concentration of caffeine, which can have different effects on the human being. The aim of this study was to understand the effect of the impact of caffeine on the autonomic nervous system, evaluating the physiological changes and subjective responses due to different levels of caffeine intake. A double-blind tasting task consisting of one within-subject factor design (caffeine level: high / double caffeine mixture (blend A) vs single-charge caffeine mixture (blend B) vs low-caffeine mixture (blend c) allowed us to assess participants' autonomic responses using Heart Rate Variability (HRV) and Pupillary Reactivity (PR). Arousal was also assessed through the Self-Assessment Manikin (SAM). Results revealed statistically significant differences in HRV and PR between coffee blends, showing the blend A,a more pronounced autonomic response that blend C. However, no significant differences were found in arousal level among coffee blends. These results are similar to previous research that pointed out to a discordance between subjective and objective measures when caffeine is consumed.

Keywords: Affective valence; Caffeine; Autonomic response; Pupil response; Heart rate variability.

Resumen

El café se consume en todo el mundo, pero existen diferentes tipos de mezclas de expreso, cada una con su concentración única de cafeína, que puede tener diferentes efectos en el ser humano. El objetivo de este estudio fue comprender el efecto del impacto de la cafeína en el sistema nervioso autónomo, evaluando los cambios fisiológicos y las respuestas subjetivas debido a los diferentes niveles de ingesta de cafeína. Una tarea de degustación doble ciega, que consiste en un diseño de factores intraindividuales (nivel de cafeína: mezcla de cafeína alta/doble (mezcla A) vs mezcla de cafeína de carga única (mezcla B) vs mezcla baja en cafeína (mezcla C), nos permitió evaluar las respuestas autónomas de los participantes utilizando la variabilidad de la frecuencia cardíaca (VFC) y la reactividad pupilar (RP). La excitación también se evaluó mediante el Self-Assessment Manikin (SAM). Los resultados revelaron diferencias estadísticamente significativas en la VFC y la RP entre las mezclas de café, mostrando la mezcla A respuesta autonómica más pronunciada que mezcla C. Sin embargo, no se encontraron diferencias significativas en el nivel de excitación entre las mezclas de café. Estos resultados son similares a investigaciones anteriores que señalaron una discordancia entre medidas subjetivas y objetivas en el consumo de cafeína.

Palabras clave: Valencia afectiva; Cafeína; Respuesta autonómica; Respuesta pupilar; Variabilidad de la frecuencia cardíaca.

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Introduction

Coffee consumption is a worldwide phenomenon (Hewlett & Wadsworth, 2012) and the most commonly consumed beverage in the world (Graham, 2001). The caffeine present in coffee is said to be a lipophilic molecule which easily crosses the blood-brain barrier, and increases neurotransmitter concentration in the brain, therefore is designated as a central nervous system stimulant. The average amount of caffeine consumed in the U.S. population has remained constant at approximately 300 mg per person per day (Liu & Song, 2015). The global retail coffee market has shown significant growth over the past 5 years (about 2.3% per year), having represented around USD 86.5 B and 5.9 M tonnes in 2018. From the roasted bean and ground segments, capsules represent 64% of market and presented an average annual progression of 3.1% between 2013 and 2018. This growth is more accentuated in unidoses solutions such as capsules, being this the product of greatest growth expected until 2024. This pace of growth in coffee consumption encourages companies in the sector to expand their product portfolio, through innovative solutions that provide new consumption experiences, and to spread their brands through strategies that support internationalization and market diversification. The caffeine present in coffee is said to be a lipophilic molecule which easily crosses the blood-brain barrier, and increases neurotransmitter concentration in the brain, therefore is designated as a central nervous system stimulant.

The effects of caffeine intake on humans

Caffeine's greatest effect takes place in the basal ganglia, where its inhibitory action on adenosine receptors and synergistic effect with dopamine turn off pathways which act to restrict motor activation signals in the brain. High caffeine doses induce adenosine antagonism and phosphodiesterases inhibition, interacting with the sympathetic nervous system and inducing ß1-receptor activation. This results in positive inotropic and chronotropic effects, accountable for an augmented heart rate and conductivity (Cappelletti, 2015). In fact, higher concentrations of caffeine increase intracellular cAMP and cyclic guanosine monophosphate (cGMP) by a nonspecific phosphodiesterases inhibition, which affects cardiac contractility secondary to calcium release.

An extensive body of literature has examined the effects of caffeine on mood, which showed that increases in low doses of caffeine resulted in increases in subjectively reported positive affect (Brunyé, Mahoney, Lieberman & Taylor, 2010; Smith & Rogers, 2000). Caffeine also appears to provide significant ergogenic effects on muscle strength and power (Grgic, Trexler, Lazinica & Pedisic, 2018). Apart from mood and exercise effects, few studies on affective modulation and emotional processing when correlated with autonomic response were found in the literature. In general, after drinking coffee, consumers report feeling more energetic, imaginative, efficient, confident, alert, and focused, as well as motivated and socially active (Griffiths & Mumford, 1995). Recent meta-analysis studies showed benefits of caffeine intake in providing significant ergogenic effects on muscle strength and power (Grgic et al., 2018), significantly increase isokinetic strength

(Grgic & Pickering, 2019) enhance components of anaerobic performance (Grgic, 2018), a protective effect on the decreasing risk of depression (Grosso, Micek, Castellano, Pajak, & Galvano, 2016; Wang, Shen, Wu & Zhang, 2016), reduction for various health outcomes at three to four cups a day, like lower risk of incidence of cancers and neurological, metabolic, and liver conditions.

A meta-analysis showed significant ergogenic effects of caffeine intake on maximal muscle strength of upper body and muscle power (Grgic et al., 2018). Caffeine's pro-arrhythmic effects at high doses are supported by animal studies (Mehta, Jain, Mehta & Billie, 1997; Balasubramaniam, Chawla, Grace & Huang, 2005), which have been performed with higher doses of caffeine and evaluation by invasive techniques. Numerous physiological and epidemiological human studies have investigated the link between caffeine and both atrial and ventricular arrhythmias (Pelchovitz, Goldberger, Jeffrey, & Goldberger, 2011), but results are not always in consonance.

The acute toxic level of caffeine is not well established, but for adults it is approximately 10 g/day, which is comparable to a consumption of approximately 100 cups of a regular espresso coffee (Greden, 1974). The consumption of caffeine is also known to increase a person's cardiac minute volume and cardiac index (Corti et al., 2002; Cano-Marquinaa, Tarínb & Canoc, 2013) and can also bind directly to the vascular smooth muscle cell receptors and, through similar mechanisms, cause vasodilation (Echeverri, Montes, Cabrera, Galán & Prieto, 2010). Caffeine was shown to be capable of delaying parasympathetic recovery but did not influence the behaviour of the respiratory rate, oxygen saturation or frequency-domain HRV indices (Gonzaga, Vanderlei, Gomes & Valenti, 2017; Gonzaga, Vanderlei, Gomes, Garner & Valenti, 2019) These effects are more pronounced in irregular caffeine consumers compared to regular consumers, who show minimal effects of caffeine on the cardiovascular system (Izzo, Ghosal, Kwong, Freeman & Jaenike, 1983). Caffeine intake produces a higher rise in diastolic blood pressure than in systolic blood pressure, which may be due to the antagonistic binding of caffeine on adenosine receptors, which results in vasoconstriction (Sudano et al., 2005; Smits, Lenders & Thien, 1990). A moderate ingestion of caffeine (100 mg) reveals no decrease in digital blood flow measurement (Knight, Pagkalos, Timmons & Jose, 2015), while higher doses of caffeine can result in an accelerated heart rate, but these effects are not common in people who consume caffeine regularly. In fact, there is evidence that the habitual consumer of caffeine develops a tolerance to its cardiovascular and neuroendocrine effects (Lane, Adcock, Williams & Kuhn, 1990; Lane, Pieper, Phillips-Bute, Bryant & Kuhn, 2002).

Further, caffeine produces mild autonomic nervous system arousal and improved mood when compared to a non-caffeinated placebo (Quinlan et al., 2000; Cappelletti, 2015). Despite several research studies that addressed coffee intake and its influence on various aspects of human life, few of them were done using the minimum quantities needed for the physiological effects to be registered. One of these studies, performed by Smit & Rogers (2000), aimed to measure the effects of small doses of caffeine (0 mg, 12.5 mg, 25 mg, 50 mg, and 100 mg) on cognitive performance and mood. The authors reported that, even in small doses, caffeine consumption resulted in improved cognitive

task performance. However, individuals who consumed caffeine habitually had larger gains in cognitive performance than those who only consumed caffeine occasionally. In another study, Brunyé et al. (2010) addressed the effects of different doses of caffeine (0 mg, 100 mg, 200 mg and 400 mg) on attention, showing that caffeine consumption produced an increase in alertness and in the performance of executive tasks. The best performance was achieved with 200 mg of caffeine on one intake or more (Brunyé et al., 2010).

Caffeine can also affect the cardiovascular response to physical activity. Normally, during physical activity, both heart rate and blood pressure increase. However, regular caffeine intake has a stabilizing effect on blood pressure, which provokes a small increase in baseline values and therefore only a modest increase during physical activity (smaller than for non-coffee drinkers) (Höfer & Bättig, 1993; 1994; Grgic, 2018). Recent studies show that caffeine ingestion increases resting cardiac autonomic modulation (Sarshin et al., 2020). With or without the taste of coffee, the caffeine effects on autonomic arousal, respiratory response, and reported alertness are well known. Caffeine, after ingestion, is absorbed by the gastrointestinal tract in approximately 45 minutes, and its concentration in the blood is highest approximately one hour after ingestion. With a half-life of between two and a half hours and four and half hours, caffeine is present in the bloodstream for about six hours after ingestion (Nehlig, 2010). However, some studies indicate that the effects of the substance are felt almost immediately, only a few minutes after ingestion (Adan, Prat, Fabbri & Sànchez-Turet, 2008). One of the most common effects reported after caffeine intake is the feeling of thirst. However, regular coffee drinkers develop a tolerance to that sensation, thus not experiencing an increase in thirst when drinking coffee (Smith & Rogers, 2000). Caffeine significantly induces regulators of mitochondrial biogenesis and oxidative metabolism, suggesting that induced physiological levels of caffeine appear to enhance cell metabolism (Schnuck et al., 2018).

There is a growing interest in the use of Heart Rate Variability (HRV) (Nathelson, 1985; Marães, 2010; Benjamim et al., 2020) and pupillary response (PR) as measures of autonomic activity (Lovallo et al., 2004; Grant & Ker, 2008; Bouffard, 2019) linked to affective and autonomic processing (Bradley, Miccoli, Escrig & Lang, 2008). HRV is a non-invasive method to assess autonomic functioning of the heart from a simple electrocardiogram recording. HRV is manifested by the variability between successive heart beats (R-R intervals), which reflects the sympathetic and parasympathetic activity of the autonomic nervous system. Pupillary activity, that is, contractions and dilations of the pupils, is also thought a reliable autonomic index and it can be recorded without any attachments to the body, through an eye-tracking system (e.g., Esteves & Rosa, 2019). However, evidence from these studies has been contradictory (Wilhelm, Stuiber, Lüdtke & Wilhelm, 2014). Moreover, studies assessing the impact of caffeine on the cardiovascular, pupillary and affective systems simultaneously while tasting coffee are not common. As we know, the knowledge about the sensory and perceptual properties of caffeine has theoretical importance as well as practical implications for coffee producers. Therefore, the main goal of the present study was to gain a deeper understanding how caffeine intake

impacts on the affective and autonomic response while tasting some commercial Portuguese espresso coffee blends, in particularly a blend that has enriched caffeine content (double charge). We pretend to verify whether the advertising claim that a "double shot" of caffeine has double the impact on the human body and brain is true, and whether a double shot is more satisfying for consumers.

We propose that the level of caffeine intake affects the affective system (arousal) and autonomic responses, so that higher levels of caffeine should lead to a higher level of arousal, an increased cardiac and pupillary activity (Wilhelm et al., 2014; Woo & Kim, 2015), so we formulated the following hypotheses:

1. Higher Pupillary Reactivity (dilatation) on blend A compared to other blends.
2. Higher SDNN for blend A than for other blends.
3. More pronounced sympathetic-vagal balance to blend A in comparison to the other blends.
4. Higher subjective arousal for blend A compared to the other blends.

Methodology

Participants

Our study consisted of a convenience sample of 20 volunteers. Of these, 60% were women (n= 12) and 40% were men (n = 8). The mean age was 40.41 years old (SD = 9.18), ranging between 22 and 56 years. Only one participant was not Portuguese (1.7%, Russian) but he has been living in Portugal for several years. With regard to the coffee consumption habits, all participants reported being regular consumers who have no brand preferences and who do not have a capsule machine for making coffee. On average, participants referred to consume 3.1 coffees (SD = 1.29) per day and they have been consuming coffee for an average of 22.26 (SD = 8.31) years. Concerning the control of caffeine intake before our task, participants referred they had not drunk coffee for an average duration of 5.9 hours (SD = 6.81). All participants were Portuguese and reported normal medical history with no hearing or visual problems. Participants were treated in accordance with the American Psychological Association's ethical code (APA, 2010).

Instruments and measures

A short Google Docs form was created in order to collect socio-demographic data (nationality, gender, age, occupation) as well as information regarding to the participants' coffee-drinking habits. The arousal, as subjective affective dimension, was assessed by using the Self Manikin Assessment (SAM; Bradley & Lang, 1994). The SAM is a pictorial measure that assesses affective responses to stimuli in the dimensions of pleasure and arousal (pleasure was not evaluated in this study) (Figure 1).

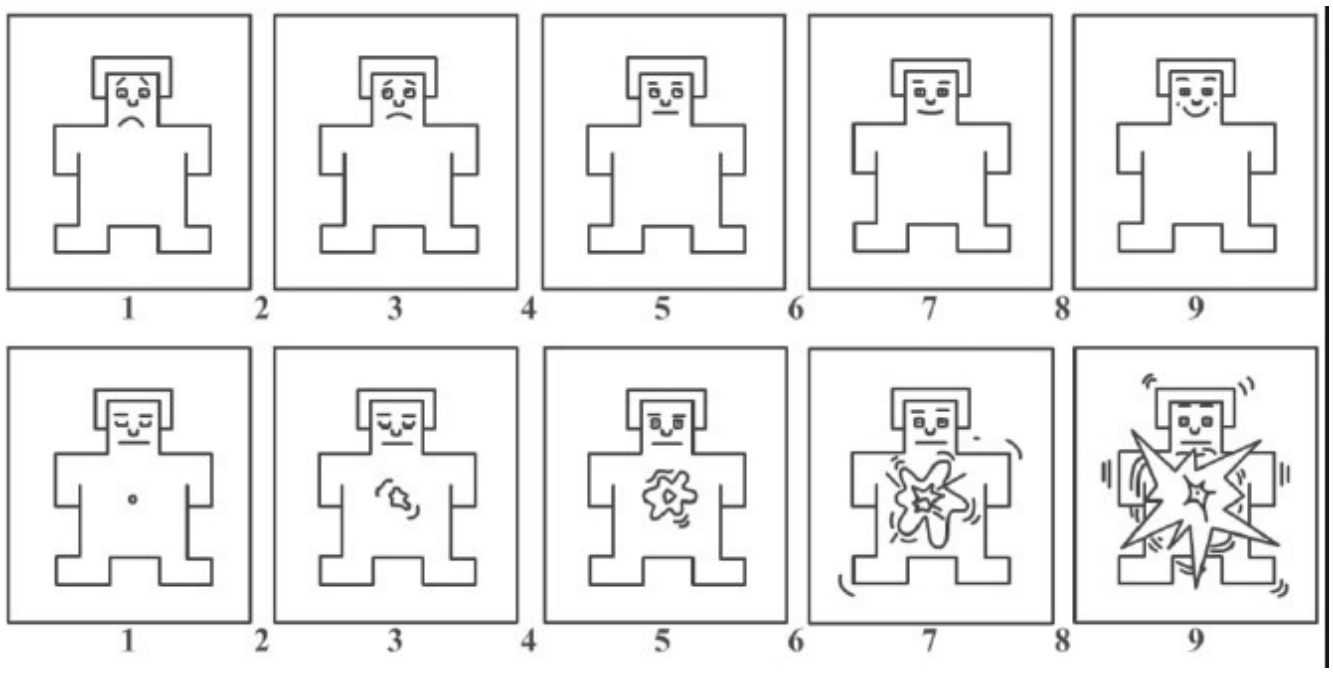

Figure 1. The Self-Assessment Manikin (SAM) measures of pleasure (top panel) and arousal (bottom panel)
Source: Authors.

Autonomic physiological indices

Two physiological indices, namely the Heart Rate Variability (HRV) and Pupillary Reactivity (PR) were examined in order to objectively assess the impact of caffeine intake on the autonomic system during the double-blind tasting task. The literature suggests HRV and PR to complement the limitation of the SAM because they reflect the state of autonomic nervous system (Carvalho & Rosa, 2020; Rosa et al., 2020).

Experimental Procedure and Apparatus

The study was conducted in one session at the neurosensory laboratory of the CATA-A (Castelo Branco – Portugal) as follows: 1) reception and general information was given to participants, 2) completion of the consent form, 3) assembly of electrodes for ECG recording, 4) eye tracker calibration; 5) the random assignment to different experimental conditions, that is, a different tasting order. Participants were instructed to remain as still as possible and to look at the eye tracker monitor throughout all the phases within the task. The SAM was applied three minutes after the consumption of each coffee blend. All blends were in espresso capsule form, dispensed by calibrated machines. Three commercial Portuguese coffee blends, particularly a blend that has enriched caffeine content (double charge) and referred to as blend A, a blend B was a normal blend from the same brand company and blend C was the direct equivalent to blend B, but from the main competing brand/company in the Portuguese market. The characteristics of the examined blends are shown at Table 1.

TABLE 1.
Caffeine level for each coffee blend.

Coffee Blend	Caffeine (mg/100ml)	Caffeine for Espresso Cup (mg/35ml)
Blend A	414,34	145,02
Blend B	281,42	98,50
Blend C	202,94	71,03

Source: Authors.

The double-blind tasting task was conducted by two technicians who had no knowledge about the study main goal. The dispensing of coffee was performed in accordance with the established technical standards. After drinking each coffee blend, participants performed a blind tasting evaluating the arousal-eliciting capacity of the tasted stimuli. They tasted 35 ml of each coffee blend and rated their arousal (one question: "How much aroused you were after drinking this coffee blend?" using a nine-point Likert scale. At the end, participants were thanked and dismissed. The participants took an average of 20-25 minutes to complete the task. The participation activity sequence is shown in Figure 2.

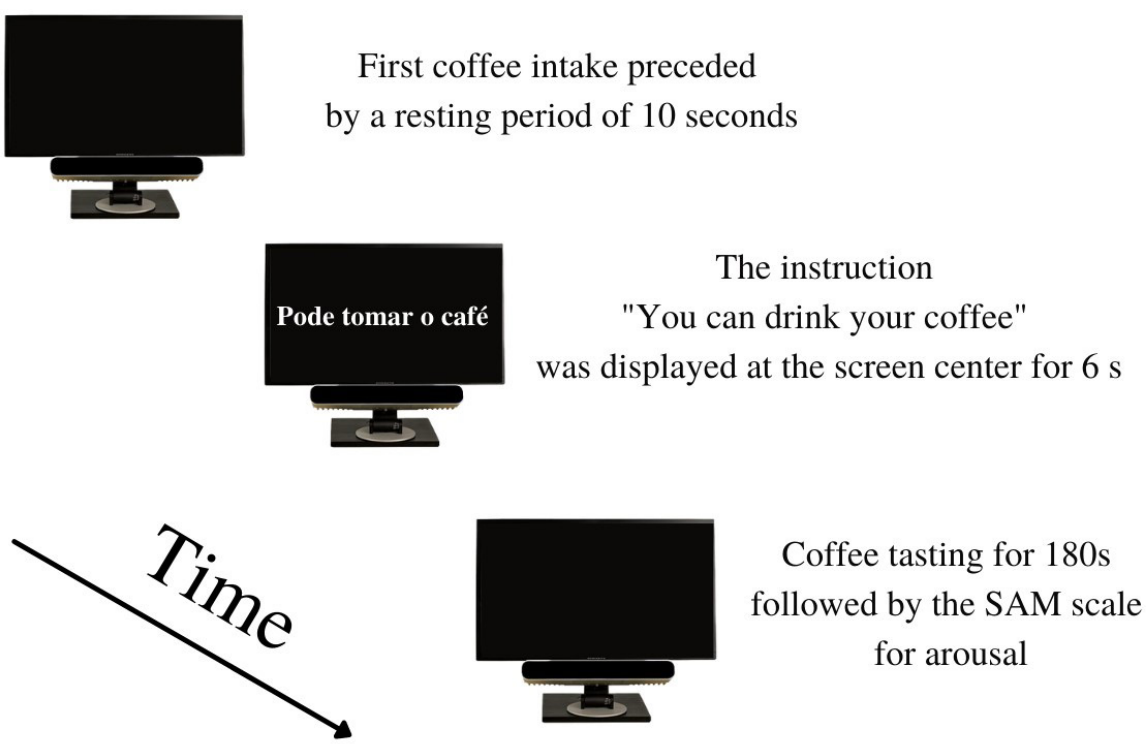

Figure 2. The sequence of the experimental task.
Source: Authors.

Cardiac activity was performed using the plugged version of the BITalino (PLUX Wireless Biosignals, 2020). The BITalino is a wireless realtime biosignals acquisition unit with multimodal sensors (Figure 3).

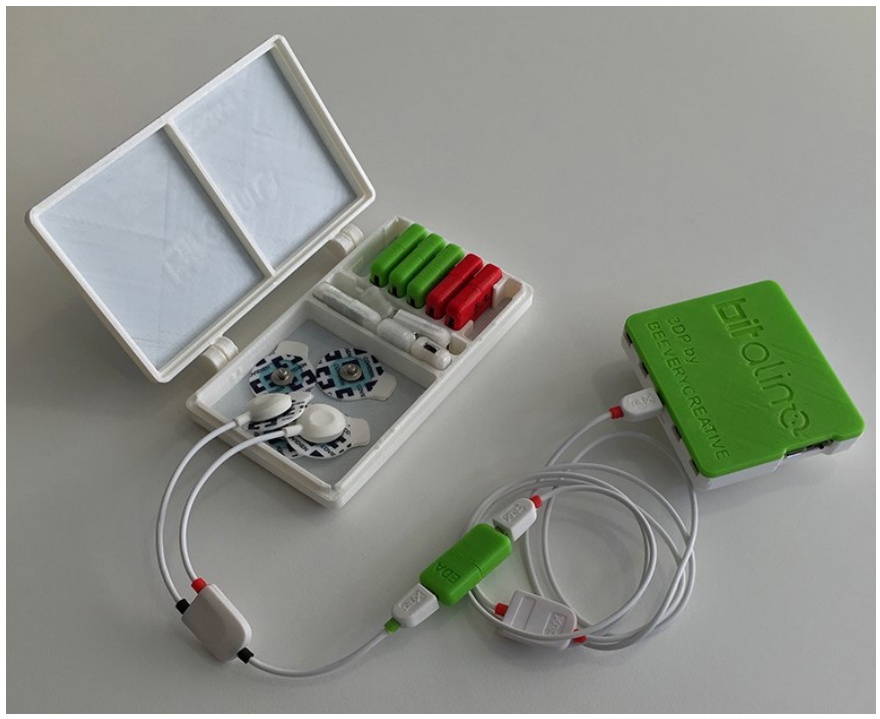

Figure 3. BITalino Acquisition Unit (plugged version).
Source. Authors.

The measurement of cardiac activity was performed using a bipolar montage, using three clip-in disposable electrodes (+, -, ground) with a sodium chloride (NaCl) based electrolytic paste. These electrodes were placed on the chest area near the heart, forming the Einthoven triangle. The electrocardiogram was recorded at 1000 Hz with the Open Signals recording software (Plux) shown in Figure 4. A manual trigger was sent via a light (lux) sensor from BITalino.

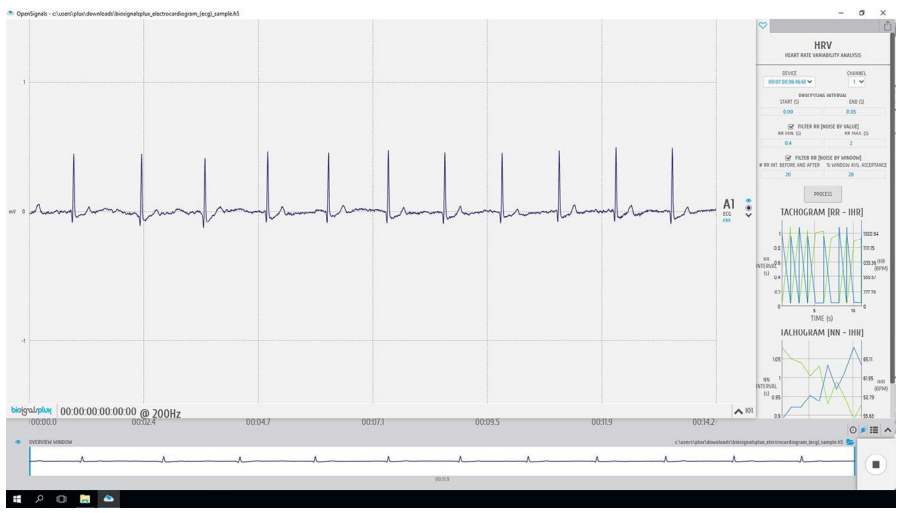

Figure 4. Cardiac activity recorded via Opensignals software.
Source: Authors.

Pupillary activity was continuously recorded at a 500 Hz sampling rate with an average accuracy of 0.5° of visual angle through the SMI (Sensometric Instruments, GmbH, Germany) RED500 eye-tracking system. All instructions were presented visually via the SMI Experiment Suite 360, a stimuli presentation program that is packaged with the SMI (Sensometric Instruments) RED500 eye-tracking system. This system, connected to a 22" LCD monitor and a Dell Intel Core2Duo laptop computer. A specific trigger was automatically built via light sensor at the beginning of each event (three in total). This allowed the computation of the baseline for both autonomic indices. Eye tracking calibration was performed using a 9-point system (Rosa et al., 2016). Participants were instructed to keep still in order to keep a distance of 60 cm from the centre of the screen during the task (e.g., Rosa et al., 2015; Rosa, 2017; Rosa, Castrillón, Castillo, Piedrahita & Díaz, 2018).

Data reduction and statistical analysis

Only 10% of the electrocardiograms (n = 2) presented excessive noise and therefore, were excluded from the analysis. Due to differences in sampling rate, PR and HRV data were analyzed separately, thus avoiding up-sampling and/or down-sampling of either measure. Eye blinks, ocular deviations, and outliers (± 3 SD) were removed from the pupillary activity raw data and linearly interpolated for each trial (Rosa, Esteves & Arriaga, 2015). Pupil artifacts were randomly distributed across experimental conditions. Pupil data was converted from pixels to millimeters and then exported individually to the software AcqKnowledge (v. 4.1). Pupil data was smoothed with a digital filter (FIR) low-pass 4Hz (Hamming windowing) with 500 coefficients. PR was evaluated based on the pupil dilation ratio. This ratio was calculated by dividing the maximum value of pupil size, measured during 180s after caffeine intake, by the maximum value of pupil diameter, measured 5s before caffeine intake. To examine the effects of caffeine intake on PR, the 180s period was subdivided into three segments of 60 seconds (Paschoal, Petrelluzzi & Gonçalves, 2002). Before spectral analysis for HRV, artifacts were detected, identified, and excluded from the analysis. Frequency bands (Very Low Frequency 0 Hz – 0.04 Hz; Low Frequency 0.04 Hz - 0.15 Hz; High Frequency 0.15 Hz - 0.4 Hz; Very High Frequency 0.4 Hz - 3.0 Hz) were analysed. The Power Spectral Density (PSD) was obtained using Fourier Fast Transform (FFT) with a Hamming windowing and a linear filter. The sympathetic-vagal balance was calculated automatically by the standard formula (LF/HF). All autonomic indices were analyzed through the software Acknowledge (v. 4.1).

All of the statistical analysis was done using the IBM SPSS Statistics (v. 20.0) for Windows. Parametric tests were applied due to its robustness to violation of the normality assumption (Marôco, 2010). The Pearson-Bravais correlation coefficient was performed to analyse linear relations between variables. Univariate analysis was conducted using t-tests and one-way ANOVAs. Multivariate analyses were performed using ANOVA for repeated and mixed measures. The Greenhouse-Geisser correction was used to report significant results. The Bonferroni correction was applied for multiple comparisons of means. All statistical tests were performed for a significance level of 0.05 (Stevens, 1992).

Results

Assessment of potential confounders

In order to identify potential confounders, the coffee consumption habits between male and female volunteers were compared. Results revealed no statistical differences for coffee consumption between males and females (Table 2).

Table 2.
Mean, standard deviation and respective significance tests for caffeine intake indicators by gender.

	Male (n = 8)		Female (n = 12)		t
	M	SD	M	SD	
Average daily coffee intake.	3.33	1.44	2.75	1.04	–0.987
Years of consumption.	21.25	6.89	24.00	10.71	–0.685
How many hours ago did you have your last coffee?	5.58	6.75	6.38	7.50	–0.246

Source: Authors.

Pupillary reactivity (PR)

The first step of our analysis was to examine whether the pupil diameter at baseline did not differ among coffee blends. Two repeated-measures ANOVAs showed neither significant difference in mean pupil size [F (2.38) = 0.434, p = 0.620] nor in maximum pupil size [F (2.38) = 1.51, p = 0.233] at baseline. Subsequently, a repeated-measures ANOVA showed no significant differences in PR between coffee blends [F (2.38) = 1.23, p = 0.304]. To examine potential differences in PR between the three distinct moments (0s-60s, 60s-120s; 120s-180s) during caffeine intake, a 2-way repeated measures ANOVA [3 (blends) × 3 (moments)] was performed.

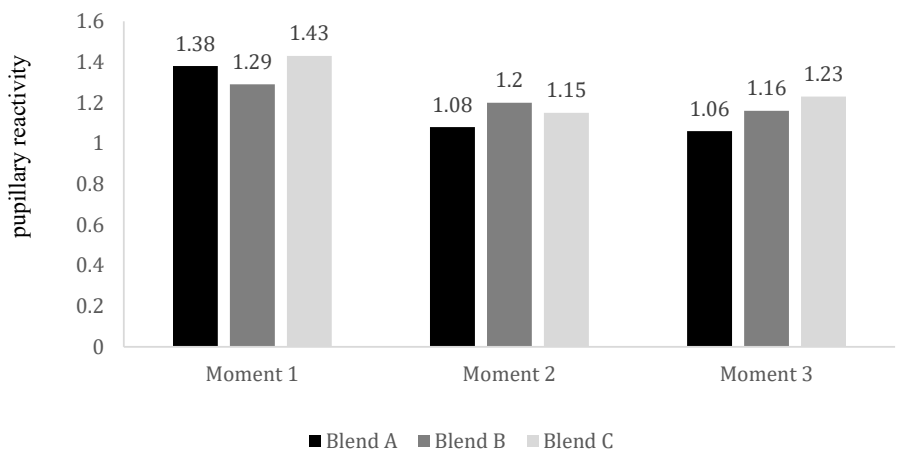

Figure 5. Pupillary reactivity (PR) as a function of coffee blend and moment (0s-60s; 60s-120s; 120s-180s).
Source: Authors.

Results showed a significant effect for the different moments [F (2.38) = 17.55, p < 0.001], with a more pronounced PR at the first moment (M = 1.37) than at the second (M = 1.14) and at the third (M = 1.15) moments, independently of the coffee blend. However, there were no differences between the second and third moments. There were neither significant main effects nor interaction effects (all ps > 0.05) (Figure 5).

Heart rate variability (HRV)

As for pupil dilation, it was examined whether the participants had similar SDNN baseline values for the three coffee blends. Results indicated no significant differences in SDNN between the at baseline for the three blends F (2.38) = 1.66, p = 0.210. Right after, the SDNN ratio (SDNN during the caffeine intake (180s - before caffeine intake SDNN) was computed for each moment, and a mixed ANOVA was performed. Results showed significant differences in SDNN ratio between coffee blends [F (2.17) = 7.190 p = 0.005], presenting the blend A a significant higher SDNN (M = 0.01) than blend B (M = –0.07), but not than blend C (M = –0.001) (see Figure 6). There were no other significant main or interaction effects.

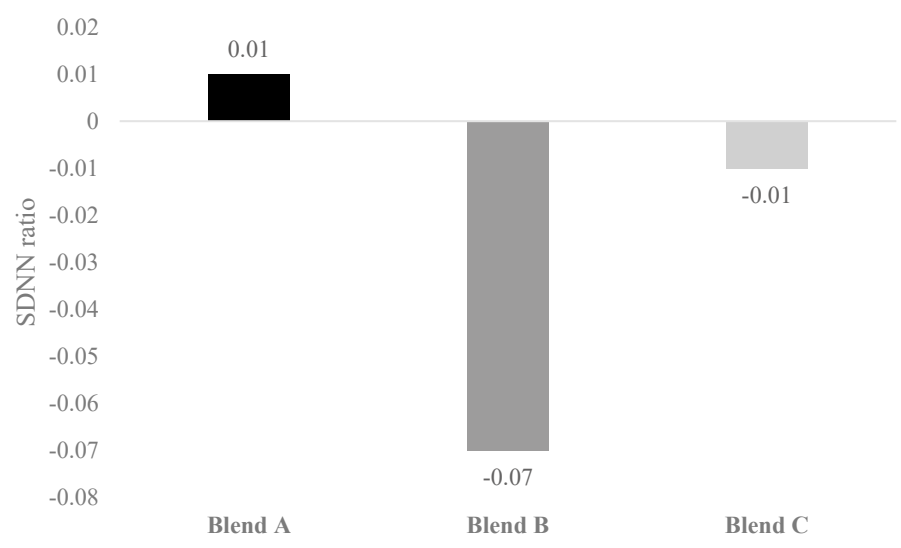

Figure 6. SDNN Ratio across blends.
Source: Authors.

In order to analyse the sympathetic-vagal balance, the HRV index (i.e., low- frequency divided by the High-Frequency power (LF / HF)) was computed. The repeated measures ANOVA showed significant differences in the sympathetic-vagal balance between the three coffee blends [F (2.38) = 19 700 p < 0.001] as shown in Figure 7.

Blend A showed significantly less sympathetic-vagal balance (M = 1.60) than blend C (M = 6.77). However, there were no significant differences between blend A and blend B.

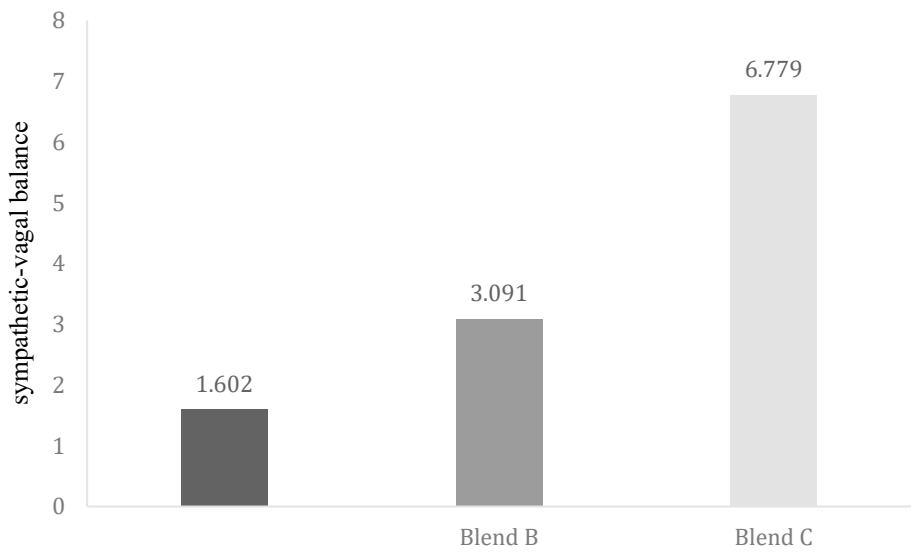

Figure 7. Sympathetic-vagal balance between coffee blends.
Source: Authors.

Subjective arousal

A repeated measures ANOVA was conducted in order to examine whether subjective arousal was different between coffee blends. Results showed marginally significant differences [F (2.36) = 2.62 p = 0.087] between the three blends. A tended to be perceived as more stimulating/arousing (M = 6.31) than blend C (M = 5.31), but not than blend B (M = 6.26) (Figure 8).

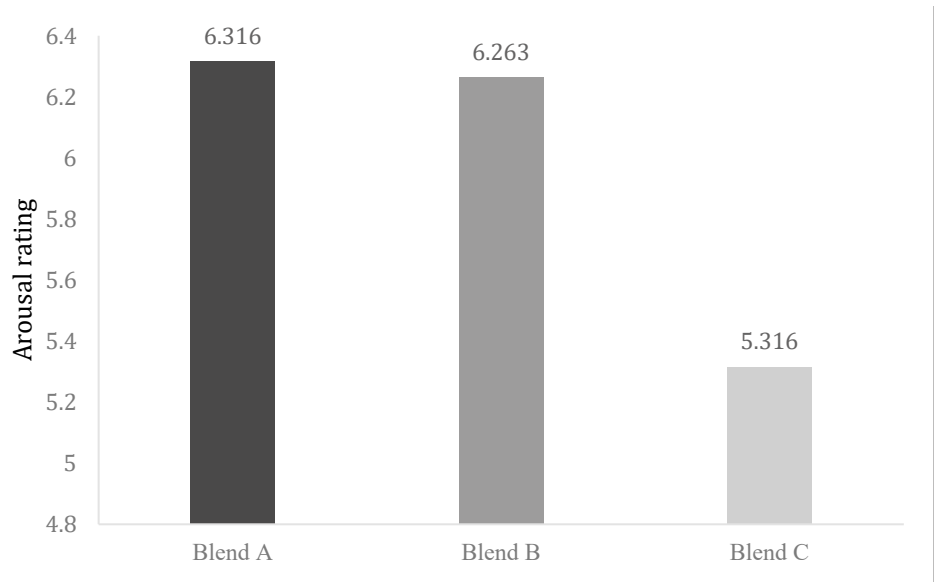

Figure 8. Subjective arousal between coffee blends.
Source: Authors.

Discussion

The present study intended to investigate how coffee blends with different caffeine level impact on the autonomic and affective system. Results partially support the first hypothesis, indicating that different levels of caffeine can influence the autonomic nervous system (Koenig et al., 2013), namely the pupillary system. Caffeine, through the activation of

noradrenergic nerves, can trigger sympathetic stimulation that results in changes in PR (Nehlig, Daval & Debry, 1992). However, contrary to our expectations, it was not observed a higher PR for blend A when compared to other blends at the first moment of the tasting task, but for blend C. This could be explained for the differences in the smell/aroma of the espresso blend has explained before that is extremely important (Samoggia & Riedel, 2019). Still, a higher PR in blend A was found at the 2nd moment. This may represent an additive effect when drinking two consecutive blends, particularly when blend B precedes blend A whose caffeine volume of the 2 blends exceeds 200mg causing reactions in the body in usual coffee consumers as previously suggested (Brunyé et al., 2010). Participants who consumed the coffee blend combination with the highest level of caffeine (blend B + blend A) showed higher PR. Our results are in concordance with studies that have shown that higher autonomic activity induced by caffeine intake led to a higher pupillary activity, specifically a larger pupil dilation (Steinhauer, Siegle, Condray & Pless, 2004; Bouffard, 2019). The small effects - we have found might be due to the sensitivity of the pupillary system to room brightness as well as to cognitive load which were not controlled in this study (Beatty & Lucero-Wagoner, 2000; Rosa, Caires, Costa, Rodelo & Pinto, 2014; Partala & Surakka, 2003).

Regarding the cardiac activity, our results partially confirmed the second/third hypotheses. There were significant differences between HRV, particularly a higher SDNN (parasympathetic activation indicator), showing the blend A, a positive SDNN variation (SDNN coffee tasking - SDNN baseline) in contrast to blend B and C, both with SDNN variation below 0. These results are in line with other studies of experimental nature (Hibino, Moritani, Kawada & Fushiki, 1997; Richardson et al., 2009; Cappelletti, 2015; Grgic et al., 2018). The results of the sympathetic-vagal balance are congruent with the SDNN, as the high frequency power is part of the denominator of the LF/HF ratio. These results are also in line with the work of Syce, Veliath and Krishnamurthy (2014). In a similar study, Hibino et al. (1997), observed that there was a significant increase in high-frequency power after ingestion of 240 mg of caffeine, that only happens on the second intake of blend A after intake blend B (M = 243.52 mg of caffeine intake). The results of this study are supported by recent research that has shown that caffeine increases cardiac vagal activity in healthy middle-aged people (Monda et al., 2009). SDNN was significantly higher in blend A when compared to blend B, indicating a recovery of the parasympathetic activity, stimulated by sympathetic-vagal balance. However, some contradictory results were obtained in certain studies, where no significant difference in SDNN nor in RMSSD bewteen situations with different levels of autonomic activitation (Tharion, Parthasarathy & Neelakantan, 2009; Melillo, Bracale & Pecchia, 2011).The concept of "sympathetic-vagal balance" reflects the autonomic state resulting from the sympathetic and parasympathetic influences, considered has being the ratio between LF and respiratory-frequency powers. Sympathovagal balance is simply the ratio of absolute LF to absolute HF power, or LF/HF (Goldberger, 1999). Reduced parasympathetic activity occurs frequently in response to drug therapy. In some cases, the drug is specifically intended to inhibit the parasympathetic system, but many drugs commonly used for other purposes also have peripheral antimuscarinic effects. At very high doses, gastric emptying and gastric secretion may also be inhibited, leading to epigastric discomfort (Tonkin, 2009). We found threre was also a significant change

in the sympathetic to parasympathetic activity represented by the LF/HF ratio, that can reflect for one side this trend to caffeine can be, at some dosage, considered as stimulant and this means that higher levels of caffeine, lower sympathetic-vagal balance.

As research has shown that caffeine intake increases mental energy and induces greater alertness (e.g., Bruce, Scott, Lader & Marks, 1986; Lanini, Fernandes & Pompéia, 2016) it was expected that this would be reflected in subjective arousal. Although blend A produced higher levels of arousal, these were not statistically significant, which not corroborate our fourth hypothesis. These results are similar to a study by Ahmadi, Mokhtari, Kazem and Mousavi (2012), which found no differences in arousal associated with caffeine intake. This study is also consistent with other studies that found a discordance between subjective and objective measures (e.g., Chivers, Gerulf, Latty & Bailey, 2004; Rosa et al., 2014, 2017).

The results in general support the idea that blend A is different in terms of the physiological responses that it induces, and when taken after blend B (aprox. 250 mg caffeine intake), supports the vision of Brunyé et al. (2010) that after 200mg caffeine intake reached the excitatory autonomic response. Nevertheless, these results need to be interpreted with caution given the experimental task design. One limitation is related to the brief time interval between blends that might create a carryover effect so the last tasted blends would reflect the autonomic effects from the previous blends. Finally, a potential caveat is that results are based on a small sample size that may increase Type II error in the statistical analyses. Future studies with larger samples would certainly give more statistical power to the results if possible, examine potential autonomic and affective differences across gender.

Conclusions

In conclusion, our results suggest that cardiac and pupillary activity are modulated by caffeine levels. We also found that affective experiences can be partially dissociated from autonomic activations (Rosa et al., 2014), which support the use of implicit measures to study consumer preferences of food and beverage in the future (Rodrigues, 2015). The findings of this study offer valuable insights into the relationship between caffeine intake and affective and autonomic responses. These results could suggest that coffee blends with higher caffeine concentration could generate larger sympathetic responses and prolong its effects, but only when the caffeine level is above 200mg as suggested in literature (e.g., Brunyé et al., 2010). In the future, other physiological measures such as electrodermal activity can be a rich source of data, supporting better our conclusions (e.g., Barceló et al., 2018). Similarly, future research using double-blind tasting tasks can also combine other types of ocular measurements such spontaneous eyeblinks as they are thought to be correlated with the autonomic nervous system.

Aknowledgements

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Research

Social Cognition in Early Multiple Sclerosis: Neuropsychological and Anatomical Approach

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La Cognición Social en la Esclerosis Múltiple Temprana: Enfoque neuropsicológico y anatómico

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Abstract

Cognitive impairment and deficits in Social Cognition (SC) are frequent in patients with Multiple Sclerosis (MS). The aim of the present work is to study SC in patients with early MS and to analyze its neuroanatomical correlation. Thirty-four patients with relapsing remitting MS, with ≤ 2 years of disease progression and EDSS and ≤ 2, and 30 healthy control subjects matched for age, sex, and educational level were recruited. Subjects performed a comprehensive neuropsychological assessment (Rao BRB). SC was assessed using the International Affective Picture System IAPS, The Eyes in the Mind Test, the Empathy Quotient, and the Faux Pas Test. The anatomical correlation of patients with deficits in social cognition was studied through brain MRI and voxel-based morphometric for which cortical reconstruction and volumetric segmentation were performed using Freesurfer processing software. Patients showed significant deficits in executive functions, verbal memory and language tests. SC assessment showed that patients presented greater difficulties in the Faux Pas Test (p = 0.023), The Mind in the Eyes Test (p = 0.014), and presented a positive bias in the interpretation of neutral images of the IAPS (P = 0.023). Furthermore, patients with CS deficits presented less cortical thickness in areas of the right supramarginal gyrus, pars opercularis, and anterior cingulum.

Keywords: Cognitive Dysfunction; Social Cognition; Multiple Sclerosis; Neuropsychological Test; Disease Progression

Resumen

El deterioro cognitivo y los déficits en la cognición Social (CS) son frecuentes en pacientes con Esclerosis Múltiple (EM). El objetivo del presente trabajo es estudiar la CS en pacientes con EM temprana y analizar su correlación neuroanatómica. Se reclutaron 34 pacientes con EM remitente recidivante, con ≤ 2 años de progresión de la enfermedad y EDSS y ≤ 2, y 30 sujetos control sanos emparejados por edad, sexo y nivel educativo. Los sujetos realizaron una evaluación neuropsicológica completa (Rao BRB). La CS se evaluó mediante el Sistema Internacional de Imágenes Afectivas IAPS, el Test de la Mirada, el Cociente de Empatía y el Test de Faux Pas. La correlación anatómica de los pacientes con los déficits en cognición social se estudió mediante resonancia magnética cerebral y morfometría basada en vóxeles, para lo cual se realizó la reconstrucción cortical y la segmentación volumétrica mediante el software de procesamiento Freesurfer. Los pacientes mostraron déficits significativos en las funciones ejecutivas, la memoria verbal y las pruebas de lenguaje. La evaluación de la CS mostró que los pacientes presentaban mayores dificultades en el Faux Pas Test (p = 0.023), el Test de la Mirada (p = 0.014), y presentaban un sesgo positivo en la interpretación de imágenes neutras del IAPS (P = 0.023). Además, los pacientes con déficits de CS presentaron un menor grosor cortical en áreas del giro supramarginal derecho, la pars opercularis y el cíngulo anterior.

Palabras clave: Disfunción cognitiva; Cognición social; Esclerosis múltiple; Test neuropsicológico; Progresión de la enfermedad

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Introduction

Multiple sclerosis (MS) is a persistent, neuroinflammatory disease of the central nervous system affecting young adults with physical, emotional and cognitive symptoms. Cognitive impairment is present in 40-70% of MS cases and different subtypes and stages of the disease have been reported (Langdon, 2011). Related difficulties mainly affect attention, memory, language, executive functions, orientation and visuospatial abilities (Chiaravalloti / DeLuca, 2008).

Social cognition (SC) is the skill to process, store and use information about social situations. SC includes several subcomponents such as theory of mind, emotion recognition, emotional reactivity, and empathy.

MS patients are likely to have some level of compromised social cognition in the specific subcomponents of the theory of mind (the skill to infer the mental state, thoughts, and intentions of others) and emotion recognition (Ouellet et al., 2010; Banati et al., 2010). A recent study also found diminished emotional reactivity to negative stimuli in MS patients (Di Bitonto et al., 2011).

Although CS in MS patients has begun to be studied in recent years, there is still little knowledge about the impact of MS on CS in the early stages of the disease, when the burden of injury is low and physical disability is not yet present.

In times where new treatments have modified the motor impact of the disease, clinical attention moves towards other symptoms that compromise these patients' quality of life. In this framework, CS plays a predominant role, as appropriate social interaction requires preserved social cognition; CS impairment can lead to interpersonal conflicts and misunderstandings. These conflicts can affect multiple areas of exchange, such as family, friends, and work spheres (Cotter et al., 2016) . This study aims to assess social cognition's level of compromise in the early stages of multiple sclerosis, even when the physical impact is not yet present. We also intend to investigate the association between CS and general cognitive functioning, neuropsychiatric symptoms, and life quality. Finally, we will look for the relationship between these symptoms and the structural damage that the disease may generate by studying magnetic resonance imaging and voxel-based morphometry techniques.

Materials and methods

Subjects

According to the McDonald et al. (2001) criteria thirty-four patients with MS in relapse and remission were recruited. Patients were classified through the neuroimmunology service of our institution. Inclusion criteria for the study: patients had to have less than two years of disease duration and a score of less than 2 points on the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). Patients with significant upper extremity motor impairment, visual acuity or visual field deficits, history of alcohol or drug abuse, head trauma, major psychiatric disorders, other neurological disorders or systemic diseases were excluded.

All patients were evaluated after 90 days recovery from the last relapse or discontinuation of steroid treatment. Of thirty-four patients, seven received interferonß, eight-dimethyl fumarate, thirteen fingolimod, two natalizumab, three glatiramer acetate and one teriflunomide.

Thirty healthy controls were recruited from a local volunteer pool, matched for age, gender, and educational level.

Both groups underwent a complete neuropsychological evaluation, with tests of social cognition. Patients with brain imaging less than one month before the assessment were included in the structural sub-study.

All subjects signed an informed consent form prior to the evaluations. Prior to this, the local ethics committee approved the protocol.

Cognitive assessment

Subjects' cognition was evaluated with the Spanish version of the Brief Repeatable Neuropsychological Test Battery (BRB) (Cáceres, Vanotti, Rao & RECONEM Workgroup, 2011). This battery includes tests of verbal memory (selective recall test), visual memory (7/24 test), language (FAS), attention (oral version of the digit-symbol test), and executive functions (PASAT 3 sec. and PASAT 2 sec.). Fatigue and neuropsychiatric scales assessing anxiety and depression (FSS and HADS) were also administered. The MusiQoL scale sets the quality of life.

Assessment of social cognition

CS was assessed with an extensive battery that included tests of several of its components. Theory of mind (ToM) was assessed with the Eyes Test and the Faux Pas Test. Emotional processing was assessed using the International Affective Imagery System. Empathy was assessed with the Empathy Quotient.

- *Eyes Test*

Task consists of describing a person's emotional/mental state based solely on their eyes' image in a fixed-choice context (Baron-Cohen & Wheelwright, 2001). Subjects were presented with the Spanish version of the task in which 36 stimuli are presented (Román et al., 2012). Subjects must identify the emotional/mental state of the image by choosing one of the four options presented.

- *Faux Pas Test*

This test consists of 10 short stories containing "faux pas" situations (someone who mistakenly says something they should not) (Stone, Baron-Cohen & Knight, 1998). These are read to the person and displayed on a screen; then, subjects are asked questions to determine whether they recognize the error. Different types of errors are computed.

- *Empathy Quotient*

The Empathy Quotient (Baron-Cohen & Wheelwrights, 2004) is a self-administered questionnaire of 60-item designed to measure empathy in adults.

- *International Affective Picture System (IAPS)*

IAPS (Lang, Bradley & Cuthbert, 2008) is a set of static imagery stimuli based on the dimensional model of emotions. The collection contains several types of images that can be scored on three main dimensions: arousal, valence, and dominance. Our work followed the integrated model that states that the first two dimensions (arousal and valence) capture the global and essential emotion elements. The stimuli consisted of 38 color images from the International Affective Imagery System, two of which were used as practice images, and the other 36 were used as target stimuli. The images were selected following the paradigm designed by Louwerse, Tulen, van der Geest, van der Ende & Verhulst (2014). This design discriminates between social content (social vs. non social) and pleasantness (pleasant, neutral, or unpleasant).

Six categories were constructed, each containing six images:

1. Social - pleasant (Valence index> 6, arousal index> 4).
2. Social - neutral (Valence index 4-6, arousal index 0-4).
3. Social - unpleasant (Valence index 0-4, arousal index > 4).
4. Non-social-pleasant (Valence index> 6, arousal index> 4).
5. Non-social: neutral (Valence index 4-6, arousal index 0-4).
6. Non-social: unpleasant (Valence index 0-4, arousal index > 4).

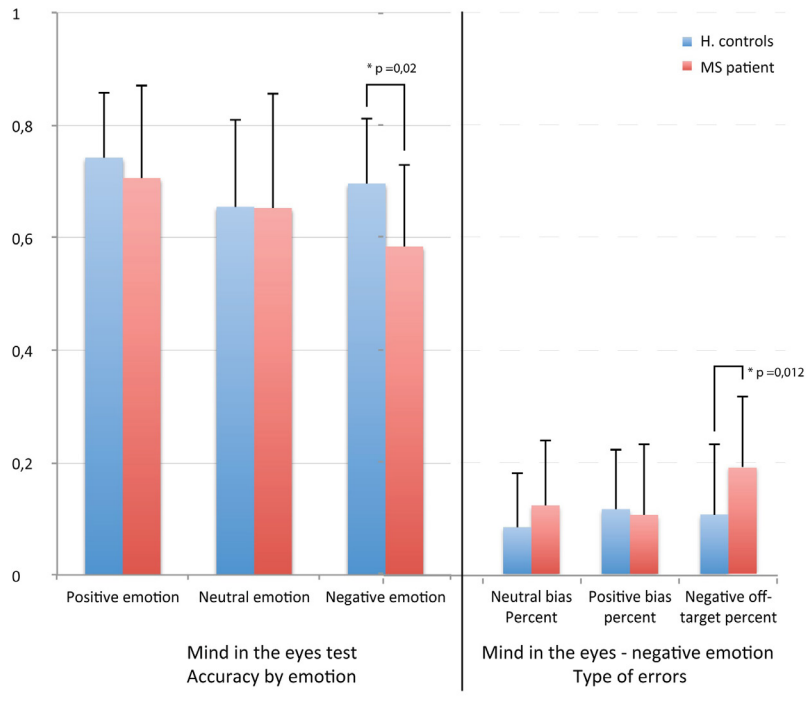

Figure 1. Eyes test.
Source: Authors.

Subjects were presented with the images on a screen and had to rate each photo using the Mannequin Self-Assessment System (Figure 1) (Bradley & Lang, 1994).

The left block shows the performance of both groups by emotion group. The adjacent graph quantifies the number of errors in detecting negative emotions. The error was to classify the image as neutral bias or optimistic bias. Despite identifying the group as unfavorable, the emotion could not be correctly identified (negative off-target).

MRI and voxel-based morphometry

The patient group was evaluated with brain MRI with volumetric sequences. Voxel-based morphometry was performed. This was followed by cortical reconstruction and volumetric segmentation using Freesurfer processing software. In previous publication technical details of these procedures are described.

- *Statistical analysis.*

Statistical analysis was performed using R version 3.6.1. For the study of the psychometric results, a T-test was used to compare means when the assumption of normality made it possible; when it was not possible, the Mann-Whitney U-test was used. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normality of the distribution.

Images were subjected after processing in Freesurfer to a group surface analysis using a general linear model with the Qdec platform. For the analysis, the group was divided into two groups, one with poor eye test performance and one with good performance. For this, the control group was used as a cut-off point for normality. The surface analysis was performed on a model of covariance with the age of the patients, and clusters of differences between the groups were obtained. For the creation of clusters, a statistical significance limit was set at 0.01, and a sensitivity threshold was set at surfaces deviating beyond 1.5 standard deviations from normalization towards both extremes.

Results

Demographic, cognitive, and neuropsychiatric outcomes

The clinical and demographic data of the participants are shown in Table 1. No significant differences were found in age, gender, educational level or neuropsychiatric scales assessing depression, anxiety and fatigue. However, patients showed significant impairment in cognitive tests of verbal memory (SRT-A $p = 0.002$, SRT-R $p = 0.029$, SRT-D $p = 0.002$), executive functions (PASAT 3 $p = 0.038$, PASAT 2 $p = 0.023$, Digits Back $p = 0.027$.) and language (FAS $p = 0.0001$). Differences were also found in quality of life (MusiQuol $p = 0.005$). There were no differences in-group performances on measures of attention (DSMT and Digit Forwards; Table 2).

Table 1.
Demographic Results.

	CS	MS	
	Mean (SD)	Mean (SD)	p
Age	33.79 (7.69)	34.71 (8.17)	0.652
Education (years)	17.1 (1.39)	16.44 (2.16)	0.162
Sex (% men)	46.70%	41.20%	0.659
Duration of illness (months)	-	17.28 (6.33)	-
MMSE	29.97 (0.18)	29.5 (0.75)	0.001

Source: Authors.

Table 2.
Cognitive Assessment.

	CS	MS	
	Mean (SD)	Mean (SD)	p
TSM-A	55.37 (9.77)	45.65 (14.04)	0.002
TSM-R	46.53 (12.96)	38.09 (16.65)	0.029
TSM-D	10.77 (1.59)	8.88 (2.79)	0.002
PASAT 3	50.13 (8.28)	44.65 (11.85)	0.038
PASAT 2	43.8 (9.36)	38.38 (9.01)	0.023
FAS	49.57 (10.50)	37.97 (11.39)	0.0001
7/24 1-5	33.2 (2.58)	31.44 (4.24)	0.053
7/24 dis	4.3 (2.15)	4.93 (1.94)	0.249
7/24 imm	6.5 (1.38)	6.47 (1.08)	0.924
7/24 diff	6.5 (1.38)	6.29 (1.22)	0.529
Dig Fow	6.6 (0.77)	6.32 (0.94)	0.208
Dig Back	5.31 (1.00)	4.65 (1.28)	0.027
Boston Naming Test	28.87 (1.38)	27.5 (2.90)	0.022
TDS	64 (9.40)	59.24 (11.89)	0.083
MusiQol	72.66 (11.11)	81.13 (11.99)	0.005
HADS- Anxiety	7.87 (2.54)	9.33 (3.40)	0.059
HADS- Depression	2.77 (2.67)	4.06 (3.49)	0.1
Fatigue Severity Scale	30.30 (10.81)	30.38 (14.22)	0.98

Source: Authors.

Social cognition outcomes

The CS and QoL results are shown in Table 3. The ToM assessment showed that patients presented more significant difficulties in identifying mental states when confronted with negative stimuli in the Eyes Test ($p = 0.014$), evidencing deficits in inferring others' states (Figure 1).

In addition, the stories score on the Faux Pas task was significantly lower in the MS group, showing ToM deficits in detecting socially inappropriate behavior (p = 0.009). In this test, the groups did not differ in control stories or memory scores, revealing no memory or comprehension biases in their response.

With respect to IAPS performance, a significant positive bias was observed in the interpretation of neutral images in the emotional reactivity test (Non-neutral social images p = 0.023). As shown in Figure 2, patients tended to assign a more positive valence to non-social imagery than normal controls. No differences were observed in empathy quotient performance.

TABLE 3.
Social Cognition Outcomes.

	CS	MS	
	Mean (SD)	Mean (SD)	p
Eye Test			
Total Score	25.23 (3.07)	24.18 (4.15)	0.257
Positive emotion	10.00 (1.49)	9.65(2.21)	0.463
Negative Emotion	9.93 (1.76)	8.68 (2.17)	0.014
Emotion Neutral	5.30 (1.42)	6.03 (1.93)	0.094
Test Faux Pas			
Faux pas stories	27.28 (4.04)	24.21 (4.91)	0.003
Control stories	9.93 (0.37)	9.59 (0.96)	0.074
Stories Memory	19.79 (0.49)	19.26 (1.33)	0.0548
Faux pas Total Score	35.97 (7.86)	33.79 (5.02)	0.005
International Affective Picture System (IAPS)			
Valence			
Non-social pleasant	6.86 (1.23)	7.16 (1.21)	0.329
Non-social unpleasant	1.85 (0.97)	1.72 (0.81)	0.563
Non-social neutral	5.12 (0.80)	5.59 (0.80)	0.023
Socially pleasant	7.38 (1.23)	7.92 (0.92)	0.050
Socially unpleasant	1.65 (0.98)	1.40 (0.57)	0.201
Social neutral	5.21 (0.72)	5.62 (0.93)	0.058
Arousal			
Non-social pleasant	5.24 (0.95)	5.09 (1.71)	0.669
Non-social unpleasant	6.73 (1.20)	6.75 (1.54)	0.951
Non-social neutral	3.87 (1.12)	3.72 (0.99)	0.556
Socially pleasant	6.07 (0.96)	5.70 (1.70)	0.296
Socially unpleasant	7.16 (1.08)	7.01 (1.57)	0.670
Social neutral	4.17 (1.17)	3.98 (1.18)	0.518

Source: Authors.

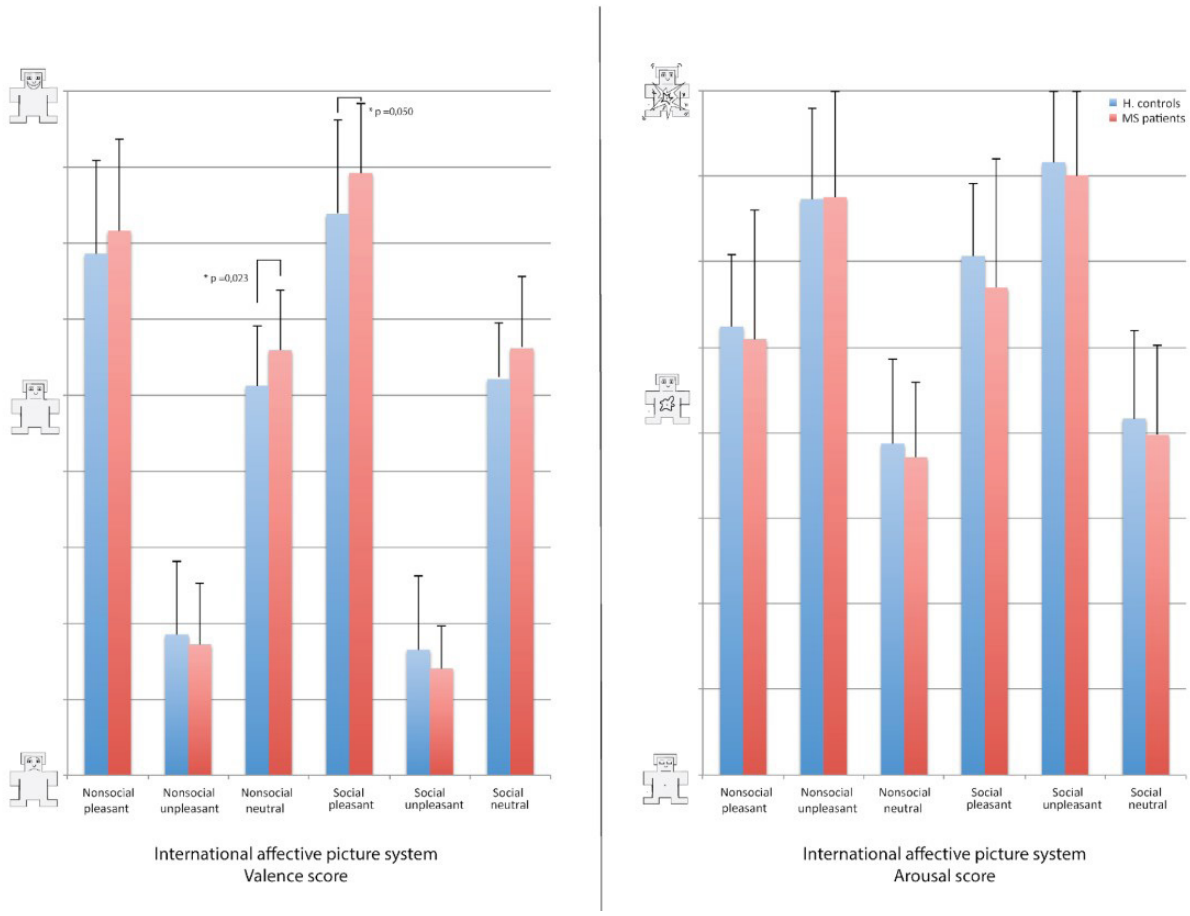

Figure 2. IAPS.
Source: Authors.

Performance of both groups in the IAPS tasks, in the left, blocks the account in detecting the valence of the perceived emotion and arousal. As a scale, the graph was constructed similar to the patient's scale score.

Influence of fatigue, depression, and anxiety on social cognition scores

Neuropsychological and social cognitive performance may be altered by fatigue and neuropsychiatric symptoms. In our study, fatigue scores assessed with the FSS showed no significant differences between groups ($p = 0.98$). Likewise, depression and anxiety, as assessed by the HADS, were not significantly different between groups ($p = 0.1$ and $p = 0.059$).

Correlation results

The correlations between neuropsychological and social cognition tests in people with MS were then assessed.

Significant correlations were found between negative emotions and PASAT 3 ($p = 0.003$, $r = 0.497$), and PASAT 2 ($p = 0.039$, $r = 0.37$). Similarly, the Faux Pas Stories score correlated with SRT storage and delayed scores ($p = 0.021$, $r = 0.39$; $p = 0.029$ $r = 0.38$). The Faux Pas total score was also correlated with SRT storage and delayed scores ($p = 0.010$, $r = 0.43$; $p = 0.029$, $r = 0.37$, respectively).

The IAPS non-social neutral total valence score showed only a positive correlation with the quality of life as measured by MusiQol ($p = 0.03$, $r = 0.27$).

Voxel-based morphometry and topographic analysis

Figure 3 summarizes the differential clusters of cortical thickness, where the comparatively lower thickness was found for the group with worse social cognition performance. The most significant differential clusters found comprise the right supramarginal gyrus, pars opercularis, and anterior cingulate. The specific extent of these areas can be visualized on the brain surface (in an inflated reconstruction of the brain to visualize gyri and sulci at the same time) on a thermal scale, regional differences, and the extent of the clusters in both hemispheres.

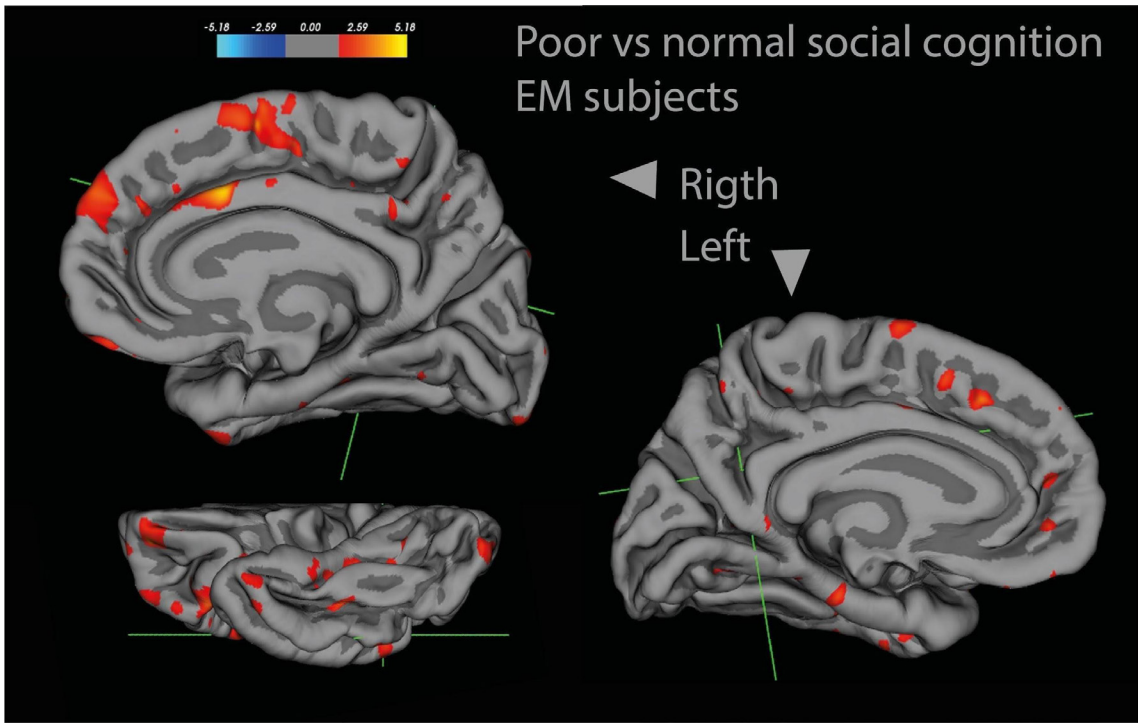

Figure 3. Reconstruction of morphometric analysis. Right brain.
Source: Authors.

Major differential clusters between patients with normal and impaired social cognition. The magnitude of the differences in standard deviations concerning the regular group is shown in the thermal scale.

Discussion

The present study assessed cognitive and CS performance in early MS and showed how patients had deficits in cognitive tests of memory, language, and executive functions. Two aspects of CS were affected: theory of mind and emotional reactivity. No difficulties were found in the self-reported empathy quotient.

There is proven evidence of cognitive difficulties in patients with MS in the early stages and CS difficulties in later stages of the disease. This suggests that there may be alterations in functional brain responses during specific emotion recognition processes (Jehna et al., 2011).

The results of the Eyes Test are consistent with previous studies in which MS patients showed difficulties in detecting facial emotions of anger and fear (Henry et al., 2009).

The two studies complement each other, as Henry's study used a task assessing emotion recognition, and our research used a task considering ToM. In our study, we specifically examined the type of emotion identified (i.e., positive, neutral, or negative) and found that consistent with Henry's results; patients did not identify negative emotions. This dissociation suggests that MS patients may have retained positive emotions and impaired recognition of negative emotions.

The literature (Calder, Keane, Lawrence & Manes, 2006) confirms dissociated neural substrates for the recognition of specific emotions and specific deficits in recognition of particular emotions for specific neurological conditions (Sprengelmeyer et al., 2002). It is, therefore, possible that particular difficulty in the interpretation of negative emotions is present in MS.

Furthermore, these results correlated with PASAT performance (3" and 2".). PASAT is a complex neuropsychological task that mainly involves selective attention, executive functions (working memory) and information processing speed. These cognitive functions could be involved in the Eyes Test. As the stimulus and response options are always present on the screen, the task does not pose any working memory. Information processing speed is not necessary for this task, as the subject has unlimited time to respond. Therefore, it is very likely that selective attention is the cognitive function that affects the subject's performance in this task.

Patients also failed to detect inappropriate responses in the Faux Pas task. MS patients successfully noticed that a faux pas was not present but did not recognize faux pas when they occurred. This suggests that they have difficulty reading or identifying subtle inappropriate behavior in social situations. The faux pas results correlated with the selective memory test results, assuming that the task may require storage and delays in verbal memory demand. However, it is essential to note that no significant differences were found between the groups in the Faux pas task's memory score. Therefore, patients could respond adequately to the memory demands of the Faux Pas test.

The IAPS results require a different interpretation. Differences in emotional reactivity were only present for neutral, non-social stimuli (patients tended to assign a more pleasant value to neutral images than controls). These results suggest that a neutral image may be more sensitive than pleasant or unpleasant images to subtle emotional reactivity changes. Other semantic systems processes are probably involved when processing a stimulus with a social component and a positive or negative valence.

We studied the empathy, theory of mind, and emotional reactivity in a sample of newly diagnosed MS subjects without motor impairment. We confirmed the presence of CS impairments and emotional reactivity deficits in early MS. These deficits are independent of neuropsychiatric symptoms, such as depression or anxiety. Global CS performance was not determined by other neuropsychiatric conditions, such as depression or anxiety because the differences between groups were not significant. However, changes in patients' quality of life was associated with emotional reactivity scores and is based more on psychological aspects than cognitive components.

Therefore, we can conjecture that a recent detection of illness leads individuals to reinterpret their emotional environment and to reconsider the value of life in terms of attributing positive value (or valence) to common objects, even bland ones, such as the non-neutral

IAPS Social Images. Furthermore, the patient's performance on this task did not correlate with cognitive performance, but correlated with quality of life. Thus, it can be inferred that emotional reactivity performance is associated with the patient's quality of life and is independent of cognitive functioning.

In our study, the regions of the right supramarginal gyrus, pars opercularis, and anterior cingulate cortex of the group of patients with deficits in social cognition showed less cortical thickness than the group of patients with good social cognition.

Consistent with our results, functional MRI studies were published in a comprehensive review (Schulz et al., 2009). Analyzed the areas involved in the generation of socially appropriate behaviors in emotional contexts. Appropriate social responses were associated with the par opercularis in the inferior frontal gyrus, the temporoparietal junction, the superior parietal lobe, and the parietal sensory association cortexes.

Furthermore, research (Apps, Rushworth & Chang, 2016), argues that the anterior cingulate cortex is involved in a wide range of behavioral and cognitive processes and contributes to social behavior by participating in human interaction's social-cognitive skills.

The anterior cingulate cortex is involved in cognition and decision-making, including social cognition (Mao et al, 2017) and social interaction. A recent study in MS patients (Batista et al., 2017) studied the correlation between different cortical areas and performance on the Eyes Test and found results consistent with ours: a positive correlation between social cognition and the fusiform gyrus. superior temporal gyrus. superior parietal gyrus. supramarginal gyrus, entorhinal cortex, medial orbitofrontal cortex and anterior gyrus cortex.

Against this background, our work sheds light on controversial issues in the disease, a critical point of contention being early grey matter involvement. The evidence for measurable participation of a cortical symptom such as social cognition with an objective parallel in the cortex's thickness merely proves the point. New questions arise from this analysis, for example, whether this structural abnormality is the result of the disease or is a predisposition (a sort of lower brain reserve) to the disease manifesting such involvement.

This study is the first to assess emotional reactivity in early MS. Di Bitonto et al. (2011) reported deficits in emotional reactivity stimuli using the IAPS, although her study was conducted with a small sample of women and did not consider time since diagnosis. In addition, IAPS images and sound were not classified into social and non-social stimuli. Therefore, these results cannot be compared with our findings.

In our study we bring a novel approach to the well-known phenomenon of social cognition deficits in MS. To this end, we apply a multidimensional approach in which we consider both the specific biological aspects (neuroimaging) and the psychological impact of the disease on patients with early MS. Our findings emphasise the importance of assessing CS in the early stages of the disease in order to intervene before these difficulties worsen and interfere with social functioning. Therefore, these results may also be relevant for the design of appropriate patient counselling strategies.

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Research

Pharmacovigilance in Neuroscience

Farmacovigilancia en neurociencia

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Abstract

Adverse Drug Reactions (ADRs) have a high impact on morbidity and mortality of the population, becoming a public health issue. Studying and publishing about these is referred as pharmacovigilance.

The primary objective of this article is to describe and compare the adverse reactions produced by drugs of nervous system action (CNS-D) and neurological ADRs produced by drugs of systemic action (Sys-D). To further develop the need of reporting adverse reactions.

This is an observational, cross-sectional, retrospective study performed on a database of neurological consultations which took place at the Neurology department. Patients meeting the inclusion criteria were selected and divided into two groups: Sys-D and CNS-D. Demographic and neurological variables were analyzed. Parametric and non-parametric statistics were used according to distribution. The Naranjo Algorithm (NA) was used to define causality.

71 ADRs were described, from which 63.38% (n = 45) were produced by CNS-D, especially antiepileptics by 47% (n = 21) and psycholeptics by 44%. Of the total, 36.62% (n = 26) were caused by Sys-D, such as antineoplastics (n = 9) and antibiotics (n = 9), being Cefepime the most frequent. The diagnosis of ADRs caused by a Sys-D was delayed prolonging hospitalization (p 0.05) due to a lower NA score (p 0.003) compared to the CNS-D group.

Multiple frequently used drugs of systemic action, such as antineoplastics and antibiotics, generate neurological adverse effects. From our analysis, it was presumed that the suspicion of a neurological ADR caused by these drugs was scarce, thus causing a higher morbidity for the patient.

Keywords: Pharmacovigilance; Epidemiology; Adverse reactions; Drugs; Neurology; Pharmacology

Resumen

Las Reacciones Adversas a Medicamentos (RAM) tienen un alto impacto en la morbilidad y mortalidad de la población, convirtiéndose en un problema de salud pública. El estudio y la publicación de las mismas se denomina farmacovigilancia.

El objetivo principal de este artículo es describir y comparar las reacciones adversas producidas por medicamentos de acción sobre el sistema nervioso (SNC-D) y las RAM neurológicas producidas por medicamentos de acción sistémica (Sys-D). Profundizar en la necesidad de notificar las reacciones adversas.

Es un estudio observacional, transversal y retrospectivo realizado sobre una base de datos de consultas neurológicas que tuvieron lugar en el servicio de Neurología. Se seleccionaron los pacientes que cumplían los criterios de inclusión y se dividieron en dos grupos: Sys-D y CNS-D. Se analizaron variables demográficas y neurológicas. Se utilizó estadística paramétrica y no paramétrica según la distribución. Se utilizó el Algoritmo de Naranjo (NA) para definir la causalidad.

Se describieron 71 RAM, de las cuales el 63,38% (n = 45) fueron producidas por SNC-D, especialmente antiepilépticos en un 47% (n = 21) y psicolépticos en un 44%. Del total, el 36,62% (n = 26) fueron causadas por Sys-D, como antineoplásicos (n = 9) y antibióticos (n = 9), siendo la Cefepime la más frecuente. El diagnóstico de las RAM causadas por un Sys-D se retrasó prolongando la hospitalización (p 0,05) debido a una menor puntuación de NA (p 0.003) en comparación con el grupo de SNC-D.

Múltiples fármacos de acción sistémica frecuentemente utilizados, como los antineoplásicos y los antibióticos, generan efectos adversos neurológicos. A partir de nuestro análisis, se presume que la sospecha de una RAM neurológica causada por estos fármacos es escasa, provocando así una mayor morbilidad para el paciente.

Palabras clave: Farmacovigilancia; Epidemiología; Reacciones adversas; Fármacos; Neurología; Farmacología

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Introduction

Pharmacovigilance (PhV) is defined by the World Health Organization (WHO) as the science and activities related to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (World Health Organization-WHO/ The Uppsala Monitoring Centre, 2001). It was developed on the early '60s, after the use of Thalidomide in pregnant women, whose newborns had malformations (WHO, 2001; Regulation No. 5358, 2012).

In 1964, the Instituto Nacional de Farmacología y Bromatología was created in Argentina. After several changes, in September 1993 the Pharmacovigilance National System was founded, as well as the ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica). In 1994, Argentina got into the monitoring system of WHO, which receives the alerts and signs of adverse effects, thus becoming the first country in Latin America to be a member of Uppsalla Monitoring Centre (Bignone & Schiaffino, 2016; WHO, 1999).

WHO defines Adverse Drug Reaction (ADR) as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or treatment of a disease, or to modify any biological function" (Regulation No. 5358, 2012). ADRs represent a high impact on morbidity and mortality of the population causing a problem to public health (Bignone & Schiaffino, 2016; Ponte, Ragusa, Armenteros & Wachs, 2013). Adverse reactions are estimated to be between the fourth and sixth cause of mortality (Bignone & Schiaffino, 2016; Regulation No. 5358, 2012; Lazarou, Pomeranz, & Corey, 1998).

According to different international publications, between 15% and 24% of hospitalized patients show adverse effects, and up to 15% of them are admitted because of adverse drug effects (Bignone & Schiaffino, 2016). In two meta-analysis carried out in the USA and in Australia, the incidence of ADR varied from 4.4% to 5.8% and 5.2% to 8.2% respectively. In Brazil, Camargo, Cardozo ,Ferreira and Heineck (cited by Chaio, Toibaro, Valicenti & Saidón, 2013) demonstrated that 43% of hospitalized patients showed adverse reactions. Likewise, meta-analysis done by Lazarou et al. (1998), not only demonstrated the high incidence rate of adverse effects in hospitalized patients, but also that 6.7% showed serious ADR. In Argentina, Chaio et al. (2013) demonstrated an incidence rate of 36% of ADR in hospitalized patients being this the cause of 11% of the admissions.

The great variability of incidence rates among the different publications could be due to their design (Chaio et al., 2013). Information regarding the frecuency of ADR is scarce in the commercialization phase in our country (Bignone & Schiaffino, 2016). Notification of the ADR by the different medicine related agencies plays an important role on PhVG (Regulation No. 5358, 2012).

Multiple factors influence the increase of ADR incidence rates. Some of them are the increase in life expectancy and the development of new medicines, among others (Bignone & Schiaffino, 2016). Elderly people, newborns and polypharmacy patients are more vulnerable to develop them. It is common for patients over 65 years old to have comorbidities leading to polypharmacy associated to pharmacokinetics and pharmacodynamics changes, increasing the risk of ADR (Ponte et al., 2013; Rattagan et al. 2016). Moreover, mistakes

in prescription, unawareness of drug interactions and self-medication influence ARD incidence (Bignone & Schiaffino, 2016; Orta, Garcia, Triolet, Gómez & Ruiz, 2008).

From the neurological point of view, neurologists usually prescribe drugs with nervous system mechanism of action (CNS-D), with further knowledge of their ADR. It is important to underline that patients with neurological disorders have more risk in developing neurological ADR (Sauro, Quan, Sikdar, Faris & Jette, 2017). In addition, studies carried out by Rattagan et al. (2016) and Rojas, Demey and Arizaga (2013) evidenced an irrational use of psychotropic medications in the country, especially benzodiazepines. This has not only extended the admission days of the patients, who are exposed to an increase of intrahospital complications, but also 21.2% of the patients did not have indications for psychotropics.

With the development of new pharmacological therapies, neurologists face different ADR with neurological symptoms that are generated by systemic drugs, such as antibiotics, immunosupressants, anti-inflammatories, etc. Since there is limited knowledge of long-term ADR, some of them might be taken for primary neurological diseases. Many factors of drug metabolism can increase the susceptibility of neurotoxicity, such as the nutritional status, cerebral blood flow, permeability of the blood-brain barrier, routes of administration, the pharmacokinetics of the drug and its metabolites (Grill & Maganti, 2011).

As above mentioned, the primary objective of this article is to describe and analyze the pharmacological adverse reactions in the neurological clinical practice. As for secondary objectives, discriminate those ADR produced by drugs used for the treatment of diseases of the Central Nervous System (CNS-D) and the ADRs related to the nervous system engagement provoked by Systemic Drugs (Sys-D), naming both situations as “Neuro-PharmacoVigilance” (NPhVG). Compare different characteristics of ADRs between these two groups. And develop the need for adverse reaction’s notification.

Materials and Methods

A cross-sectional retrospective observational study was conducted over the database regarding in-patient and outpatient clinic of our Department of Neurology between the 1st July 2005 and 1st July 2017. The search of clinical histories was carried out and the required information was analyzed to collect the data in special worksheets. These included personal data (age, gender, nationality, scholarship), admission data (date of entry and exit, reason for hospitalization, admission in a general ward or critical care unit), adverse drug reaction (type, Naranjo score, severity, re-exposure, notification, beginning and ending of symptoms), background and usual medication of the patient.

As inclusion criteria, patients with ADR related to clinical neurological practice within the period described were selected. They had to fulfill the definitions described in the ATC code, ICD-10 and the classification of psychotropic drugs as described below (WHO/Centre for Drug Statistics Methodology, 2021, WHO, 2010, Bolaños, 2016). Patients under 18 years old, patients with drug intoxications (4 patients) and patients from whom no data of the drug that produced ADR was described (3 patients) were excluded from this category.

Once the screening was done, patients were assigned within two groups; Sys-D and CNS-D.

The patient information leaflet of each drug, were analyzed according to local regulatory agencies to determine if the adverse reaction had been previously described (National Drug Formulary-VNM, s.f.). In order to determine the causality of the reactions, the Naranjo Score and the classification of the categories according to the Uppsala Monitoring Centre were used (WHO, 2001; Naranjo et al. 1981).

Definition of variables

- *NPhVG*: Science which tries to collect, watch, investigate and assess adverse effects at the level of the nervous system by systemic drugs, or the drugs with activity in the nervous system that produce adverse effects.
- *ADR*: Harmful and unwanted reaction that occurs after the administration of a drug, at doses commonly used in the human species, to prevent, diagnose or treat a disease, or to modify any biological function (WHO/The Uppsala Monitoring Centre, 2001; Regulation No. 5358, 2012).
- *CNS-D*: The primary mechanism of action is the nervous system. For example: antiepileptics, psycholeptics, and psychoanaleptics.
- *Sys-D*: Main mechanism of action outside the nervous system. For example: antibiotics, antineoplastics, immunosuppressants, antiarrhythmics, diuretics, etc.
- *Neurological ADR* (ADR-N): Adverse effect that causes neurological symptoms or diseases.
- *Systemic ADR* (ADR-S): Adverse effect in any system or organ, except for the nervous system.
- *Re exposition*: The assessment related to causality, when the reaction or event reappears after the administration of a suspicious medicine (Regulation No. 5358, 2012).
- *Categories of causalities according to Uppsala Monitoring Centre*: Defined, Probable, Possible, Not related, Conditioned, Dismissed (WHO/The Uppsala Monitoring Centre, 2001).
- *Scoring according to Naranjo Algorithm* (AIN) (Naranjo et al. 1981).
- *Classification of adverse reactions* by Edward and Aronson (2000).
- *Serious Adverse Reaction* (SAR): It is considered serious any ADR that causes death or death threat, requires or extends hospitalization, produces congenital anomalies or leaves a permanent effect or consequence (WHO/The Uppsala Monitoring Centre, 2001; Bignone & Schiaffino, 2016).
- *Unexpected Adverse Reaction* (UAR): It is an adverse reaction which nature or intensity is not consistent with the local information, the commercialization authorization or it is not expected due to the pharmacological characteristics of the medication. The predominant element in this case is that the effect must be unknown (WHO/The Uppsala Monitoring Centre, 2001).

- *Psychotropic drugs classification* according to Delay and Deniker (cite by Bolaños, 2016).
- *Anatomy, Treatment and Chemical classification* (ATC code): System of coding medicines and drugs depending on the pharmacological effect, its therapeutic instructions and its chemical structure (WHO/Centre for Drug Statistics Methodology, 2021).
- *International Classification of Illnesses*, tenth version (ICI-10): It determines the classification and coding of illnesses and a great variety of signs, symptoms, uncommon findings, reports, social circumstances and external causes of damage and/or illness (WHO/Centre for Drug Statistics Methodology, 2021).
- *Evolution Timing*: timing in days from the administration of the molecule and the ADR.
- *Time from the beginning of ADR and the discontinuing of the drug*: time in days from the beginning of ADR and the discontinuing of the molecule.
- *Days of ADR*: Time in days from the beginning to the end of ADR.
- *Drug Poisoning* (DP): Harmful physiological effects due to the exposure to pharmaceutical products, illegal drugs or chemical substances (Bolaños, 2016).
- *Polypharmacy*: Simultaneous consumption of five drugs or more (Rattagan et al., 2106).

Statistical analysis

Descriptive statistical and non-parametric testing were done using the Mann-Whitney Test to compare quantitative variables between two groups and the Chi Cuadrado Test, with Fisher corrections, for dichotomous variables. The SPSS statistical package was used considering significant statistical values with $p < 0.05$. This study was carried out according to the Good Clinic Practice of ICH, 1964 last revision of Helsinki Declaration. Due to the nature of the study, the explicit approval of an ethical committee of scientific research was not required, though the confidentiality of the data used was scrupulously respected in every moment in such a way that the anonymity of the patients was guaranteed. For that reason, the data has been used only once on the database, without any direct identification of the patients involved.

Results

Total sample of ADRs

Out of 64 patients included, 55 (38%) ($n = 36$) were men and 44.81% ($n = 29$) were women with a median age of 62.73 (DS ± 17.30) showing an average of 63 years old (ranging 25-96). In total there were 71 ADR with seven patients having more than two ADRs.

Concerning hospitalization, the average number of admission days was 21.6 (DS 25.06), with a median of 13 days (ranging 1-135). ADR caused the hospitalization in 53.52% ($n = 33$) of the sample. ADR occurred during hospitalization in 29.57% ($n = 21$) while 25.35% ($n = 18$) extended it. Regarding the evolution timing, the average was 5.36 (DS = 7.54) and the median was 3 days (ranging 0-30). 67.6% of the sample showed serious

ADR, 12.67% (*n* = 9) showed an unexpected ADR, while 8.45% (*n* = 6) had a re exposition and 40.84% (*n* = 29) was under polypharmacy (Table 1).

TABLE 1.
Demographic and descriptive variables of the sample.

	Total sample (*n* = 71)	CNS-D (*n* = 45)	Sys-D (*n* = 26)	p
Gender				
Female *n* (%)	32 (45.07%)	22 (48.9%)	16 (61.5%)	0.30
Male *n* (%)	39 (54.9%)	23 (51.1%)	10 (38.5%)	
Age	62.73 (SD17.89)	62.24 (SD 17.75)	63.88 (SD 16.79)	0.70
Hospitalization				
Hospitalization days	21.60 (SD 25.06)	18.02 (SD 22.47)	26.46 (SD 28.86)	0.17
Reason for admission *n*(%)	33 (53.52%)	26 (57.8%)	7 (38.9%)	0.17
During hospitalization *n*(%)	21 (29.57%)	10 (22.2%)	11 (77.8%)	0.07
Extended hospitalization *n*(%)	18 (25.35%)	8 (17.8%)	10 (38.5%)	0.05
Time of evolution (days)*	5.36 (SD 7.54)	4.5 (SD 5.89)	5.93 (SD 8.63)	0.65
Severe ADR *n*(%)	48 (67.60%)	31 (68.9%)	17 (65.4%)	0.76
Unexpected ADR *n*(%)	9 (12.67%)	6 (13.3%)	11.50%	0.87
Re exposition *n*(%)	6 (8.45%)	4 (8.9%)	2 (7.7%)	0.86
Notification ANMAT *n*(%)	2 (2.81%)	0 (0%)	2 (7.7%)	0.05
Polypharmacy *n*(%)	29 (40.84%)	20 (44.4%)	9 (34.6%)	0.41

Data expressed as median and SD (Standard Deviation); CNS-D: Central Nervous System Drugs; Sys-D: Systemic Drugs. *Time of evolution: Timing in days from the administration of the molecule and the ADR.

ADRs developed by drugs used for neurological diseases (CNS-D)

48.9 % (*n* = 22) of CNS-D were female patients, whereas 51.1% (*n* = 23) were male patients. The median age was 62.2 years (SD 17.8). The average admission days for this group was 18 days (SD 22.47), with a median of 11 days (range 2-126). The CNS-D group motivated the hospitalization in 57.8% (*n* = 26). An ADR was produced during hospitalization in 22.2% (*n* = 10) and it extended the hospitalization in 17.8% (*n* = 8) of the sample. Within the CNS-D group that most frequently produced ADR, the ones which stood out were antiepileptics (AED) (Figure 1), and between those, diphenylhydantoin (DFH) and carbamazepine (CBZ) (Figure 2) were prominent. Psycholeptics represented 44% (*n* = 20) being lithium the most frequent (*n* = 9). Concerning the time of evolution of the ADR, the median was 4.5 days (SD 5.89). 68.9% (*n* = 31) showed serious ADR. 13.3 % (*n* = 6) showed unexpected ADR while 8.9% (*n* = 4) had a re exposition to the molecule. 44.4% (*n* = 20) showed polypharmacy at the time of hospitalization (Table 1).

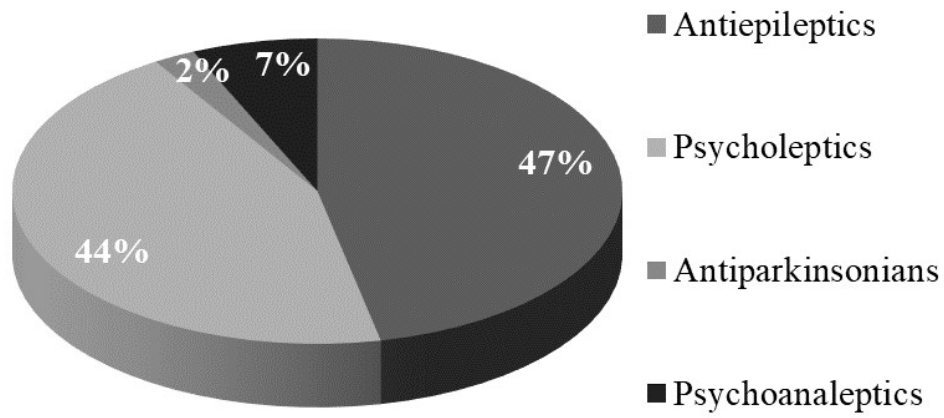

Figure 1. Neurological drugs that caused ADR (n = 45).
Source: Authors.

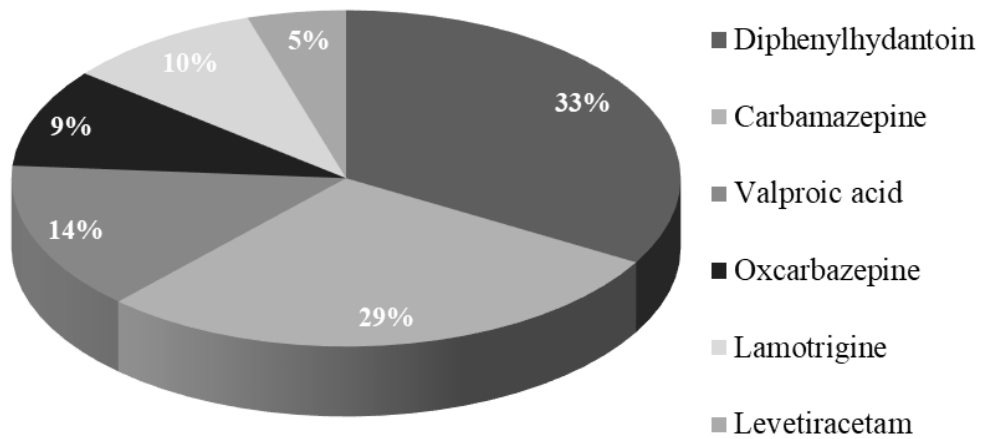

Figure 2. Antiepileptic drugs that caused ADRs (n = 21).
Source: Authors.

According to the score of Naranjo Algorithm, 73.3% (n = 33) showed a probable cause of ADR, while 26.7% (n = 12) were possible. The median of the score was 5.22 points (SD 1,4). (Table 2).

TABLE 2.
Imputability variables and types of ADRs.

	Total sample (n=71)	CNS-D (n=45)	Sys-D (n=26)	p
Naranjo Algorithm				
Category				
Confirmed	0%	0%	0%	0.003
Probable	43 (60.6%)	33 (73.3%)	10 (38.5%)	
Possible	28 (39.4%)	12 (26.7%)	16(61.5%)	
Score	4.90 (SD± 1.50)	5.22 (SD ±1.49)	4.34 (SD ±1.38)	0.017
ADR type				
A	45 (63.4%)	33(73.3%)	12 (46.2%)	0.022
B	26 (36.6%)	12 (26.7%)	14 (53.8%)	

Source: Authors.

It is important to mention the case of a patient who was prescribed levetiracetam (LVT) due to a focal epilepsy. After a few months, he developed behavior disorders which improved once the medicine was stopped. Another patient showed rhabdomyolysis after the use of DFH. And another one showed hyperammonemia after using valproic acid.

ADR caused by systemic drugs

61.5% (n = 16) of Sys-D group were females whereas 38.5% (n = 10) were males. The median age of the sample was 63.88 years (SD ± 16.8) with a median of 60 years (range 28-90). The average days of admission for this group was 26.5 days (SD ± 28.86) showing a median of 18 days (1-135). The Sys-D group motivated hospitalization in 38.9% (n = 7). ADRs were produced during hospitalization in 77.8% (n = 11) and it extended hospitalization in 38.5% (n = 10) of the sample. Within the most frequent Sys-D group, antiarrhythmic and antibiotics stood out with 34% (n = 9) for both groups (Figure 3).

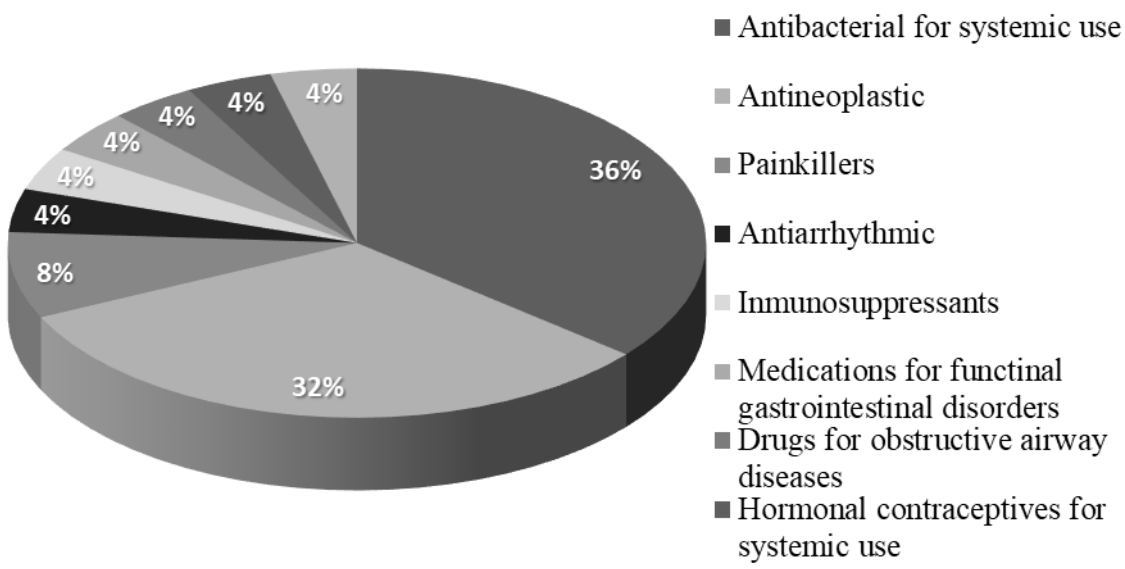

Figure 3. Systemic drugs that caused ADRs (n = 26).
Source: Authors.

Concerning the time of evolution of ADRs, the median was 5.93 days (SD = 8.63). 65.4% (n = 17) showed serious ADRs. 11.5% (n = 3) showed unexpected ADR whereas 7.7% (n = 2) had re exposition to the molecule. 34.6% (n = 9) showed polypharmacy at the time of hospitalization (Table 1).

According to the score of Naranjo Algorithm, 38.5% (n = 10) of the sample showed a probable causality of ADR while 61.5% (n = 16) were possible. The median of the score was 4.34 days (SD ± 1.38) (Table 2).

In this group, a patient in treatment with pazopanib (tyrosine kinase inhibitor) had Posterior Reversible Encephalopathy Syndrome (PRES). Another patient with lupus (LES) showed aseptic meningitis by Trimethoprim-Sulphametoxazol (TMS) with a Physicochemical of Cerebrospinal Fluid (CSF) of 1000 cells Predominantly Polymorphonuclear (PMN) requiring an exhaustive analysis of differential diagnoses. In this particular case the diagnostic key was the re exposition to the drug with the same symptoms and their

disappearance hours later after its suspension. Other cases of encephalopathy induced in two patients by axitinib (tyrosine kinase inhibitor) and tacrolimus are mentioned, with improvement after the withdrawal of the drug. Also, a case of cerebritis secondary to cytarabine is highlighted.

Comparative analysis between CNS-D and Sys-D

It was observed that in Sys-D group hospitalization was extended in 38.5% (n = 10) compared to the CNS-D group, with 17.8% (n = 8) (p = 0.053). Other comparisons can be seen in Table 1 without any significant statistics.

According to Edward and Aronson adverse reactions classification, it was seen that the CNS-D group presented a higher percentage of ADR type A (73.3%; n = 33) and the Sys-D group had a higher frequency of ADR type B (53.8%; n = 14) with a p = 0.0022.

Discussion

One of the main aims of PhVG is to report the ADRs due to its implications in public health (Bignone & Schiaffino, 2016; Ponte et al., 2013). Polypharmacy and ADRs cause a higher number of hospitalizations, extending the time of hospital stay thus generating a higher demand of supplies which produce an economic impact (Ponte et al., 2013; Chaio et al., 2013). There are a few publications on this subject especially on neurological ADRs.

In Neuro-Pharmacovigilance there are different scenarios where the neurologist finds himself in everyday practice. This study allows to describe these different scenarios through the analysis of the characteristics of ADRs. On one hand, ADRs produced by CNS-D which are the ones the neurologist finds constantly allowing a higher level of suspicion. According to Ponte et al and Chaio et al Neuropsychiatric ADRs were 118 (4.87%) and 9 (8%) respectively (Ponte et al., 2013; Chaio et al., 2013). In the current study antipsychotic and antiepileptic drugs produced ADRs with higher frequency in the CNS-D group.

On the other hand, most of the Sys-D showed neurotoxicity, like antibiotics or antineoplastic drugs. These ADRs are a diagnosis challenge because they have a low suspicion, or they could be confused with other neurological diseases. Thus, this highlights the different neurological diagnosis without any etiology that has a time relation with consuming a medication in a short, medium or long period.

It is important to emphasize the imputability of ADRs, considering the time between the drug administration and the event, the medical or pharmacological plausibility and the probability or exclusion of other causes (WHO/ The Uppsala Monitoring Centre, 2001). Therefore, a comparison was done based on the Naranjo Score between ADRs produced by CNS-D and Sys-D. It was observed that Sys-D group showed a high percentage of ADRs in the “possible” category. On the contrary, CNS-D group showed a high percentage in the “probable” category, indicating a significant statistic. Consequently, it is possible to find a major difficulty in making an ADR diagnose by systemic drugs because there are distractive elements. The view is even more complex to determine the timing between the drug and the event in a large number of patients due to the scarce knowledge of the neurological ADR of new pharmacological therapies.

As above mentioned, when comparing CNS-D and Sys-D groups on the basis of the ADR type according to Edward and Aronson classification, it was observed that the first group showed a high percentage of ADR type A and Sys-D group has a high frequency of ADR type B (Edward & Aronson, 2000). This finding reinforces the concept of the diagnosis challenge of neurological ADR produced by Sys-D because they are uncommon, they do not show any relationship with the mechanism of action in some cases and they show unpredictable mechanisms of action in others.

On this scenario, health professionals should be encouraged to increase the number of notifications of ADRs in order to gain knowledge on ADR. The reduced number of publications plus the underreported notifications, generate limited statistical data, delaying the detection of signals and causing underestimation of the real magnitude of the problem. Hence the unawareness of the medicine during its commercialization stage.

There are multiple reasons that influence the lack of notifications, like underdiagnosis, fear of reprisals, scarce information on PhVG, short time, among others (Grill & Maganti, 2011; Bolaños, 2016). Regarding underdiagnoses, it is possible that ADRs are not considered as a cause of a disease.

The population with highest risks of developing ADRs is on the age extremes (newborns and the elderly ones) and polypharmacy patients (Ponte et al., 2013). Firstly, ADRs could be originated from changes in pharmacokinetic and pharmacodynamics (Rattagan et al. 2016). Secondly, elderly patients are exposed to polypharmacy due to the high prevalence of chronic disease. Our research is in accordance with the current literature, which is, a high level of polypharmacy thus causing an increase in the probability of showing an ADR.

The limitations of our data include the observational retrospective nature, so that the scarce availability of demographic data and the exposition time did not allow to have a higher number for statistical analysis. Only hospitalized patients were included, therefore, a great number of patients were not included in the sample which explains its limited size. For this purpose, patients who do not show serious ADRs are not requested neurological consultant and not all hospitalized patients are assessed by this specialty.

Considering the major assets of the current research and the few ones published in Argentina, this might be the first one which has a detailed analysis of neurological diseases (Martino et al., 2019).

Therefore, it is important to make a proper statement to the authorities to have national data to take sanitary measures. Finally, by excluding drug intoxications uncertainty was avoided at the time of analyzing different ADRs.

Conclusions

In the diagnostic algorithm of a patient who shows neurological symptoms, it is convenient to suspect of an ADR as a possible etiology. It is the only way to avoid an exhaustive and unnecessary diagnostic research as well as empiric treatments that could be unjustified. In many cases, diagnosis and treatment could be delayed because medication might not be considered as a cause.

There are ADRs seemingly rare because they are less frequent. However, they are already described in the national prospects. Therefore, they are not rare themselves but unknown to the health professional. It could be useful to check the drug prospect on a regular basis, especially in cases where there has been a meaningful time relation between the drug and the beginning of the event.

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Short Survey

DIAN-TU ARGENTINA

A great human story of a small group of people

DIAN-TU ARGENTINA

Una gran historia humana de un pequeño grupo de personas

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Abstract

Alzheimer's disease is, by far the first, cause of dementia and the more frequent neurodegenerative disease. Considered as a result of multifactorial causes, aging is the main risk factor for the classical form of the disease and because of global aging, a very significant increase in the prevalence is expected in the upcoming decades, especially in countries in development. Several drugs with different targets have been tried so far and, still with no success. Frenzied efforts seeking a new disease-modifying drug are constantly being pursued and innovative models of the clinical trials have emerged. The DIAN initiative studies individuals with known mutations in the deterministic genes of the disease. Autosomal Dominantly Alzheimer Disease (ADAD) showed to be a more predictable model in terms of whom and when will get the disease. This allows testing novel therapeutics agents by choosing the drug according to the biological moment of the disease. But ADAD is also a uniquely human story full of courage and hope. The DIAN trial has started in Argentina and a new anti-tau age has begun as well.

Keywords: DIAN-TU Argentina; ADAD; anti-tau; Taco Pozo; FLENI

Resumen

La enfermedad de Alzheimer es por mucho, la primera causa de demencia y la enfermedad neurodegenerativa más frecuente. Considerada como resultado de causas multifactoriales, el envejecimiento sigue siendo el principal factor de riesgo en su forma clásica y debido al envejecimiento global, se espera un aumento muy significativo de la prevalencia en las próximas décadas, especialmente en los países en desarrollo. Hasta ahora se han probado numerosos fármacos con diferentes dianas aunque aún sin éxito. Constantemente se realizan descomunales estudios en busca de un nuevo fármaco que logre modificar el destino de la enfermedad y así han surgido innovadores modelos de ensayos clínicos. La iniciativa DIAN estudia individuos con mutaciones conocidas en los genes determinantes de la enfermedad. La enfermedad de Alzheimer autosómica dominante (ADAD) demostró ser un modelo más predecible en términos de quién y cuándo contraerá la enfermedad. Esto permite probar nuevos agentes terapéuticos eligiendo el fármaco según el momento biológico de la enfermedad. Pero ADAD es también una historia muy humana llena de coraje y esperanza. El ensayo DIAN ha comenzado en Argentina y también ha comenzado una nueva era anti-tau.

Palabras clave: DIAN-TU Argentina; ADAD; antitau; Taco Pozo; FLENI

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Introduction

For more than a decade (2010), the DIAN [Dominantly Inherited Alzheimer Network] led by the Washington University School of Medicine in St. Louis, USA, and mostly funded by the National Institutes of Health (NIH), the Alzheimer's Association, and donations from philanthropic funds, have embarked on a multinational effort to better understand Alzheimer's disease (AD) and test novel potential treatments (Morris et al., 2012). In this case, this aim is pursued on the study of a particular and minority group within AD, such as autosomal dominant Alzheimer Disease (ADAD). DIAN studies families with mutations in the deterministic genes of AD (PS1, PS2, and APP), named in such a way because they guarantee that those who inherit the mutations will develop the disease at an early age (average 45 years, range 30 to 60 years) and with a chance close to 100% (complete penetrance). In general, these individuals, due to their youth, do not present any other health problems. Another distinctive feature is that the estimated age of onset is maintained with very little variation between generations. Both conditions provide something very difficult to obtain in medicine, which is: absolute predictability of who will develop the disease and, even more, when it will develop. From there arises the scientific and unique importance that this minority of cases of ADAD constitute. In other words, the ADAD represents the purest and most predictable model of AD.

But it is precisely these peculiar characteristics that generate a real drama in families when it is found some of the deterministic mutations of ADAD. As if suffering from AD were not enough, it is much more dramatic to have it at an early age in life, fully productive; having seen it happen in parents, uncles, grandparents; with the risk of having transmitted it to their children (50% risk); and living each year as a true countdown. In this sense, ADAD also represents the paradigm of dominant genetic disease and a real challenge for genetic counseling (Rahman et al., 2012; Aschenbrenner et al., 2020).

Currently, the DIAN is divided into three main lines of research: the DIAN Obs (observational) was the pivotal study (2010) and is dedicated to investigating, in the most exhaustive possible manner, mutation-carriers, comparing them with non-carriers. The study is carried out in a series of visits with a frequency established according to the age of the individual and the difference the participant has with its parent's age at onset. Cognitive evaluations, DNA and RNA extractions, cell immortalization, plasma, CSF, MRI, PET with PIB, FDG, and TAU are carried out. In the "Obs", both those who learnt their genetic status and those who know they are not carriers (and therefore do not have any risk) are allowed to participate, the latter functioning as a control group. It is, in any case, the vocation of the participants to contribute to science some degree of knowledge, the main reason for which they enroll. This line of study has already been followed for 11 years and has revealed important findings in terms of novel biomarkers (in CSF and blood) of AD, at the same time that it has ratified the same sequence of molecular events as in the Classic form of AD (Bateman et al., 2012; Bateman et al., 2011).

The DIAN TU (intervention unit, from English: "trial unit"), started in 2012, is intended to test new potential treatments. It has a dynamic design in order to test the cohort with the best possible treatment. In general, it is proposed to test more than one drug at the same time in different branches in parallel and its arms were projected until 2028 (Bateman et al., 2017). The "TU" has also been split into primary preventive or secondary preventive based on the time before the estimated age of onset. By doing so, different drug mechanisms could be tested according to the biological moment of the disease. Naturally, this DIAN line is the one that generates the greatest hope in the participants and their families. Only carriers participate (whether or not they know their genetic status) and non-carriers who do not know their genetic status. At the beginning of 2020, the results of the first two arms were announced, which began in 2012 with very encouraging results at the biomarker level for the anti-amyloid antibody gantenerumab (arm II of the TU). For this reason, gantenerumab has entered in an open phase branch (open-labeled extension). But only the participants of that first trial were included. Two more arms, solanezumab (arm I) and atabecestat (arm III) did not progress further or were suspended due to lack of effectiveness or adverse effects. Now (2021), a new test arm (IV) was announced with an anti-Tau antibody specific for the mid-region and microtubule-binding sites (E2814).

Finally, there is a third line which is the DIAN EXR, whose main function is to spread information and invite new families to participate through a digital registry that allows direct communication between family members and researchers.

In Argentina, the DIAN Obs began its enrollment in the FLENI institute in December 2014 under the national subsidy PICT2015-2110. To date, 11 participants from 6 families with 5 different mutations have been enrolled. Of these, 9 are currently in progress (1 withdrawal and 1 deceased) and a total of 28 in-person visits have been made. In 2018, FLENI had been assigned the possibility of entering DIAN TU arm III, but as mentioned, this branch was suspended at the time.

Meanwhile, between 2018 and 2019 as part of DIAN EXR, a team of researchers from FLENI, together with doctors from Salta, moved to the city of Taco Pozo, Province of Chaco, since a large branch of a family of Buenos Aires resides there. This family branch consists of approximately 50 individuals, 21 of them donated blood and it was determined that half of them are carriers (Figure 1). Later, on a second trip, the same team traveled to Paraná, Entre Ríos province, together with doctors from the San Martin Hospital in search of families of Volga German descent (Russian Germans), known to have a specific mutation in PSEN2. With such a large community located in Argentina, fieldwork was carried out. After interviewing 20 families, the finding was confirmed in one of them and there are two more highly suspicious (Figure 2).

The incorporation of these families who are in other provinces represents a logistical and resource challenge. Because of this, the DIAN central committee has requested new international grants for the expansion of DIAN in Latin America. This time the Alzheimer's Association has allocated 1 million dollars for the opening of new sites in Mexico, Colombia, Brazil, and an additional site in Argentina (Libre-Guerra et al., 2020). The latter will be located in the Province of Salta, Argentina and it will work out as a satellite center for FLENI to carry out the observational study.

Satellite Site, “Salta-Taco Pozo”

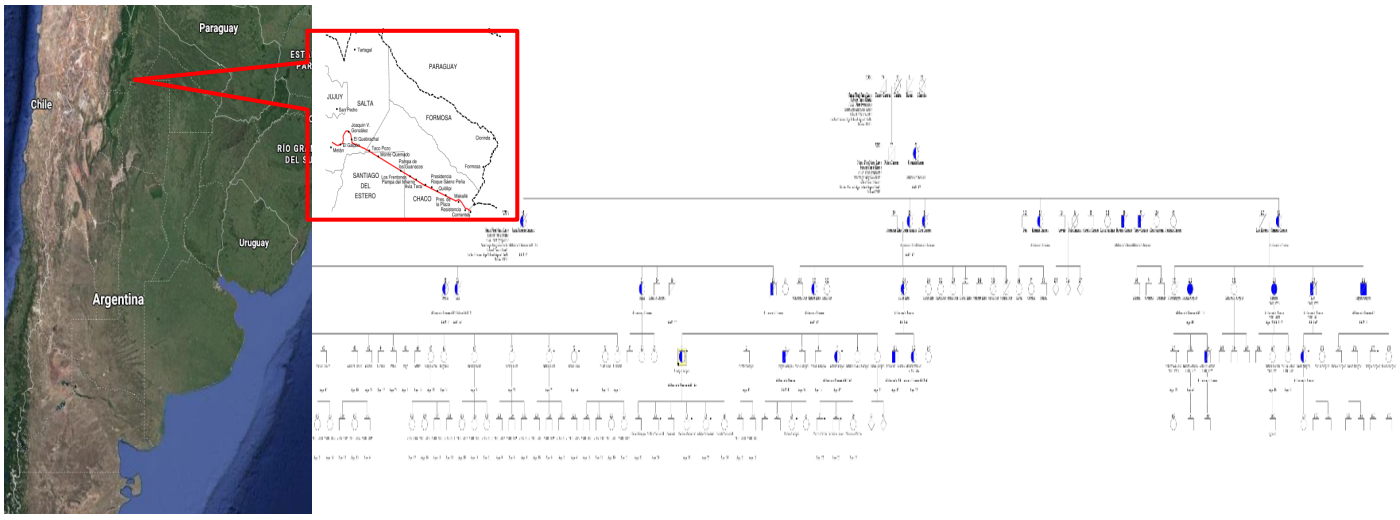

Figure 1. Shows next satellite site opened in Argentina as part of DIAN LatAm initiative, and the pedigree of the family founded in this location as part of the DIAN EXR.
Source: Authors.

DIAN EXR-Arg Entre Ríos

Volga-German communities in ARG
(Calculated 500.000 inhabitants)

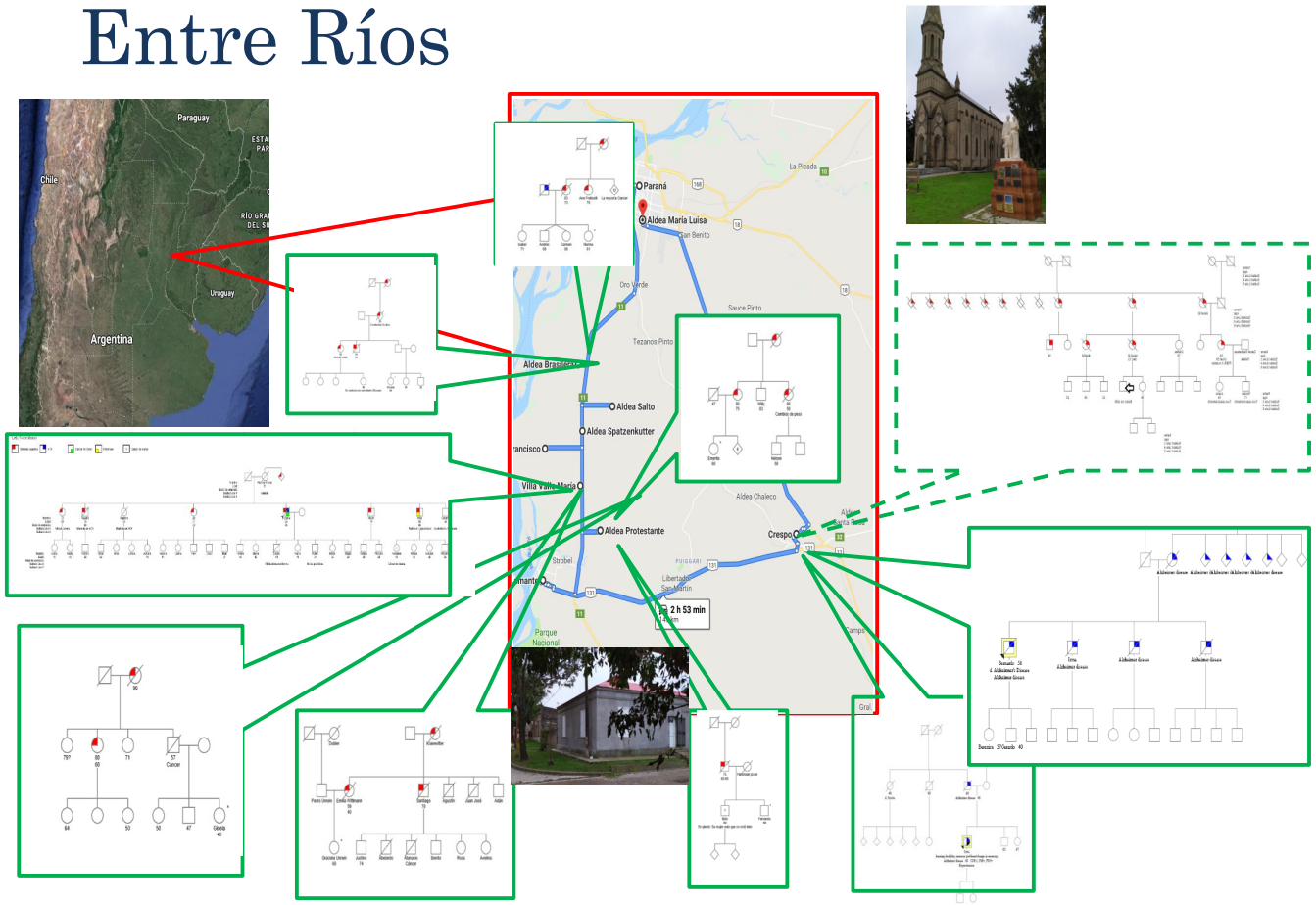

Figure 2. Route map of the fieldwork carried out for identifying possible familial cases within Volga-German communities in Entre Rios province (Argentina).
Source: Authors.

The greatest news for Argentinean families with ADAD occurred at the beginning of 2021 since the enrollment for the aforementioned arm IV of the TU in FLENI began. The first participant has already been enrolled and the rest of the "Obs" is expected to follow in its footsteps. Although the E2814 will not be available for testing before the end of 2021, the TU has begun with a cognitive pre-study (CRI of English; Cognitive Run-in) that guides the cognitive tests as they were receiving the drug. This way, it will be possible to enhance the statistical analysis when the active arm is tested and facilitate the incorporation and adherence of the participants to the study.

In conclusion, participating in the DIAN invites us to a unique experience: young patients and families mobilized in an early intervention study, where the most advanced knowledge in the field of genetics, biomarkers, and therapeutics with potentially disease-modifying drugs, converge. All this takes place in a dynamic of shocking human content, accompanying these families on a complex path, with a growing hope of being closer to the delay (or cure) of the disease.

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Short Survey

Creative minds and neurosciences…

Mentes creativas y neurociencias...

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Abstract

Creativity is the ability to generate original ideas in the arts or sciences, leaving traditional stereotypes behind, ultimately introducing innovation to the social context in which they arise. It has been associated with "divergent thinking" which prioritizes the generation of multiple solutions, different from traditional ones. Some authors have observed creative individuals present higher incidence of affective disorders, possibly related to hypomania or disinhibition. Similarly, "creativity" has been described in patients with frontotemporal dementia, a brain region linked with creativity on fMRI. Creativity is one of the most salient characteristics that human beings possess

Keywords: Creativity; intelligence; divergent thinking; psychiatry; neurology; anatomy

Resumen

Creatividad es la habilidad de generar ideas originales en arte o ciencia, dejando atrás los estereotipos y produciendo innovaciones en el contexto social en el cual ocurren. Creatividad es asociada con pensamiento divergente que prioriza la generación de múltiples soluciones diferentes a las tradicionales. Algunos autores refirieron que era muy frecuente los trastornos afectivos en los pacientes creativos, esto probablemente mas relacionado a la hipomanía o la desinhibición como también ocurre en la demencia fronto-temporal. Estas regiones cerebrales fueron descriptas en los trabajos con resonancia funcional. La creatividad es una de las características mas relevantes que posee el ser humano.

Palabras clave: Creatividad; inteligencia; pensamiento divergente; psiquiatría; neurología; anatomía

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Introducción

What was happening in Jorge Luis Borges' brain while he was writing "The Library of Babel", or in Rafael Nadal's when he won at Roland Garros? In what way were Albert Einstein and Pablo Picasso's brains different?

Creativity is one of the most important characteristics that human beings possess (Andreasen & Ramchandran, 2012). One of the greatest challenges is defining the term "creativity". At the beginning of the 20th-century, creative people were considered geniuses, Howard Gardner described multiple types of creativity and referred to this as "multiple intelligence" Today the term refers more to individuals who make creative contributions.

There were three-stages in the history of theories on creativity (Sun-Hyung, Kwang Ki & Jarang, 2016):

1. The first was the He-paradigm, that of the "lonely genius", the classical view of creativity, a great man like Leonardo Da Vinci for example, who produced an outstanding body of creative work (H-creativity or big C).

2. The second stage was the I-paradigm based on individual creativity. This position considers all individuals can develop creativity (P-creativity, personal creativity, or little c).

3. The last stage was the We-paradigm, which argues that culture and cognition are correlated, and creativity is a cognitive process influenced by social context.

Simonton (2012) describes a continuum between "big C" (only a few individual geniuses) and "little c" (ordinary creativity which all people possess).

Currently, creativity is considered the ability to generate new and original ideas, leaving traditional stereotypes and patterns behind, introducing innovations into the social context in which these ideas arise. We live in a changing and increasingly complex world, in which creativity implies a reaction to the difficulties and challenges of the future; this innovative, transformative, and constructive capacity represents one of the engines of humanity's scientific and cultural evolution (Sun-Hyung et al., 2016). Art is but one example where humans demonstrate the capacity for creativity, but it would be a fallacy to believe that creativity is a characteristic unique to the artistic world. Today, creativity includes the arts (painting, literature, poetry, music, etc.) and sciences (mathematics, physics, chemistry, biology, etc.) (Zaidel, 2014). When brain activations are compared, findings give no support to the idea that artists and scientists represent two separate cultures. Both respond in similar ways, showing activation of brain circuits involved in higher–order socio-affective processing, and in REST (Random Episodic Silent Thought)/ the default mode network (resting-state on Brain MRI) (Andreasen & Ramachandran, 2012).

The essential personality trait of a creative mind is "openness to new experience," which is translated into a particular interest in varied experimentation, which some call "intellectual curiosity". We should not equate creativity with intelligence. They can occur together, but also separately. In the case of intelligence, "convergent thinking" is prioritized to find the only, or if not that, at least an adequate solution to a problem. Creativity on the other hand is associated with "divergent thinking" which

prioritizes the generation of many response possibilities, different starting points, and multiple solutions, different from traditional ones. Ordinary creativity can be stimulated and can develop in many people throughout their lifetime. Extraordinary creativity however, is innate, genetic, and only be seen in geniuses like Leonardo Da Vinci.

In the 18th century, Lombroso (1881) postulated the source of genius was a constitutional defect related to insanity, whereas others thought it represented the greatest capacity of the human race (Galton, 1869). A more modern approach to the concepts of geniality and insanity, has been to replace the terms with creativity and mental illness (Hare, 1987). Some studies indicate creative individuals present higher incidence of affective disorders, and that geniuses tend to be introverts, in whose families there can be relatives with schizophrenia (Newton, Einstein, and Russel) (Hare, 1987). Under these circumstances, the discovery of an original and different solution can be mistaken for the extravagance of a delusion. Vincent Van Gogh for example, who suffered throughout his life from a severe mood disorder, produced more than 300 of his greatest works during periods of psychotic mania. Other famous and creative individuals exhibiting mood disorders include: Ernest Hemingway, Winston Churchill, and Theodore Roosevelt (Andreasen, 2008). Many writers seeking to trigger the effects of creativity while working (and some artists too, but few scientists it seems), have resorted to using drugs during the creative process (Hare, 1987). Alcohol has been the one chosen most often, but absinthe (Hemphill, 1961), or even cocaine have been other options, to name a few (Thornton, 1986). In these situations, disinhibition, or loss of impulse control is often mistaken for creativity. The study of the relationship between creativity and mental illnesses remains a relatively open territory, with much work still to be done to further the field (Andreasen, 2008).

What do we know about creativity in neurological and psychiatric diseases? Our brains are made up of circuits responsible for our behaviours. Nevertheless, they are still always the same circuits in the same brain. Zaidel (2014) for example speculated that in the healthy brain, cognitive associative networks in the left or right hemisphere (working alone or together), can contribute to the creative process in art. Other authors working with fMRI found greater participation of the left hemisphere in creativity (Gonnen-Yaacovi et al, 2013). Patients with lesions (e.g., tumours) in the temporal lobes, exhibit disinhibition and increased creativity, whereas those with frontal lesions present apathy, rigidity and inflexibility as well as decreased creativity. Functional neuroimaging data from healthy subjects shows the prefrontal cortex plays an important role in cognitive processes involved in creativity (Gonen-Yaacovi et al., 2013). In drawings made by patients with Alzheimer's dementia, decreased ability to appreciate details is observed as well as a tendency to disorganized disposition, a preference for darker tones, and a more significant distortion of faces (Serrano, Allegri, Martelli, Taragano & Ranalli, 2005). In patients with frontotemporal dementia (Pick's disease), inhibitory controls are lost, and increased creativity can be seen (Serrano y Allegri, 2005; de Souza et al., 2014). Belief that psychiatric patients have high creative potential is quite widespread. Eysenck has suggested that creativity is related to psychoticism and

that both underlie a cognitive style that can be identified as over-inclusiveness, which is closely related to divergent thinking. Over-inclusiveness may be due to a failure of inhibition present in psychotics and necessary in creatives. However, one must be prudent and not fall into false generalizations. This theory does not describe a direct association, it simply details common brain mechanisms that ultimately share neural circuits.

Where is creativity generated within our brains? Sperry's experiments in 1961 showed that the left and right hemispheres were functionally different. The right hemisphere was described as creative, operating in a holistic and globalizing fashion, and the left as logical, analytical, and rational. The error in this concept was to think only of artistic creativity for which the right hemisphere is responsible, anf forget about scientific creativity which is handled by the left hemisphere. Authors such as Flaherty in 2005 have proposed creative ideas are generated through an interaction between frontal and temporal lobes and the limbic system. In this hypothesis, neurotransmitters such as dopamine facilitate voluntary and single-goal-oriented activities while inhibiting competitive behaviours, striking a balance between frontal cortex-based rationality and temporal-limbic cortex-based emotions.

Results from functional brain MRI studies showed divergent thinking correlated with well distributed bilateral brain activation in the left prefrontal cortex and the right medial temporal lobe, with deactivation of the right temporoparietal junction. Whereas when retrieval of old ideas was compared to generation of new ideas, increased activation was observed in the inferior parietal cortex of the left hemisphere (Benedek et al., 2014; Sun-Hyung et al., 2016).

Is the brain of a genius different from that of a normal individual? Einstein's brain, one of the most studied in history, was significant in the search for brain characteristics indicative of genius and creativity. Einstein did think uniquely even though his brain weighed only 1 230 grams, significantly less than the average in adults which is around 1 400 grams. For many years, this was taken as evidence to support the paradigm of a lack of relationship between brain structure and function. It was only in 1999, that a study was published in which researchers found that the region responsible for mathematical thinking and visual-spatial skills was 15% larger in Einstein's brain compared to others. Even if this was probably the source of Einstein's greater logical-mathematical ability, we still do not know where in his mind his creativity was harboured.

Conclusions

Jorge Luis Borges, Rafael Nadal, Albert Einstein, and Pablo Picasso all share the unique quality of the human genius, namely creativity in the highest degree together with the underlying brain processes that determine it. Creative minds are the ones pushing the evolution of the arts and science forward in societies, and ultimately the development of the human being.

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