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The Neural Correlates of Expectations Effects

THESIS

Presented to the Faculty of Science and Medicine of the University of Fribourg (Switzerland) in consideration for the award of the academic grade of *Doctor of Philosophy in Medical Sciences*

By

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From

Le Glèbe (FR)

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Abstract (English)

Placebos are inert substances or sham procedures encompassed within a positive psychosocial context whose self-healing properties are termed placebo effects. Of relevance, “There’s not one single placebo effect, but many” (Benedetti, 2014). Consequently, placebo effects are formed and triggered by distinct processes such as classical conditioning and expectations which are supposedly supported by different neural mechanisms.

In Study 1 entitled “Neural correlates of expectations-induced effects of caffeine intake on executive functions” (Wicht et al., 2021a), my colleagues and myself contrasted the effects of caffeine and caffeine expectations on neurocognitive performance at two cognitive tasks in a population of conditioned individuals (i.e., moderate caffeine consumers). Our results indicated that neither caffeine nor expectations were able to enhance cognitive performance. Still, we showed that caffeine and expectations activate the same neural networks, but to a different extent.

In Study 2 entitled “Experience with opioids does not lead to the recruitment of distinct brain network during placebo analgesia” (Wicht et al., 2021b), my colleagues and myself aimed at demonstrating that expectations formed through conditioning (i.e., conditioned expectations) or verbal suggestions (i.e., verbally-induced expectations) rely on distinct neural underpinnings. For that purpose, we relied on the model of acute pain in the context of placebo analgesia and by contrasting groups of individuals with or without prior experience with opioids. We demonstrated that the two types of expectations do not recruit different brain networks to produce comparable placebo analgesia.

Overall, the thesis project illustrates that no matter the type of expectations, they tend to reactivate the same neural network as the substituted active intervention to produce comparable effects. Most importantly, it seems likely that there is not one general neurobiological substrate supporting all type of expectations but that they are dependent on contextual information initially provided by the active intervention substituted by the placebo.

Abstract (Français)

Le Placébo prend la forme d'une substance inerte ou d'une intervention trompeuse intégré dans un contexte psychosocial positif et dont les propriétés d'auto-guérison sont appelées les effets placébos. Il est important de relever qu'il n'existe pas qu'un seul effet placébo, mais plusieurs (Benedetti, 2014). De ce fait, les effets placébos sont formés et déclenchés par des processus distincts tel que le conditionnement classique ou les attentes que l'on suppose être soutenus par différents mécanismes neuronaux.

Dans l'Étude 1 intitulée "Neural correlates of expectations-induced effects of caffeine intake on executive functions" (Wicht et al., 2021a), nous avons comparé les effets de la caféine et des attentes sur les performances neurocognitives à deux tâches cognitives dans une population d'individus préalablement conditionnés (c.-à-d., des consommateurs modérés de caféine). Nos résultats indiquent que ni la caféine ni les attentes ne sont capables d'améliorer les performances cognitives. Néanmoins, nous avons montré que la caféine et les attentes activent les mêmes réseaux neuronaux, mais avec une intensité différente.

Dans l'Étude 2 intitulée "Experience with opioids does not lead to the recruitment of distinct brain network during placebo analgesia" (Wicht et al., 2021b), nous avions pour objectif de montrer que les attentes formées au travers du conditionnement (c.-à-d., les attentes conditionnées) ou par les suggestions verbales (attentes verbalement induites) dépendent de réseaux neuronaux distincts. Pour ce faire, nous avons employé le modèle de la douleur aigue dans le contexte de l'analgésie placébo tout en comparant des groupes d'individus avec ou sans expérience préalable des opioïdes. Nous avons démontré que les deux types d'attentes ne recrutaient pas des réseaux neuronaux différents pour produire des effets analgésiques placébos comparables.

Dans l'ensemble, le projet de thèse illustre que peu importe le type d'attentes, celles-ci ont tendance à réactiver les mêmes réseaux neuronaux que ceux activés par l'intervention active remplacée par le placébo, dans le but de produire des effets comparables. Plus

important encore, il semble probable qu'il n'existe pas de substrat neurobiologique général qui supporterait tous les types d'attentes mais que ces bases neuronales dépendent des informations contextuelles initialement fournies par l'intervention que le placébo remplace.

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List of abbreviations

ACC	Anterior Cingulate Cortex
BPD	Balanced Placebo Design
CB1	Cannabinoid Type 1
CMS-DRL	Common Mode Sense-Driven Right Leg
CondExp	Conditioned Expectations group
CR	Correct Rejection
CS	Conditioned Stimulus
CYP1A2	Cytochrome P450 1A2
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalography
ERP	Event-Related Potential
ESI	Electrical Source Imaging
FA	False Alarms
GC/TD	Give-Caffeinated/Told-Decaffeinated coffee
GD/TC	Give-Decaffeinated/Told-Caffeinated coffee
GD/TD	Give-Decaffeinated/Told-Decaffeinated coffee
GFP	Global Field Power
GMD	Global Map Dissimilarity
HARKing	Hypothesizing After the Results are Known
LAURA	Local AUtoRegressive Average
MFG	Middle Frontal Gyrus
mPFC	Medial Prefrontal Cortex
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NSAID	Non-Steroidal Anti-Inflammatory Drug
NAc	Nucleus Accumbens
OFC	Orbitofrontal Cortex
OLP	Open-Label Placebo
PA	Placebo Analgesia
PD	Privatdozent

PE	Placebo Effect
PET	Positron-Emission Tomography
PFC	Prefrontal Cortex
PhD	Philosophiae Doctor (Doctor of Philosophy)
rACC	Rostral Anterior Cingulate Cortex
RCT	Randomized Controlled Trial
RR	Registered Report
RT	Reaction Times
RVIP	Rapid Visual Information Processing
SD	Standard Deviation
SNR	Signal-to-Noise Ratio
UncondExp	Unconditioned Expectations group
US	Unconditioned Stimulus
VAS	Visual Analog Scale
WMN	Weighted Minimum Norm

General Aim and Context

This self-funded PhD project is the result of a $3^{1/2}$-year PhD program for which I was granted a career fund from the Swiss National Science Foundation to be conducted in PD Dr Lucas Spierer's laboratory and under the co-supervision of Prof Jens Gaab. The project grew in a laboratory whose multidisciplinary expertise ranged from the investigation of neural plasticity-based cognitive enhancement and neurorehabilitation using neuroimaging, brain stimulation methods and gamified interventions.

Overall, I aimed at extending current understanding of the neural correlates underlying expectations effects. Relying on dedicated designs, I could disentangle the pure pharmacological effects of a substance from the mere effects of its expectations. More specifically, I wanted to provide empirical evidence supporting recent neurobiological models suggesting that distinct neural networks underlie different types of expectations effects.

Chapter 1: Introduction

Throughout mankind's history, self-declared physicians have always been creative in creating absurd and often repulsive remedies. As such, in ancient Egypt, medications like "crocodile dung, swine teeth, the hoof of an ass, putrid meat and fly specks" (Findely, 1953) were often prescribed. Centuries thereafter, Hippocrates, the father of medicine, was likewise accustomed to prescribing "flesh of vipers, the spermatic fluid of frogs, horns of deer, animal excretions" (Leslie, 1954). Even more absurd was the use of fabled unicorn horn as antidotes or powdered Egyptian mummy to heal wounds between the 16th and 18th century. Over the same period, a French physician successfully cured psychological disorders by suspending patients by their feet whose method was later replicated by a second physician who reversed its patients once more and suspended their heads upward this time. These far-fetched examples highlight that placebos have always been part of mankind's pharmacopeia, even if the understanding of their underlying mechanisms and widespread usage in clinical trials were yet to come.

1.1 Placebos and placebo effects

Placebos (from the Latin: *I shall please*; Shapiro, 1960) can be conceptualized as inert substances or sham procedures surrounded by a set of social (e.g., psychosocial context) and sensory stimuli (e.g., words, rituals). Placebos paradoxically hold therapeutic properties even though their mechanism of action is in direct contradiction with current biomedical understanding of active substances effects. In other words, placebos do not carry proper active treatment's pharmacological properties. The healing properties of placebos, which are referred to as the Placebo Effect (PE), have been increasingly described in the medical literature for over two centuries (Beecher, 1955; Edward Shorter, 2011). More specifically, the PE can be defined as a psychobiological reaction to an inactive substance (e.g., sugar pills) occurring in one's brain, body and behavior (Finniss et al., 2010; Benedetti et al., 2011b) which targets individuals' beliefs about the undergoing treatment and their expectations of a potential health improvement (Ongaro and Ward, 2017). According to Kirsch (1985), this

effect relates to one's expectations or beliefs concerning the deceptively administered placebos, which are designed to resemble to the hilt to the active intervention they replace (e.g., taste, shape, color; *see* Ballou et al., 2017).

1.2 Historical grounds

Earliest reports of placebo controls date back to the 16th century when Catholics offered individuals "possessed" by the devil deceptive divine objects to see whether they'd still react with painful contortions, torments or agony as if they were genuine relics or holy waters (Kaptchuk et al., 2009). Along with the Renaissance religious skepticism, Montaigne in his essay *On the Power of Imagination* (1580) condemned the fraudulent practices of physicians abusing their patients' credulity with "false promises" while their treatment efficacy could only be attributed to the "power of imagination" (*see* Kaptchuk et al., 2009). In the late 18th century, the concept of placebo controls in a medical context became more concrete with the examination of Mesmer's theory of animal magnetism by the Franklin Commission appointed by King Louis XVI (Finniss et al., 2010).

Franz Anton Mesmer, an Austrian physician, claimed to have uncovered an invisible "fluid", the "animal magnetism", which was flowing through every living being and whose invisible forces were concomitantly the cause and cure of every illness. Through a series of deceptive experiments, the Franklin Commission composed of Benjamin Franklin and Antoine-Laurent Lavoisier amongst others could demonstrate that animal magnetism was a hoax as the clinical benefits solely followed from the patients' "imagination" and beliefs in the power of Mesmer himself (**Figure 1**). Unintentionally, Benjamin Franklin and his colleagues shed light on the PE and paved the way for the advent of today's gold standard Randomized Controlled Trial (RCT; Kaptchuk et al., 2009; Dingfelder, 2010).

Following from this disclosure, the 18th and 19th Centuries most successful physicians prescribed plethora of sham pills, fake powders or tinted waters to give patients "peace of mind" (Kaptchuk, 1998). These precursors massively introduced placebos in the pharmacopeia

Figure 1. Benjamin Franklin, as part of the Franklin commission, is exhibiting his conclusions of animal magnetism which led Mesmer to escape on a witch's broom. Anonymous French cartoon, *Magnetism Unveiled*, 1784.

without knowing from where they drew their potencies. It is only in the 20th century that Dodge (1912) introduced the idea that expectations where the mechanisms through which placebos induced a corresponding conscious experience.

1.3 Expectations and expectancies

Also referred to as expectancies or top-down beliefs (Gu et al., 2016), expectations are determined by if-then conditionals and precede the occurrence of nonvolitional responses (Kirsch, 1985; Hyland, 2011).[1] As such, the expectations-mediated mindset can affect cognitive

[1] Of note, a distinction has recently emerged between expectations and expectancies where the former corresponds to a subset of verbalizable and consciously accessible expectancies while the latter are defined as psychological predictions that can be implicit and thus arise without full awareness (Corsi and Colloca, 2017;

and physiological responses according to what the individual believes to be true (Crum and Langer, 2007; Draganich and Erdal, 2014). Of note, these responses do not stem from the mere expectation of their occurrence but rather from the expectation of relative subjective experience, what Kirsch (1985) defined as "response expectations". According to this author, under the assumption of mind-body identity, expectations are hypothesized to alter subjective experience, overt behavior, and physiological function. Placebo expectations generators are thought to comprise a combination of both the probability of a change in behavior to be reinforced and the magnitude of this expected reinforcement which could depend for example upon apparent dosage (Ross and Olson, 1982) or upon slight variations in instructions shaping expectations (Finniss et al., 2010).

Overall, the PE corresponds to the portion of the outcome not elicited by the specific effect of a treatment but rather attributed to one's mindset and resulting expectations (Benson and Friedman, 1996; Crum and Langer, 2007).

1.4 Theories accounting for placebo effects

Seeking interpretations for expectations-induced physiological alterations, Frank (1973) hypothesized that placebos engender feelings of hopefulness which supposedly promotes physical healing. Hope is a complex emotion comprised of expectations, cognitive reflection, deep feelings, and cultural rules of what to expect in the future (Ballou et al., 2017). Accordingly, the Anxiety Theory stipulates that feelings of hopefulness triggered by placebos might cause a reduction in overall anxiety which in turn promotes PEs (Evans, 1985; Meyer et al., 2015). In such a case, expectations would trigger automatic and self-confirming reactions to a specific intervention such as unfavorable affect diminution (Juliano et al., 2011). While

Kube et al., 2017; Kirsch, 2018). Since the current thesis does not specifically focus on unconscious, subliminal PEs, I will exclusively refer to *expectations* throughout the manuscript.

explaining PEs in terms of emotional and affective downregulation might be accurate in some cases, this has been discredited in others were PEs demonstrated their utmost effectiveness when the stress or anxiety levels were at their strongest (Beecher, 1955).

Apart from the Anxiety Theory, two leading theories describe PEs underlying mechanisms based on distinct processes, namely the i) Classical Conditioning Theory, which relies on associative and pre-cognitive learning and the ii) Mentalistic Theory, later renamed the Expectancy Theory (Kirsch, 1985, 1997), which focuses on suggestions, verbal cues and attributional processes (*see for reviews* Haour, 2005; Benedetti et al., 2011; Hyland, 2011).

Regarding the Classical Conditioning Theory, the environmental stimuli associated with the administration of a drug (i.e., the unconditioned stimulus; US), for example the packaging, labels, size, or color of a pill, may become conditioned stimuli (CS) through the repetition of an associative procedure. These CS can then trigger a conditioned response comparable to the unconditioned response elicited by the drug itself (i.e., the US), even in the absence of the US. Concerning the Mentalistic Theory, PEs are postulated to be shaped by individuals' conscious knowledge, beliefs, and expectations.

While the Classical Conditioning and the Mentalistic Theories where initially thought to be irreconcilable, evidence repeatedly demonstrated that they are in fact intertwined and present additive or synergistic properties (Montgomery and Kirsch, 1997; Haour, 2005; Ongaro and Ward, 2017). Accordingly, with the scope to unite these leading theories, Reiss (1980) hypothesized that one mean by which expectations are acquired is classical conditioning. Indeed, conditioning procedures have been demonstrated to shape forthcoming expectations (Ballou et al., 2017), which in turn reinforces the strength of the resulting PEs (Pacheco-López et al., 2006; Wager and Atlas, 2015). Reiss' claim was further supported by groups of researchers suggesting that PEs resulting from repeated administrations of an intervention influence psychophysiological state through learning-based expectations about the effects of the actual intervention (Haour, 2005; Finniss et al., 2010; Benedetti et al., 2011b).

In the same vein, according to the Expectancy Theory (Kirsch, 1985, 1997), classical conditioning would constitute one of the main mechanisms by which expectations are formed. In this context, classical conditioning has been redefined as the process of learning of relations between events (Robert, 1988). Conditioning, whose fulfilment is based on the information that the CS (e.g., smell, taste, popular knowledge regarding a substance) provides about the US (i.e., the actual substance) and not on contiguity (Reiss, 1980; Kirsch, 1997) will shape expectations that certain events will follow others ultimately leading to a conditioned physiological response (Siegel, 1983).

Nonetheless, evidence challenged the synergistic nature of conditioning and expectations as suggested by the Expectancy Theory. On the one hand, it was demonstrated that PEs can be conditioned and elicited in the absence of expectations relying on the subliminal presentation of conditioned stimuli (*see for reviews* Colagiuri et al., 2015; Bąbel, 2019). On the other hand, conditioning alone cannot account for PEs i) experienced by individuals never exposed to the US (Amanzio and Benedetti, 1999) and those ii) whose direction of effects can be manipulated by expectations independently of the underlying conditioning procedure (Montgomery and Kirsch, 1997).

Following from Atlas and Wager (2012) assumption that conditioning may precede both association-based plasticity and expectation-based learning, Kirsch et al. (2016) proposed a comprehensive Cognitive Model of PEs (**Figure 2**) in which expectations are built either through classical conditioning or verbal suggestions while conditioning alone can also produce PEs without involving expectations. In this manuscript, I have revised the terminology of the Cognitive Model by further differentiating the conscious outcomes that arise from classical

conditioned, i.e., the conditioned expectations, from those that originate from verbal suggestion, i.e., the verbally-induced expectations (**Figure 2**).

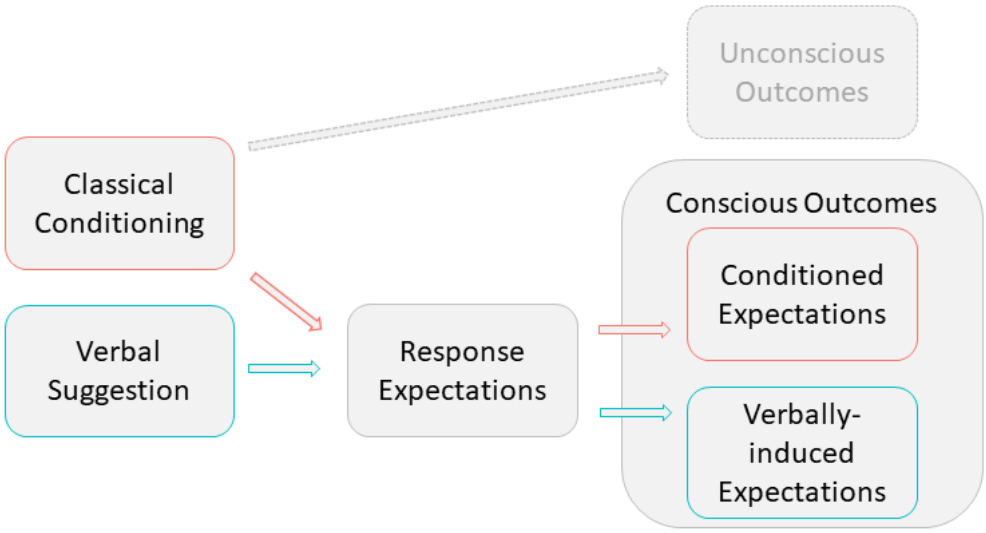

Figure 2. Cognitive model representing the involvement of classical conditioning and verbal suggestion in inducing placebo effects with or without triggering expectations which respectively lead to conscious and unconscious outcomes. Conscious outcomes were divided in conditioned expectations (stemming from response expectations built on classical conditioning) and verbally-induced expectations (originating from expectations build on verbal suggestion). Adapted from "Controlling for the placebo effect in psychotherapy: Noble quest or tilting at windmills?" by Kirsch, I., Wampold, B., Kelley, J.M., 2016, *Psychology of Consciousness: Theory, Research, and Practice, 3,* p.125.

1.5 Placebo experimental designs

The post-World War II era announced the widespread implementation of double-blind RCTs to objectify the extraordinary development of medical research in which placebos were to play a predominant role (Kaptchuk, 1998; Edward Shorter, 2011). Perhaps the most noteworthy example relates to the anesthesiologist and medical ethicist Henri Beecher who published in 1955 *The Powerful Placebo,* the first proto-meta-analysis of placebo treatment effects where he demonstrated that 35% of patients responded positively to placebos (Beecher, 1955). As of today, it is known that his results were slightly inflated by the fact that he did not control for the myriad of unspecific factors that are too often confounded with PEs, such as the natural course of a disease, regression towards the mean, fluctuation in symptoms or rater bias (Ernst and Resch, 1995; Finniss et al., 2010; Ballou et al., 2017; Linden, 2017).

Nevertheless, thanks to Beecher's ground-breaking work, scientists' consideration of the placebo slowly shifted from perceiving it as a "humble humbug" (Anon, 1954) to describing it as a potent therapeutic tool capable of mimicking the effects of active drugs (Kaptchuk, 1998). Of relevance, Beecher's conclusions symbolized the starting point of the criticisms towards the double-blind RCTs. As pointed out by Kaptchuk (1998), to efficiently disentangle PEs from the non-specific factors such as the natural course of a condition, the adjunction to RCT paradigms of a "third no-treatment no-placebo arm" would be warranted.

Consequently, since the late 1960s, the clinical research's gold standard double-blind RCT has been receiving an increasing number of critics (Healy et al., 2010; Edward Shorter, 2011). First of all, the placebo condition in RCTs aims to control for unspecific and undesirable factors such as the natural course of a disease, the regression towards the mean, the fluctuation in symptoms, rater bias while these confounds actually contribute to the healing process (Ernst and Resch, 1995; Finniss et al., 2010; Linden, 2017). Secondly, because of its double-blind inherent property, the ecological validity of the RCT design in therapeutic settings is questionable. Indeed, expectations of therapeutic benefits regarding the active medication ought to be deemed relevant since patients are not given any reason to doubt that their physician is prescribing them anything else than a pharmacologically active treatment (Kirsch and Weixel, 1988). These early criticisms warranted for the implementation of experimental designs that could isolate PEs from pharmacological effects as well as from non-specific factors.

To compensate for the shortcomings of the RCT, Carpenter (1968) proposed the antiplacebo design, also known as the silent administration condition. In this design, both inert and active compounds were delivered to the participants with the instruction that they had received the placebo agent. Conceptually, the antiplacebo design enabled to isolate the pure pharmacological effects of a drug by keeping constant the influence of learned effects such as expectations. This major change in perspectives paved the way for the introduction of more complex paradigms designed to specifically tackle expectations effects.

Thus, with the aim of combining the RCT and the antiplacebo experimental designs to independently manipulate pharmacological and expectations effects, Marlatt and Rohsenow (1980) introduced the now-famous Balanced Placebo Design (BPD). The BDP consists of a 2-by-2 matrix comprising 4 conditions: i) told drug/receive drug (Open), ii) told drug/receive placebo (Placebo), iii) told placebo/receive drug (Hidden), iv) told placebo/receive placebo (Control; **Figure 3**). Thereupon, the specificity of the expectations is accounted for by contrasting conditions i) & ii) while that of the pharmacological effects are isolated when comparing conditions iii) & iv). Initially developed to assess the pure pharmacological effects of psychotropic medications (Ross et al., 1962; Lyerly et al., 1964), this four-cell experimental design reveals the influence of prior knowledge-based expectations in measured effects. To illustrate the discrepancy between the BPD and RCT designs, Kirsch and Weixel (1988) demonstrated that the deceptive administration of decaffeinated coffee presented as containing caffeine produced opposite physiological reactions compared to double-blind RCT conditions where participants were told they might receive either caffeine or a placebo.

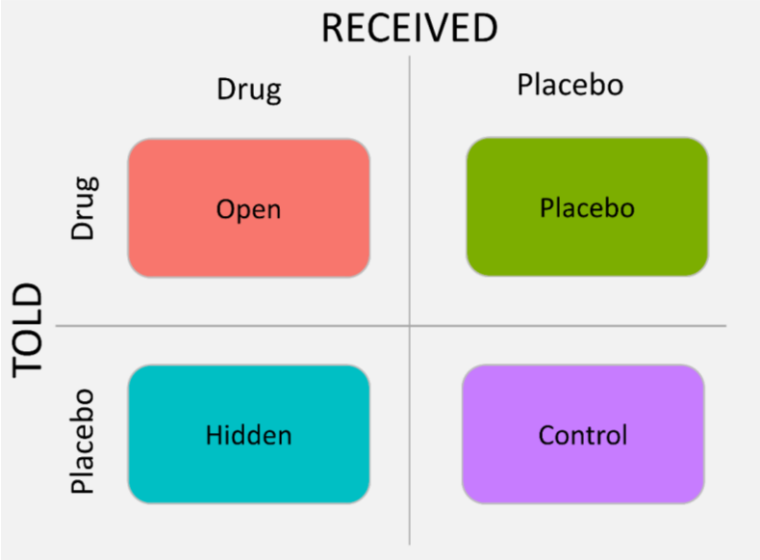

Figure 3. Representation of the four-cells balanced placebo design contrasting substances (Received: Drug Vs Placebo) and instructions (Told: Drug Vs Placebo) to isolate the mere expectations from the unique pharmacological effects of an intervention. Adapted from "The placebo effect: From concepts to genes" Colagiuri, B., Schenk, L.A., Kessler, M.D., Dorsey, S.G., Colloca, L., 2015, *Neuroscience, 307,* p.180.

Nowadays, The BPD is considered a very efficient and elegant paradigm to isolate PEs and to accurately assess the influence of expectations in the overall effect of a substance.

Nevertheless, the BDP raises ethical concerns since it implies to deceive individuals in two of the four cells and thus limits its application especially in vulnerable populations.

1.6 Deception

Howard Brody in his classical paper *The lie that heals: The ethics of giving placebo* (1982) raised awareness on the fact that placebo interventions require to manipulate beliefs and expectations by deceptively misleading patients through overselling "not utterly false statements as well as artful silences" (Justman, 2013).

In fact, since the introduction of the Helsinki Declaration in 1964, the principle according to which one should not lie to patients in research frameworks was raised to a concept of utter moral reality (Edward Shorter, 2011). Exercising deception in experimental setups results in a conflict between means and ends, namely the aim of discovering a scientific truth is sought by deliberately providing untruthful instructions (Miller et al., 2005). Even though the deception is revealed by debriefing participants at the conclusion of an experiment, it may cause distress and distrust regarding general scientific research practices (Fleming et al., 1989).

One way to circumvent this issue is to disclose to participants that the placebo is a pharmacologically inactive substance whose significant improvements, repeatedly demonstrated in clinical trials, come from psychological mind-body processes that support self-healing (Kaptchuk et al., 2010). Such experimental frameworks are called Open-Label Placebo (OLP) designs and they offer the prospect to harness PEs while fulfilling ethical guidelines (Blease et al., 2016). Accordingly, recent evidence demonstrated that the placebo response still occurs after full disclosure of the deceptive nature of the intervention though generally of a smaller magnitude (Sandler and Bodfish, 2008; Kaptchuk et al., 2010; Kam-Hansen et al., 2014; Ballou et al., 2017; Locher et al., 2017; Mundt et al., 2017).

Conclusively, while the postulate according to which deception can be fully abolished from any placebo interventions is still under debate, OLP designs hold promising prospects

regarding the forthcoming introduction of placebos intervention in routine medical practice (Miller et al., 2005; Waring, 2008; Barnhill and Miller, 2015).

In parallel to the efforts invested in refining placebo methodological designs while minimizing the ethical dilemma of deception, PEs have gained considerable interest in the past 20 years with the advent of state-of-the-art biomedical imaging techniques which enabled to uncover their neurobiological mechanisms of action.

1.7 Neural correlates of placebo effects

With the advent of state-of-the-art biomedical imaging techniques, the neurobiological correlates of PEs have been increasingly studied over the past few decades. In such a context, neuroscientists have been trying to find neural substrates specific to expectations and conditioning effects to support claims arguing about either their distinctiveness or their interrelationships.

1.7.1 The Dual-Process model and the Placebo-Reward hypothesis

Thus, following the dual-processed model of Schafer et al. (2018) (*see section 1.4*), "System 1" supporting conditioned expectations learning is hypothesized to recruit subcortical dopaminergic structures involved in reward mechanisms while "System 2" supporting verbally-induced expectations learning would engage cortical structures such as the Prefrontal cortex (PFC) involved in top-down processes (*see for reviews* Qiu et al., 2009; Tu et al., 2019; Young et al., 2005).

Concerning the dopaminergic reward-circuit in System 1, animal models highlighted that midbrain dopamine neurons underlie reward-related Pavlovian conditioning (Tsai et al., 2009; Saunders et al., 2018), especially those originating from the Nucleus Accumbens (NAc; Young et al., 2005). Furthermore, recent evidence highlighted that brain activity in the ventral striatum, a key area in the dopaminergic reward-circuit, and the rs4680 met/met catechol-O-methyltransferase allele phenotype displaying high levels of dopamine both predicted

conditioned effects of PEs in the context of analgesia (i.e., Placebo Analgesia, PA; Yu et al., 2014). As such, de la Fuente-Fernández (2009) proposed the Placebo-Reward Hypothesis according to which expectations of a reward triggers the released of dopamine in the ventral striatum, specifically in the NAc. According to this author, expectations will produce a reward possibility which will trigger tonic inputs from dopaminergic neurons to the striatum and the PFC. Hence, the dopaminergic mesolimbic pathway may be recruited to support conditioned expectations (*see also* Benedetti et al., 2011b).

Regarding the involvement of the PFC in System 2, evidence indicates that its intactness is a prerequisite for expectations to manifest, specifically regarding the Dorsolateral Prefrontal Cortex (DLPFC) and the Orbitofrontal Cortex (OFC) (*see for reviews* Benedetti, 2014; Colagiuri et al., 2015; Meyer et al., 2015; Peciña and Zubieta, 2015). In sum, higher-order cortical areas may support top-down regulations of the neuroendocrine and autonomic systems through expectations (Saper, 2002; Benedetti et al., 2015; De Pascalis and Scacchia, 2016).

Based on Kirsch et al. (2016) Cognitive Model of PEs, the two systems proposed by Schafer et al. (2018) should be intrinsically connected to some extent. Indeed, the PFC and the striatum are receiving expectations-mediated tonic inputs stemming from the nigrostriatal dopamine neurons (*see for a review* Pacheco-López et al., 2006). These authors postulated that expectations both feed to and receive inputs from a dopaminergic network comprising the medial forebrain, the striatum, and the Anterior Cingulate Cortex (ACC). In relation to the Cognitive Model, System 1 is hypothesized to recruit identical reward-related brain structures across the different types of PEs (Colloca and Benedetti, 2005), while System 2 ought to be specifically dependent on the pharmacodynamics of the real intervention it mimics (Lidstone et al., 2005).

1.7.2 The Reactivation Hypothesis

As Benedetti (2014) elegantly stated “There’s not one single placebo effect, but many”. Hence, there might not exist a domain-general physiological mechanism underlying PEs, but

on the contrary PEs may be modality-specific in terms of the recruited brain networks. Thereupon, most placebo neuroscientists currently agree that placebos tend to mimic the effects of the active substance or the intervention that they replace by triggering the same neurobiological mechanisms (*see* **Figure 4**). To improve readability throughout the manuscript, I decided to rename this theory as the Reactivation Hypothesis.

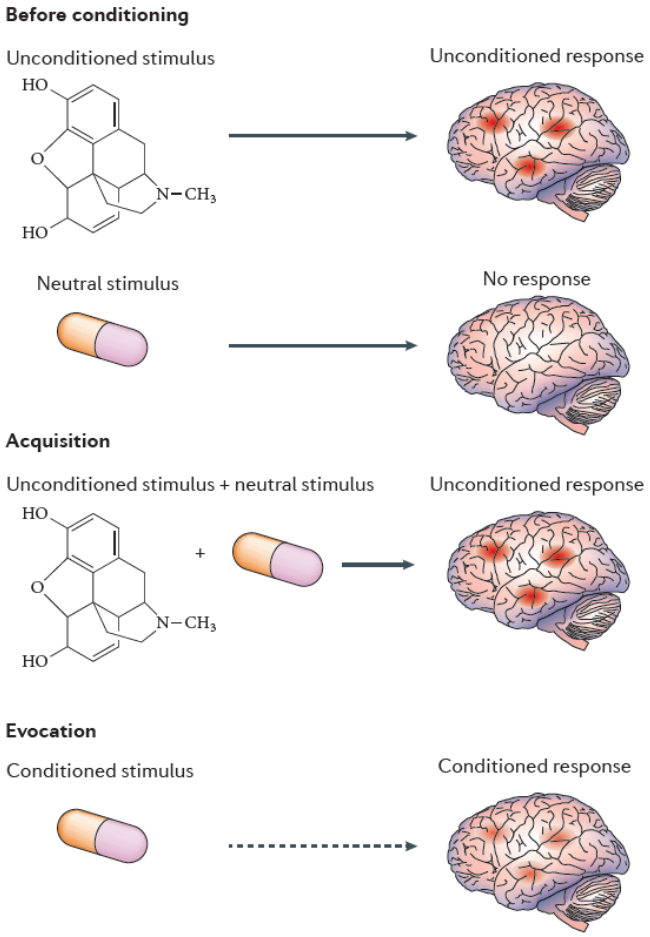

Figure 4. Process through which the repeated association of an unconditioned stimulus with a neutral stimulus leads the latter to become a conditioned stimulus that will reactivate the neural network to produce a comparable response. This classical conditioning paradigm is the root mechanism through which placebo effects are generated when a conditioned active substance is surreptitiously replaced by an inactive placebo. Adapted from "The placebo response in medicine: Minimize, maximize or personalize?" by Enck, P., Bindel, M., Schedlowski, M., Ried, W., 2013, *Nature Reviews Drug Discovery, 12,* p.192.

The first evidence came from Levine et al. (1978) who demonstrated that PA could be blocked using Naloxone, a μ-opioid receptor antagonist. This finding suggests that placebos produce analgesia by engaging endogenous μ-opioid receptors similarly to pharmacological

opioid analgesics. Similarly, Giang et al. (1996) demonstrated that, in the context of repeated administration of cyclophosphamide, an immunosuppressive drug, surreptitiously replacing the drug by a placebo led to diminished peripheral leukocyte counts comparable to the drug's mechanism of action. Of interest, Benedetti et al. (2003b) highlighted that conditioning based on a 5-$HT_{1B/1D}$ receptor agonist was responsible for observed physiological PEs (i.e., growth hormone and cortisol concentration changes) when replacing the drug with an inactive substance while verbal suggestions had strictly no modulatory effects on the physiological response. Since then, many more experiments have been conducted on stimulant, analgesic, anxiolytic, antidepressant drugs, etc. and they suggest that conditioning reactivates the pathway that the active substance relies on to produce comparable effects, independent of expectations (*see for reviews* Haour, 2005; Pacheco-López et al., 2006; Benedetti et al., 2011; Meissner et al., 2011; Benedetti, 2013, 2014; Enck et al., 2013; Colloca, 2014; Wager and Atlas, 2015; Atlas, 2021).

Nevertheless, providing first-ever evidence about the neural substrates of expectations effects, Amanzio and Benedetti (1999) showed that PA triggered by expectations cues could be reversed by naloxone. Most importantly, these authors indicated that PA conditioned with opioid drugs could be suppressed using naloxone while PA conditioned with a non-opioid drug (ketorolac) was naloxone insensitive. Thus, their data demonstrate that PE resulting from verbally-induced expectations tend to rely on the opioid system while PE triggered by conditioned expectations specifically depend on the pharmacodynamics of the substituted active substance, at least in the context of analgesia.

To further disentangle the neural correlates of verbally-induced expectations- and conditioned expectations and to provide empirical data supporting current neurobiological models of expectations, I have oriented my investigations to extensively studied pharmacological models of PEs with opposite pharmacodynamic profiles, namely psychostimulant and analgesic drugs.

1.7.3 Caffeine cognitive enhancing model (Study 1)

Caffeine is the most widely consumed psychostimulant with roughly 80% of the world's population using it on a daily basis (James, 1997). In Switzerland, the average daily intake of caffeine is ~200mg while it is consumed as brewed coffee in 83% of cases (Rochat et al., 2020). These statistics are highly relevant for the study since moderate coffee consumers (i.e., ~300mg/day; McLellan et al., 2016) in the Swiss population will have formed and further reinforced caffeine-related expectations each time they drank a cup of coffee. Consequently, contextual information such as holding a warm cup or the color, the taste, and the smell of coffee will enable triggering their conditioned expectations.

Pharmacologically, caffeine antagonizes adenosine receptors, which in turn relieves the inhibition exerted by this neurotransmission system on the sympathetic nervous system (Smith et al., 2003; Einöther and Giesbrecht, 2013). Caffeine neurocognitive effects are hypothesized to be mainly driven by striatal adenosine A_{2A}-dopamine D_2 receptor heteromers, which are abundant in the dopamine-rich putamen (Ferré, 2016; Mishina and Ishiwata, 2014; Bauer et al., 2003) and by adenosine neurons of the Locus Coeruleus, the major noradrenergic nucleus (Grant and Redmond, 1982; Samuels and Szabadi, 2008).

Caffeine constitutes an advantageous model to study PEs because i) it displays reliable cognitive and neurophysiological effects (**Figure 5**; Glade, 2010; Franke et al., 2012; Einöther and Giesbrecht, 2013; Dance, 2016); and ii) it is the most widely used psychostimulant, with its effect thus well-known and widely shared among the general population (Schreiber et al., 1988; Turton et al., 2016; Ludden et al., 2017).

At the behavioral level, caffeine consistently enhances attention (Hasenfratz and Bättig, 1994; Warburton, 1995; Rees et al., 1999; Smit and Rogers, 2000; Yeomans et al., 2002; Haskell et al., 2005, 2008; Maridakis et al., 2009; Foxe et al., 2012; Wilhelmus et al., 2017) and inhibitory control performance (Barry et al., 2007, 2014; Bruce et al., 2014; Dodd et al., 2015; Pasman et al., 2017) (*see for a review* Einöther & Giesbrecht, 2013). These effects are reflected

at the neurophysiological level, such that caffeine modulates electrophysiological correlates of executive attention (Martin and Garfield, 2006; Diukova et al., 2012; Trunk et al., 2014; Kahathuduwa et al., 2017) and inhibitory control electrophysiological correlates (Barry et al., 2007, 2014; De Pauw et al., 2017). These neurocognitive effects have been localized in the frontal and cingulate cortices (Diukova et al., 2012) further suggesting that caffeine tends to increase cortical arousal (Martin and Garfield, 2006). While these studies provide consistent results, they cannot account for the influence of caffeine expectations on the reported (neuro-)cognitive effects, due to the nature of their design.

To date, only scarce evidence distinguishing expectations from caffeine effects provides support for the involvement of expectations in the behavioral effects reported above (**Figure 5**). As such, the mere expectation to receive caffeine seems to similarly improve measures of attention (Oei and Hartley, 2005; Harrell and Juliano, 2009; Elliman et al., 2010), and inhibitory control (Dawkins et al., 2011; Heinz et al., 2013; *see for a review* Shabir et al., 2018). Since these experiments focused on populations of habitual coffee consumers, they specifically assessed the effects of conditioned expectations. In more depth, Harrell & Juliano (2009) demonstrated by contrasting the substance (caffeinated vs decaffeinated coffee) with given instructions (Told-Impair vs Told-Enhance performance) that participants displayed higher sustained attention performance when they expected the substance to enhance their

COGNITIVE FUNCTION	CAFFEINE		CAFFEINE EXPECTATIONS	
	BEHAVIOR	BRAIN	BEHAVIOR	BRAIN
Sustained Attention	↗	↗	↗	?
Inhibitory Control	↗	↗	↗	

Figure 5. Summary of caffeine and caffeine expectations neurocognitive effects. Overall, caffeine and caffeine expectations similarly enhance (↗) performance related to sustained attention and inhibitory control. This enhancement in performance is reflected at the neurophysiological level in the case of caffeine effects but is currently unexplored in relationship to caffeine expectations.

performance (i.e., Told-Enhance condition), independent of the administered substance. Similarly, Elliman & al. (2010), contrasting the administered substance (caffeinated vs decaffeinated coffee) with Instructions (i.e., Told-caffeinated vs Told-decaffeinated coffee) revealed that participants displayed higher sustained attention performance when they were instructed to have received caffeine (i.e., Told-caffeinated coffee) and actually received a caffeinated coffee, compared to all other conditions. Finally, using the same design, Dawkins & al. (2011a) reported that participants performed better at an inhibitory control task when they expected to receive a caffeinated coffee (i.e., Told-caffeinated coffee), but this time independently from the substance administered. Still, while caffeine expectations effects on executive functions have reliably been demonstrated, their neurophysiological correlates remain completely unresolved.

Along these lines and based on the Reactivation Hypothesis, I tested the assumption that conditioned expectations about caffeine effects would reactivate the neurotransmission pathways formerly activated by caffeine, in a population of pre-conditioned, moderate caffeine consumers.

1.7.4 Acute pain induction model (Study 2)[2]

PEs in relationship to pain have been the phenomena most extensively studied at the neurophysiological level (Büchel et al., 2014) considering that the neural circuitry underlying pain processing, the so-called pain matrix (Legrain et al., 2011; Salomons et al., 2016) is rather well understood (*for a review see* Peerdeman et al., 2016). More specifically, PA is mediated by the activation of the i) opioid-dependent structures such as the DLPFC, OFC, the rostral

[2] In this chapter, to specifically refer to analgesia, the terminology that was defined in **Figure 2** will be adjusted accordingly: *conditioned expectations* will be termed *conditioned PA* and *verbally-induced expectations* will be renamed *verbally-induced PA*.

Anterior Cingulate Cortex (rACC), Amygdala, Insula, Thalamus and brainstem structures (Periaqueductal Gray and rostral Ventromedial Medulla), and ii) concurrent opioid- and dopamine-mediated ventral basal ganglia, especially the NAc (**Figure 6**; *see for a review* Qiu et al., 2009). Furthermore, related to non-opioid PA, Benedetti et al. (2011a) reported that rimonabant, a CB1 cannabinoid receptor antagonist, was not able to reverse PA in individuals conditioned with morphine, a μ-opioid receptor agonist, while it could cancel out PA conditioned with ketorolac, a non-opioid, Non-Steroidal Anti-Inflammatory Drug (NSAID). On the opposite, naloxone was able to block PA conditioned with opioids while having no impact on PA conditioned with NSAIDs (Amanzio and Benedetti, 1999; Benedetti et al., 2007). These findings are of utmost relevance since they further support the assumption that the mechanisms underlying conditioned PA exclusively depend on the active compound used in the conditioning procedure. Since then, additional neuropharmacological studies provided support for opioid-dependent and -independent mechanisms of PA (Wager et al., 2007; Scott et al., 2008; Eippert et al., 2009; Berna et al., 2018).

Inspired from Voudouris et al. (1985) pioneer study on conditioned PA, scarce evidences with contradictory outcomes have aimed at disentangling the neurobiological basis of conditioned from verbally-induced PA (Voudouris et al., 1990; Ader, 1997; Montgomery and Kirsch, 1997; Amanzio and Benedetti, 1999). Amanzio and Benedetti (1999) provided first indications that verbally-induced PA differs from conditioned PA in that the former recruits endogenous opioids while the latter depends on neurotransmission pathways initially activated by the substance used for conditioning. This distinction is further supported by findings suggesting that the dopamine system underlies the pre-cognitive anticipation of PA, i.e. conditioned PA, while the cortical opioid structures support conscious expectations, i.e. verbally-induced PA (Scott et al., 2007; Peciña et al., 2014).

While these studies mainly relied on conditioning procedure performed in laboratory settings, I was interested in determining whether such distinction in neural networks would

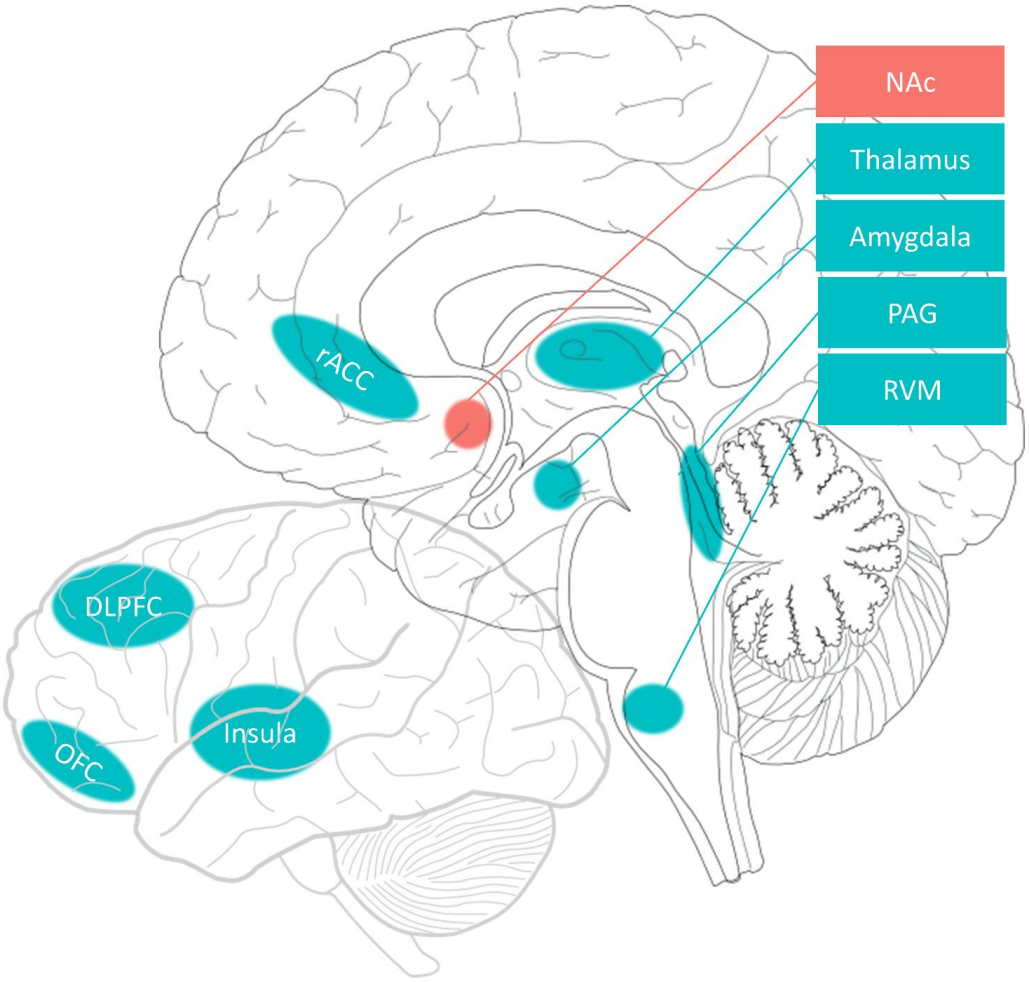

Figure 6. Neural basis supporting opioid-dependent expectations (in blue) and concomitant opioid- and dopamine-dependent conditioning structures (in red). The difference between conditioned and verbally-induced expectations may stem from the involvement of dopaminergic NAc signals. DLPFC = Dorsolateral Prefrontal Cortex; NAc = Nucleus Accumbens; OFC = Orbitofrontal Cortex; PAG = Periaqueductal Gray; rACC=rostral Anterior Cingulate Cortex; RVM = rostral Ventromedial Medulla.

also manifest in a more ecological framework. In that context, I aimed to disentangle the neural substrates of conditioned and verbally-induced PA of sham morphine administration while contrasting individuals with or without prior experience with morphine. I relied on the model of sham morphine for the following reasons: i) at least half of morphine analgesia is PEs (Levine et al., 1981; Benedetti et al., 2003a), ii) knowledge of morphine antalgic properties is widely shared across the population (de Sola et al., 2018) since it is an antalgic drug extensively used in and out the hospital settings (Vallano et al., 2007; Herzig et al., 2014; Jena et al., 2016) and iii) placebo morphine has been reliably shown to induce analgesia (*see for*

reviews Price et al., 2005; Colloca, 2014; Okusogu and Colloca, 2019). Accordingly, morphine analgesia represents a very suitable candidate to disentangle the neural correlates of conditioned and verbally-induced PA.

Chapter 2: Methods

For the two thesis projects I relied on multimodal data collection to assess the neural correlates of conditioned and verbally-induced expectations effects in contexts of caffeine cognitive enhancement (Study 1) and acute pain induction (Study 2). Accordingly, in Study 1 I implemented two computerized cognitive tasks indexing sustained attention as well as inhibitory control performance. In Study 2, I implemented a protocol assessing pain to acute heat-pain induction. In both experiments, I recorded participants behavioral performance (Reaction Times, RT, and accuracy in Study 1 and pain estimates in Study 2) and physiological measures such as electroencephalography (EEG). Regarding the latter, my colleague and myself developed an automated EEG pre-processing software (Najberg and Wicht, 2021) to clean the EEG recordings.

2.1 Experimental paradigms

2.1.1 Computerized cognitive tasks (Study 1)

To assess the research question related to caffeine and caffeine expectations effects, I relied on cognitive tasks targeting two executive functions: i) the Rapid Visual Information Processing task (RVIP) and ii) the Go/NoGo task indexing, respectively, sustained attention and motor inhibitory control performance.

Rapid Visual Information Processing task

The task was based on the RVIP version from Cambridge Neuropsychological Test Automated Battery (Sahakian & Owen, 1992) and further adapted by Hilti et al. (2010; **Figure 7**): Participants saw sequences of white numbers (0-9, except 1) that appeared on a black screen in pseudo-random order. They had to detect target sequences (i.e., “2–4–6”, “3-5-7”, “4–6–8”) and press a button when the last number of a target sequence appeared, while ignoring other non-target sequences (i.e., composed of random numbers termed fillers). The stimuli were presented in 16 blocks each containing 12 target sequences (i.e., 4 of each 3-

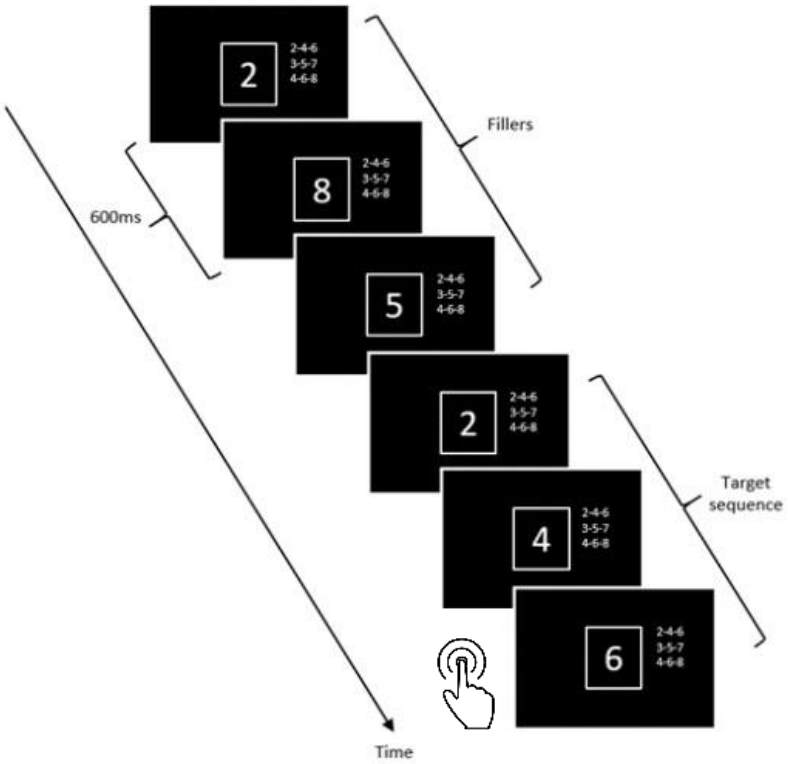

Figure 7. Sequential procedure of the rapid visual information processing task. Participants were presented either with target sequences (e.g., "2-4-6") or random numbers called "Fillers", each displayed for 600ms. Participants were requested to press a button as soon as they recognized the last number of a target sequence (here, "6").

digits sequence) and 114 fillers. The target sequences were always reminded between each block, and they were also written on the top-right corner of the screen during the whole session to minimize the memory load. Response times (RT) and the number of correct sequences detected (HITS) were recorded.

Go/NoGo Task

The task was adapted from one of my research group's previous published studies (**Figure 8;** Hartmann et al., 2016). Participants were presented with white letters (i.e., A, E, O, M, S or T) on a black screen in blocks of 70 trials each. In each block, one of the letters was randomly designated to represent the NoGo stimulus while the remaining letters were Go stimuli. Participants were instructed to press a response button as fast as possible when presented with Go stimuli, while withholding their response to NoGo stimuli. Each block

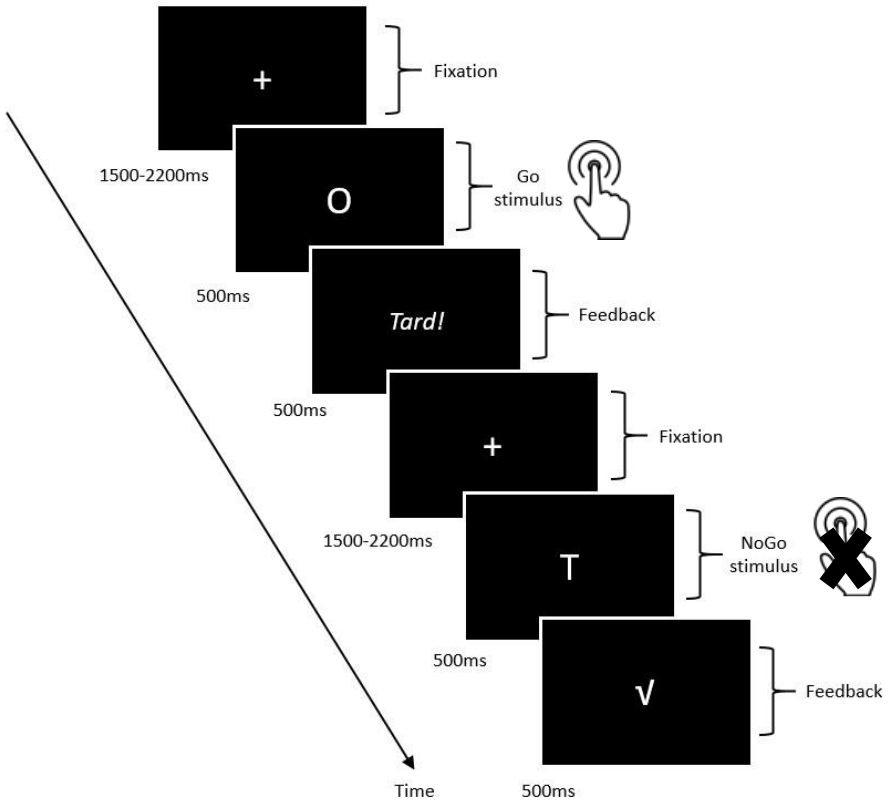

Figure 8. Sequential procedure of the Go/NoGo task. Participants were presented either with Go (here, "A-E-O-M-S") or NoGo stimuli (here, "T"), each displayed for 500ms and separated by a fixation cross. Participants were requested to press a button as soon as they detected Go stimuli while withholding their response to NoGo stimuli.

intentionally included more Go than NoGo trials (i.e., 50 Go and 20 NoGo trials) which enabled to increase the pressure to reply and to raise the number of errors. RT for Go trials, as well as accurate (i.e., Correct Rejection, CR) and failed rejections (i.e., False Alarms, FA) for NoGo trials were recorded.

2.1.2 Acute pain stimulation paradigm (Study 2)

Participants underwent three protocols of acute pain stimulation which were all performed with the PATHWAY CHEPS device (Medoc Advanced Medical Systems, Rimat Yishai, Israel) using a thermofoil thermode positioned on the right volar forearm (**Figure 9**).

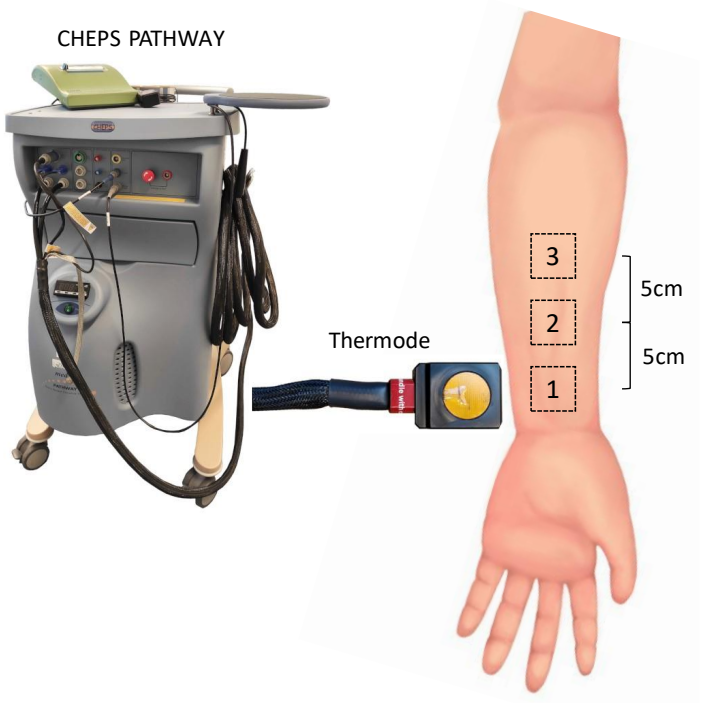

Figure 9. Heat pain device and stimulation sites that were used in Study 2. The CHEPS PATHWAY device delivered heat-pain stimulations through the thermode that was placed on the volar forearm. For the first two protocols, the thermode was attached to the second position. For the last protocol (i.e., experimental pain stimulation phases), the thermode was moved after every trial from position 1 to 2 to 3.

Protocol 1: Pain Stimulation Threshold and Tolerance

First, I applied two stimulations between 32°C and 52°C increasing at a rate of 0.3°C to assess the individual heat pain threshold and tolerance. Participants were asked to indicate, respectively, when they started to experience a pain sensation and when the pain became unbearable.

Protocol 2: Individual Pain Stimulation Level

Secondly, I assessed pain stimulation thresholds to determine the individual stimulation intensity that would produce comparable pain feelings across participants. I wanted to ensure that all the participants would later be stimulated with a comparable intensity. Hence, participants were administered with short-lasting stimulations ranging from 42°C to 52°C by steps of 1°C. After each stimulation, they were requested to rate their pain on a continuous Visual Analog Scale (VAS) from 1 to 10. The temperature corresponding to a VAS of at least 8

(or 52°C in case the last VAS estimate was lower than 8) would be used as the individual stimulation temperature in the experimental phase.

Protocol 3: Experimental Pain Stimulation Phases

Finally, the experimental stimulation phases were performed before and 15 min after the injection of sham morphine. Each phase was composed of two blocks of 12 trials each. For each trial, participants were stimulated with their individual target temperature determined during the pain stimulation threshold protocol. Of note, since the temperature was kept constant across trials, the experimenter moved the thermode between three positions after each trial (**Figure 9**) to avoid sensitization and/or habituation. Finally, participants were requested to evaluate their pain every six trials using the 1-10 VAS scale. The VAS estimates were then averaged separately for each phase as to compute global pain ratings before and after injection.

Regarding the two projects, I was especially interested in assessing expectations effects at the electrophysiological level. Thus, the next chapters will briefly introduce the history of EEG and present the processing and analysis steps that I relied on.

2.2 Electroencephalography

The German psychiatrist Hans Berger is considered the founding father of EEG which he described in his seminal paper (1929) as a “window into the brain”. At the time, due to the lack of available neuroimaging techniques, the discovery of EEG paved the way for an exponential growth in the understanding of neuroscience and of neurological disorders. Specifically, the human scalp EEG largely improved the understanding of electrical brain activity bridging the gap between the microscopic and macroscopic scales. Accordingly, it has been discovered that the brain topography reflected at the scalp EEG originates from postsynaptic activity of thousands of synchronized pyramidal neuronal cells organized in

columns in cortical layer IV aligned perpendicularly to the cortical surface (**Figure 10**; Michel et al., 2009).

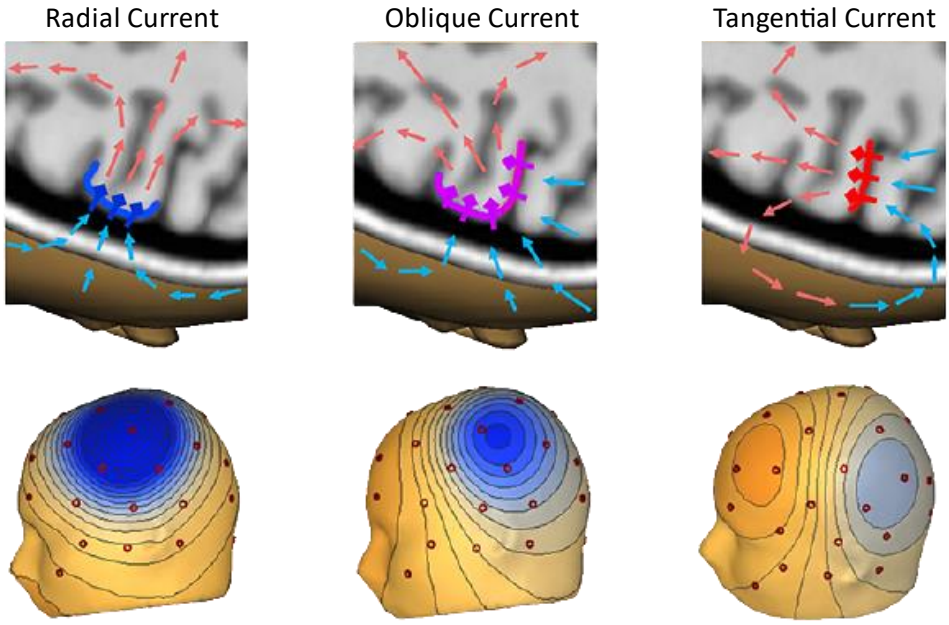

Figure 10. Illustration of the relationship between different cortical current flows and their projected scalp topography. Adapted from "Taking the EEG back into the brain: The power of multiple discrete sources" by Scherg, M., Berg, P., Nakasato, N., Beniczky, S., 2019, *Frontiers in Neurology, 10,* p.3, CC BY 4.0.

Mesulam postulated in (1998) that neurons are distributed in delineating networks each supporting separate brain functions such as cognitive functions. Correspondingly, functional neuroimaging studies have largely focused in describing the modules composing functional networks underlying specific mental tasks (Michel et al., 2004). While EEG is a non-invasive method with a very precise temporal resolution (i.e., sub-millisecond timescale), its spatial resolution is far behind other functional neuroimaging techniques such as Magnetic Resonance Imaging (MRI) or Positron-Emission Tomography (PET). Thus, EEG has been mainly used to explore the temporal properties of neural circuits and brain responses to time-locked events or stimuli (i.e., the Event-Related Potentials, ERPs).

2.2.1 Event-Related Potentials

Richard Caton was a pioneer electrophysiologist who first described in 1875 (Dalrymple-Champneys, 1959) that "feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points of the external surface". Related to the brain, these very small currents are described as ERPs. They index the summation of postsynaptic potentials generated by a group of similarly oriented pyramidal neurons firing synchronously (Sur and Sinha, 2009). ERPs are triggered by sensory, cognitive, or motor stimuli and are categorized as components according to the latency and amplitude of their waveforms (**Figure 11**).

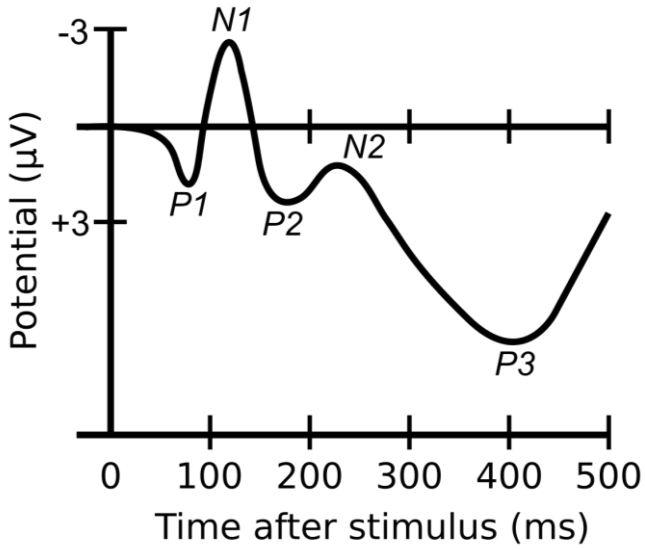

Figure 11. Schematic waveform displaying the most common event-related potentials components. As an example, P3 corresponds to a centrally distributed component with positive (P) deflection appearing roughly 300-400ms after stimulus onset. Adapted from Event-related potential (n.d.). In *Wikipedia*. Retrieved December 24, 2021, from https://en.wikipedia.org/wiki/Event-related_potential, CC BY-SA 3.0.

Regarding Study 1, I focused on ERP components underlying the key sustained attention and inhibitory processes: The Attention-P3 for the RVIP, as well as the NoGo-N2 and NoGo-P3 ERP components for the Go/NoGo task. The Attention-P3 is a central positive ERP component manifesting 300-500ms post-stimulus onset (Key et al., 2005; Hoyniak et al., 2015). The NoGo-N2 and NoGo-P3 are fronto-central negative and positive ERP components manifesting, respectively, 200-400ms and 300-500ms after stimulus onset (Hayashi et al., 2018). These ERP

components represent ideal candidates to examine caffeine expectations in my experimental setting because they have been associated with sustained attention and inhibitory control performance (Folstein and Van Petten, 2008), have a demonstrated sensitivity to caffeine (Diukova et al., 2012; Bailey et al., 2016b), and their neural generators partly overlap with the areas known to be modulated by caffeine (Mangalathu-Arumana et al., 2012; Stock et al., 2016; Justen and Herbert, 2018; Ragazzoni et al., 2019).

Concerning Study 2, I focused on the N2 and P2 ERP components which are specifically sensitive to nociceptive stimulations (Wager et al., 2006). The N2 and P2 components arise respectively 200-400ms and 300-500ms after stimulation (Bromm and Treede, 1987). More specifically, the N2 component is hypothesized to index top-down attentional mechanisms, while P2 mainly reflects bottom-up attentional orienting mechanisms (Legrain et al., 2005, 2003, 2002). These two components represent ideal candidates to investigate PA since they are correlated to the magnitude of pain perception (Colloca et al., 2009; García-larrea et al., 1997; Iannetti et al., 2005) and they mainly originate from brain areas involved in PA (Apkarian et al., 2005; *see for reviews* Benedetti, 2014; Wager and Atlas, 2015).

2.2.2 EEG data acquisition and preprocessing

For both Study 1 and 2, EEG was recorded at a sampling rate of 1024Hz (i.e., 1024 data points collected at each millisecond of recording) using a 64 electrodes EEG Biosemi ActiveTwo® system (**Figure 12**) referenced to the Common Mode Sense-Driven Right Leg (CMS-DRL) ground (Biosemi, Amsterdam, Netherlands).

Since raw EEG signals are largely constituted of electrical and physiological noises (e.g., electrical line noise, muscles artifacts, etc.), developing algorithms to pre-process raw data and thus improve the signal-to-noise ratio (SNR) without losing much of the true signal has been one of the greatest challenges over the past twenty years (Delorme et al., 2011). On this basis, a myriad of pre-processing pipelines have emerged (Bigdely-Shamlo et al., 2015; da Cruz et al., 2018; Gabard-Durnam et al., 2018; Debnath et al., 2020). They mostly rely on different

algorithms, processing order and recommended parameters ultimately leading to discrepancies in results and interpretations (*see for examples* Delorme et al., 2012; Chaumon et al., 2015). Thus, to ensure the replicability and transparency of EEG results in my group, my colleague and myself implemented our own pre-processing pipeline specifically dedicated to Biosemi 64 electrodes setups (Najberg and Wicht, 2020, 2021). This MATLAB-based software heavily relies on EEGLAB functions (Delorme and Makeig, 2004), the most widely used and validated software for EEG processing (Hanke and Halchenko, 2011), and it strictly follows one of their team member recommendations, i.e. Makoto's pre-processing pipeline (Miyakoshi,

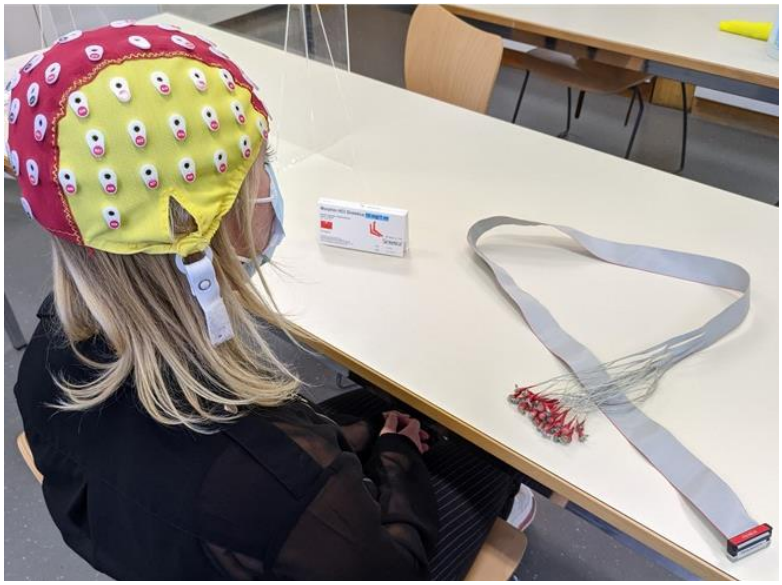

Figure 12. Example of the Biosemi 64 electrodes electroencephalogram setup used in my laboratory. The electrodes are attached on the scalp and are then connected to an amplifier. To enhance the quality of the signal, a conductive gel is applied at each electrode position right before attaching them.

2021).

More precisely, our pipeline is ordered accordingly:

- I first re-reference the recordings to the central Cz electrode. Since the EEG activity corresponds to a voltage difference between one electrode and its reference, changing the reference will adjust the origin of the coordinate system (Michel et al., 2009) and the Cz signal will then be equivalent to zero.

- Then, band-pass filtering between 0.5 and 40Hz is applied. The purpose is to remove, respectively, baseline drifts and electrical direct current noise as well as any high-frequency non-brain related artifacts (de Cheveigné and Nelken, 2019).
- At this point and for each recording, channels which are visually deemed irrecoverable are removed to avoid injecting high-amplitude noise into the data cleaning algorithms as well as to preclude from contaminating the average reference (Bigdely-Shamlo et al., 2015).
- Afterwards, CleanLine (Mullen, 2012), Blinker (Kleifges et al., 2017) and Artifact Subspace Reconstruction (ASR; Mullen et al., 2013, 2015) algorithms are applied sequentially to remove the remaining artifacts. Specifically, CleanLine is used to remove sinusoidal line noise at 50Hz and 100Hz, corresponding, respectively, to the utility frequency of the power grid and its main harmonic. Blinker is dedicated to identifying and removing epochs containing eye blinks. Finally, I use ASR to detect non-stationary, high-variance signals such as sudden muscle artifacts. Based on a Principal Component Analysis, high-variance components which are more than 10 standard deviations (SD) away from a mixing matrix calculated on a clean "reference" section of the recording are identified as artifacts (*see for parameters* Chang et al., 2018). The identified noisy windows are then reconstructed based on the mixing matrix, following the same reasoning as bad channels interpolation (see below).
- Now that the EEG signals can be considered relatively cleaned, I isolate epochs around the stimulus onset and for each file, depending on the expected latency of the components of interest (-100 to 700ms for Study 1 and -100 to 1000ms for Study 2).
- I then apply a baseline correction on each individual epoch over the whole timescale. The basic principle is to correct for the activity induced by temporal drifts often occurring in the pre-stimulus period which are unrelated to the engaged cognitive processes.
- Soon after, the bad channels that were identified and removed prior to applying the cleaning algorithms are interpolated so that each ERP will be composed of

the same number of channels as the raw recording. Specifically, interpolation is performed using a multiquadric interpolation algorithm relying on radial basis functions (*see* Jäger et al., 2016; Janin, 2018; Buhmann and Jäger, 2019).

- Additionally, any remaining artifacts-contaminated epochs are rejected if one of their data points exceed the 80μV threshold criterion or if the voltage difference from one data point to the next is larger than 30μV (i.e., indicative of a drift).
- At this point, the epochs are averaged according to stimulus types (e.g., all CR epochs for the GNG task) for each participant separately.
- Finally, the averaged ERPs are re-referenced to the common average reference which corresponds to the average of all electrode signals. Since human heads are spherical and their neural currents spread in an isotropic way, the average potential over all electrodes approximates zero (Yao et al., 2019). This reference is favored at this stage to facilitate results comparability across studies.

2.2.3 ERP analyses

Historically, ERP analyses have solely been conducted at the sensor level, namely on local electrodes showing the largest signal amplitude in the time window of the component of interest (e.g., Cz for N1). While this method has been largely validated, its interpretation is marred by the fact that the choice of the reference will have a significant impact on the shape of the component (Dong et al., 2019). Most importantly, the interpretability of such results is limited since there is no direct relationship between the position of the electrode on the scalp and the brain sources which the electrical current originates from.

Interestingly, Lehmann and Skrandies (1980) demonstrated that a change in voltage amplitude measured at the scalp follows from a change in the strength or in the configuration of the underlying electrical generator. Hence, these authors introduced reference-independent scalp measures that could distinguish between the strength and the configuration of ERP signals and could summarize all electrodes data as a single value.

Global Field Power (GFP)

In that sense, the Global Field Power (GFP) measure was introduced as a global measure that provides information of the strength of electrical generators while being independent of arbitrary choices in the selection of limited number of electrodes such as in local electrodes analyses (Michel et al., 2004). GFP is computed as the mean potential difference between all possible pairs of electrodes (Lehmann and Skrandies, 1980). Importantly, high GFP values correspond to highly synchronized neural firing and thus indicate periods of strong SNR (Michel et al., 2009).

Global Map Dissimilarity (GMD)

Global Map Dissimilarity (GMD) is a global measure indexing the configuration of the underlying electrical generators. GMD is calculated as the square root of the mean of the squared differences between all electrodes normalized by instantaneous GFP (Michel et al., 2009). Of note, since GFP is not influenced by topographic changes in the potential distribution and GMD is normalized by GFP, both measures are considered orthogonal and can thus be interpreted independently from one another (Ribordy Lambert et al., 2020). Accordingly, when the GFP value is high, GMD is usually low and vice versa (**Figure 13**). Since GMD is a difference score between two maps, a value of 0 indicates that the maps are homogeneous while a value of 2 suggests that the polarity of the two maps is completely inverted.

Electrical Source Imaging (ESI)

While GFP and GMD measures are robust estimators of brain activity at the scalp level, they do not provide information on the exact location of the underlying electrical generator in the brain, what is commonly referred to as the inverse problem. Accordingly, Helmholtz (1853) described that an electrical potential distribution on a surface enclosing a 3D space can originate from plenty possible current density distributions in this volume. Following this assumption, Electrical Source Imaging (ESI) methods emerged in the past years to provide estimates of electrical source localization (*see* Michel and Brunet, 2019). To reduce the number of unknowns of the inverse problem, ESI methods rely on a priori assumptions based

on mathematical, physiological, biophysical, and anatomical constraints about electrical source generation and propagation (Michel and Murray, 2012). As an example, assumptions according to which EEG activity is limited to gray matter from which only synchronous postsynaptic potentials from large clusters of cortical pyramidal neurons can be recorded will help narrow down the uniqueness of the inverse solution (Michel et al., 2009).

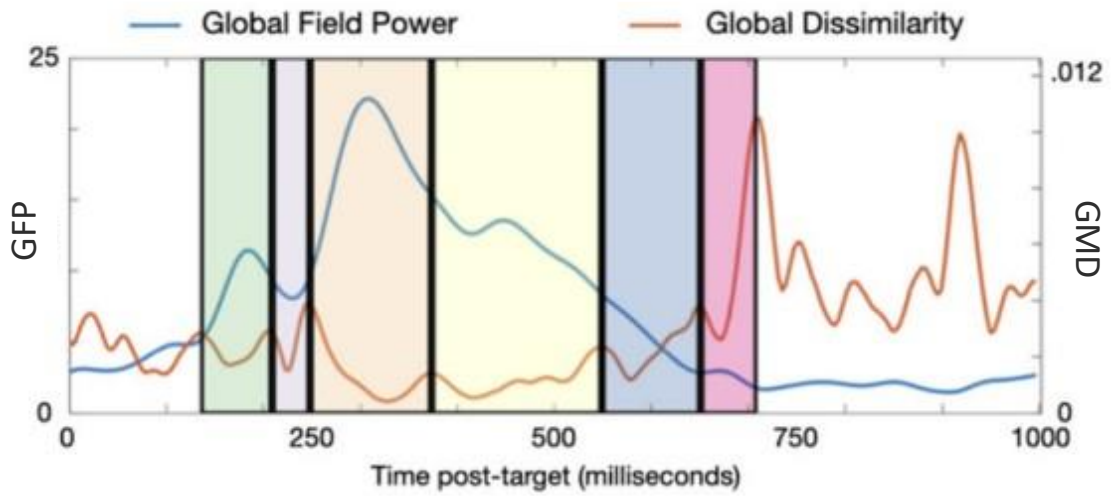

Figure 13. Orthogonal relationship between Global Field Power (GFP; blue) and Global Map Dissimilarity (GMD; orange) measures computed at each time frame on an ERP. As can be observed, when the GFP value is high, GMD is low and inversely. Thus, GFP peaks represent moments of high neural synchrony, while GMD peaks index moments of high topographic instability, i.e., usually assuming a change in the underlying network of sources. Adapted from "Event-related potentials reflect prediction errors and pop-out during comprehension of degraded speech" by Banellis, L., Sokoliuk, R., Wild, C.J., Bowman, H., Cruse, D., 2020, *Neuroscience of Consciousness, 6,* p.5, CC BY 4.0.

To solve the inverse solution problem, ESI evolved from single dipole iterative models to 3D distributed source localization methods (Michel and Murray, 2012). For my studies, I exclusively relied on the Local AUtoRegressive Average (LAURA) model (Grave De Peralta Menendez et al., 2004) which is an alternative to the non-adaptative Weighted Minimum Norm (WMN) distributed source imaging solution (Wang et al., 1992). More specifically, LAURA accounts for the dependency between neighboring solution points in accordance with electromagnetic and biophysical laws (*see for details* Grave De Peralta Menendez et al., 2004). Of relevance, Michel et al. (2004) demonstrated that, independent of the number of scalp electrodes, the mean dipole localization error was three times smaller with LAURA compared to most other inverse solution algorithms.

Moreover, ESI algorithms require that a lead field matrix comprising anatomical information and related electrode positioning on the scalp be defined (Zorzos et al., 2021). Hence, for both studies, the solution space was calculated on a realistic head model comprising 6005 solution points uniformly distributed in the grey matter of the Montreal Neurological Institute (MNI; Evans et al., 1993) average brain (**Figure 14**).

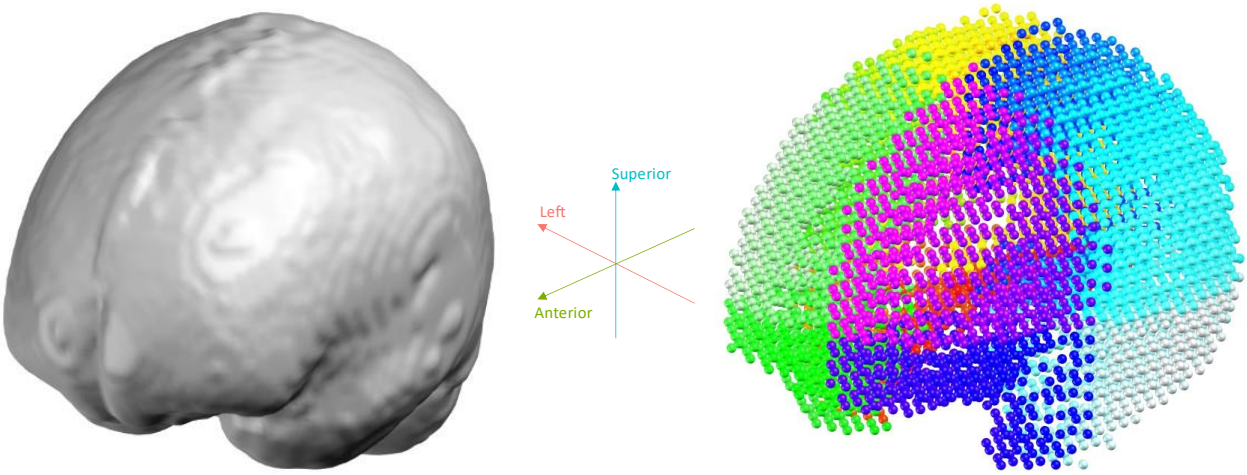

Figure 14. Realistic head model based on the MNI125 template (left) and lead field matrix comprising 6005 uniformly distributed solution points (right).

While the advent of ESI enabled to compensate for the initial low spatial resolution of EEG, it still suffers from several limitations. First, to increase source localization accuracy, high-density EEG systems need to be used (Michel et al., 2004). Secondly, the co-registration of electrode positions related to the head model as well as the alignment of the actual position of electrodes during the recordings is crucial for the accuracy of the solutions (Homölle and Oostenveld, 2019). Thirdly, since defining the head model as individual MRI scans is often too costly, most studies rely on a template MRI which again weakens the source localization accuracy, especially in large cohorts (Brodbeck et al., 2011). Finally, ESI calculations are largely biased by signal artifacts in that the predicted brain activity areas may in fact be ghost sources or be entirely misplaced (Whittingstall et al., 2003). Overall, ESI represents a clear-cut progress with decent estimation of intracranial source localization but its interpretation has to be weighed against the accuracy of the computational model, lead field matrix, electrodes co-registration and the quality of the EEG signal.

The next sections will be dedicated to detailing the design, hypotheses and methodology underlying both studies.

2.3 Design and Hypotheses

The within-subjects design of Study 1 was an adapted version of the BPD (**Figure 3**) including 3 of the original 4 arms:

- Give-Decaffeinated/Told-Caffeinated coffee, GD/TC (Placebo condition)
- Give-Caffeinated/Told-Decaffeinated coffee, GC/TD (Hidden condition)
- Give-Decaffeinated/Told-Decaffeinated coffee, GD/TD (Control condition)

The 4th arm of the BPD (Give-Caffeinated/Told-Caffeinated coffee, i.e., GC/TC condition) was not included in Study 1's design since it was not appropriate to address our hypotheses and also because of time and financial constraints.

Regarding Study 2 the between-subjects design was composed of two groups:

- conditioned expectations (CondExp) group: individuals holding expectations of morphine analgesic properties through past experiences with opioids.
- Unconditioned Expectations (UncondExp) group: individuals holding verbally-induced expectations of morphine analgesic properties but who have never experienced opioids.

The operational hypotheses of Study 1 and Study 2 are summarized in **Table 1**.

Study 1: Caffeine expectations			
Hypotheses	Contrast	Dependent Variables	
		Behavior	Physiology
Ha: Caffeine effects **Hb:** Expectations effects **Hc:** Caffeine Vs. expectations effects	**Ha:** GD/TD **<** GC/TD **Hb:** GD/TD **<** GD/TC **Hc:** GD/TC **<** GC/TD	**RVIP**: Hits	**RVIP** (HITS P3) and **Go/NoGo** (CR N2 & P3) components: - Voltage amplitude

			- GFP - **RVIP**: Attention-P3 TPJ, STG and Precuneus CSD - **Go/NoGo**: NoGo-N2 MFG, Cingulate Cortex and Precentral Gyrus CSD & NoGo-P3 MFG and ACC CSD
	Ha: GD/TD **>** GC/TD **Hb:** GD/TD **>** GD/TC **Hc:** GD/TC **>** GC/TD	**RVIP**: RT **Go/NoGo**: FA & RT	
Study 2: Placebo analgesia			
Placebo Morphine effect	CondExp ≠ UncondExp		PostInject POI-averaged GMD values separately for: - N2 - P2

Table 1. Summary table of hypotheses for Study 1 and Study 2**.** ACC=Anterior Cingulate Cortex; CR=Correct Rejection; CSD=Current Source Density; CondExp=conditioned expectations group; FA=False Alarms; GC=Give-CAF; GD=Give-DECA; GFP=Global Field Power; GMD=Global Map Dissimilarity; MFG=Middle Frontal Gyrus; PostInject=Post-injection phase; STG=Superior Temporal Gyrus; TC=Told-CAF; TD=Told-DECA; TPJ=Temporo-Parietal Junction; UncondExp=Unconditioned Expectations group; VAS=Visual Analogue Scale.

Overall, the two studies conducted as part of this thesis aimed at providing empirical data to first support the theory that expectations tend to rely on the neural networks of the substance they are based on to produce comparable PEs (Study 1). Then, building on the first evidence, I focused on testing the assumption according to which the neural networks underlying conditioned and verbally-induced expectations may slightly differ to produce comparable PA, relying on the Placebo-Reward Hypothesis (Study 2).

2.4 Cover Stories

Because the credibility of deceptive procedures is a prerequisite to the success of placebo experimenters involving deception, I implemented the following cover stories as previous findings demonstrated their usefulness in placebo experiments (Elkins-Brown et al., 2018).

For Study 1, I collected saliva samples from participants 20 min after coffee consumption, during each of the three sessions. This procedure adapted from Elkins-Brown et al. (2018) was presented to the participants as a test that would indicate whether the content of caffeine in their saliva was high or low enough (depending on the condition) to proceed with the cognitive tasks. The experimenter wearing a laboratory white coat proceeded to a chemical reaction in front of the participants (**Figure 15**). The latter were

informed that if the solution precipitated and changed color from yellow to dark-blue it would mean that the concentration of caffeine was high. On the contrary, if the solution remained yellow it would mean that the caffeine concentration was so low that it could not even be detected. This chemical reaction was actually a trickery based on the iodine-starch test (Colin and Gaultier de Clauby, 1814).

In Study 2, I implemented a method relying on cardiovascular readings to enhance

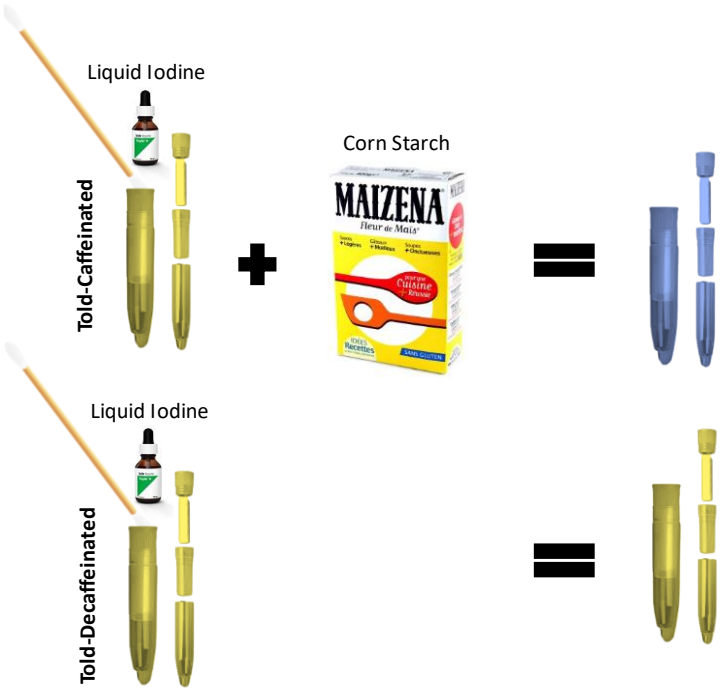

Figure 15. Process of the cover story used in Study 1. In both cases, participants' cotton-tipped applicators were replaced with identically looking applicators as to manipulate them in the desired direction. In the Told-Caffeinated case (i.e., GD/TC condition), a cotton-tipped applicator covered in corn starch was mixed with water and liquid iodine which led to a chemical reaction that changed the liquid color inside the test tube from yellow (i.e., the natural color of iodine) to blue. In the Told-Decaffeinated case (i.e., GD/TD and GC/TD conditions), the cotton-tipped applicator was clean and thus when mixed with iodine, the color of the test lube liquid remained yellow.

participants' beliefs that they have been administered morphine. I informed participants that I would proceed to cardiovascular assessments right before morphine administration as well as 15min after (i.e., roughly the time necessary to reach the peak concentration; Stuart-Harris et al., 2000; Wickham, 2017). I instructed them that morphine is well-known to lower blood

pressure and heart rate. To mislead participants, I developed a toolbox that would display the same results to all participants in real-time on their screen (**Figure 16**). Accordingly, they were led to believe that their cardiovascular functions were slightly higher than the norm before the injection (i.e., as though they were marginally stressed), while 15min after the injection

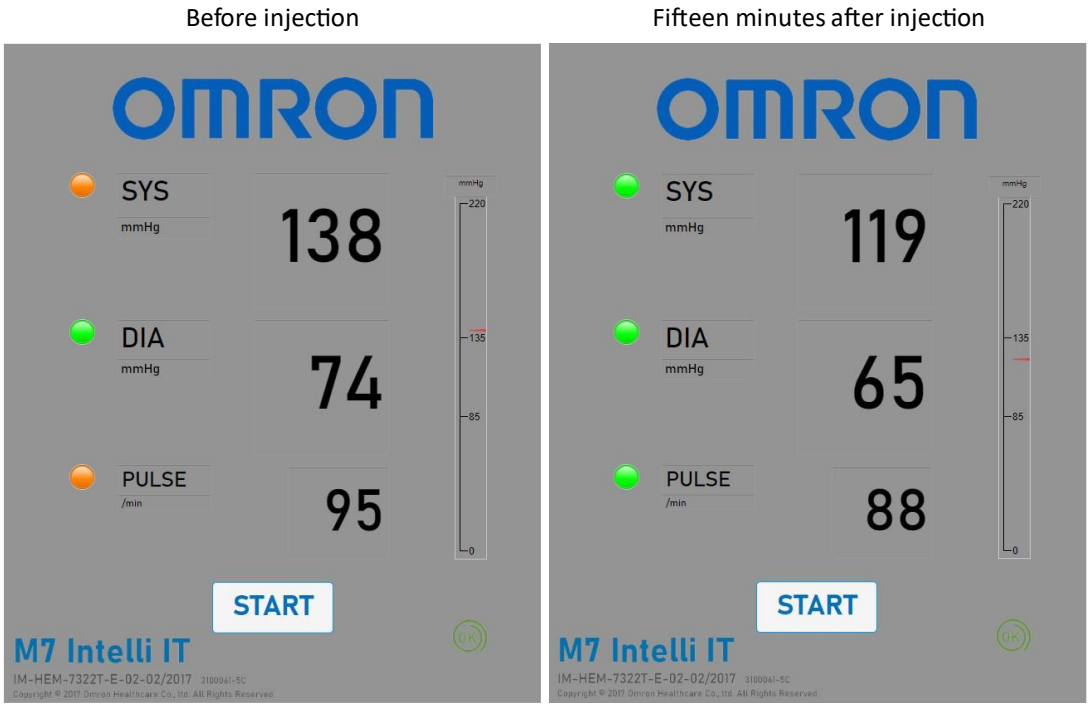

Figure 16. Screen displays of the two sham cardiovascular readings presented to participants as part of Study 2 cover story. On the left side, the values presented before the injection suggest that the participant is marginally stressed. On the right side, the values displayed 15min after the injection indicate that the cardiovascular function slowed down and came back to normal. I informed participants that this was an expected side-effect following morphine administration.

their readings would slow down and come back to normal.

2.5 Open Science Practices

Recently, the replication crisis has emerged as it has been discovered that roughly 70% of published social and medical sciences findings could not be replicated (Baker and Penny, 2016). Because the reproducibility of empirical findings is fundamental to the scientific method (Staddon, 2018), the theories and applications which were built on erroneous data may be compromised. This colossal drawback is the result of an

exponentially increasing pressure to publish (i.e., “Publish or perish”) which lead to an overall poor quality of publications (Rawat and Meena, 2014). As a result, the following fallacious practices emerged (Hagger et al., 2010):

- *P-hacking*: the action of performing as many statistical tests as needed to find a significant result to report (also called fishing for significance).
- *Optional stopping*: the action of interrupting participant recruitment as soon as the desired effect is statistically significant.
- *Selective reporting*: the tendency to exclusively report significant results while omitting others.
- *HARKing*: the tendency to adjust the hypotheses after the results are known to suggest that the data confirmed the expectations.

One way to circumvent theses fallacious practices while improving the overall quality of science is Preregistration, whose publications are termed Registered Reports (RRs). Preregistration is a publication format aiming at minimizing publication bias by ensuring that researchers cannot alter their methodology and hypotheses as soon as the data collection process has begun. The first attempt at improving publication quality with a format comparable to RRs dates back to the 1970s when the *European Journal for Parapsychology* introduced the possibility to publish negative results (Chambers, 2019). Decades later, in 2013, *Comprehensive Results in Social Psychology* was the first journal to officially offer RRs as they are still currently implemented. As of today, over 300 journals have joined the effort (see for a list: https://www.cos.io/initiatives/registered-reports) with nearly 600 RRs published in the past decade (Chambers and Tzavella, 2021).

In details, RRs are empirical publications which undergo a two-stage reviewing process after which they are being attributed an In-Principle-Acceptance if the content of the manuscript is validated by scientific peers (*see for a review* Chambers and Tzavella, 2021). (**Figure 17**). During Stage 1, reviewers will judge the validity of the research question and hypotheses which need to be grounded in scientific evidence as well as the soundness of the

methodology designed to test the hypotheses. Importantly, a priori power calculations at this stage ensure the reliability of the results such that a pre-determined fixed sample size will provide high-accuracy evidence that the targeted phenomenon manifests with a magnitude corresponding to, or higher than the effect size of interest. If the manuscript is approved at this stage, the authors are awarded Stage 1 In-Principle-Acceptance and are thus allowed to begin data collection. At this point, the content of the Stage 1 registered manuscript (i.e., the Abstract, Introduction and Methods sections) cannot be altered anymore. Importantly, provided the authors strictly follow their registered methodology, they are ensured to get

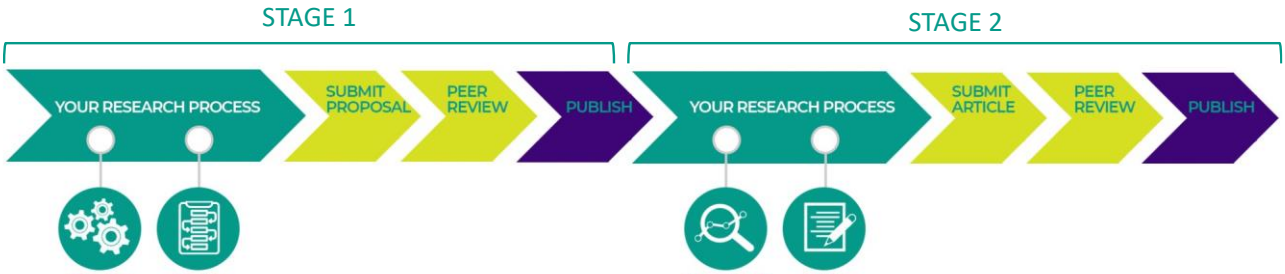

Figure 17. Publication stages specific to Registered Reports. Adapted from "Registered Reports: One Year at PLOS ONE" by Benetreau, Y., 2021, *PLoS Blogs*.

published no matter the results.

Once data collection is completed, authors can submit the whole manuscript for Stage 2 reviewing process usually performed by the same reviewers. Of relevance, reviewers will solely be judging i) whether the data are suitable for testing the study hypotheses, ii) whether the sections registered at Stage 1 remained untouched, iii) whether the authors strictly followed their methodology and iv) if the authors' conclusions are consistent with the observed data.

This publishing format has the advantage of minimizing publication bias and frauds in deductive science while providing a framework allowing to report negative results. Overall, preregistration favors hypotheses-driven high-quality publications over novel and eye-catching findings. For that reason, I have submitted for the first time in my research group two EEG studies as RRs in *Cortex* and in the *European Journal of Neuroscience*.

Of note, RRs imply that papers are published following the open-access principle and are thus made freely accessible (Stage 1 approved manuscripts for Study 1: https://osf.io/2vabk and Study 2: https://doi.org/10.5281/zenodo.4541048). In the same vein, study data, analysis scripts and experimental materials ought to be submitted to a public archive and are thus also accessible without restriction (Study 1: http://doi.org/10.5281/zenodo.4500849; Study 2: http://doi.org/10.5281/zenodo.5749398).

2.5.1 Power analyses

One of the fundamental requirements of RRs is to plan designs that can answer a research question with a predetermined level of statistical power. Statistical power is defined as the probability that a statistical test will lead to significant results (Cohen, 1988). Since traditional scientific journals largely favor publishing experiments reporting significant results (Koletsi et al., 2009), the overall false positive rate gets inflated as a large majority of published empirical studies do not provide sufficient power to ensure the reliability of their conclusions. Thus, in RRs, a priori power analyses must be submitted for each statistical contrast of interest as part of the Stage 1 manuscript and their soundness is evaluated during the reviewing process.

Statistical power can vary according to factors such as the significance threshold, the effect size, the sample size as well as the experimental design. Some of these factors may be fixed such as power in the case of RRs (i.e., 90% power for both *Cortex* and the *European Journal of Neuroscience*) or the significance threshold (i.e., 2% and 5% alpha levels respectively for *Cortex* and the *European Journal of Neuroscience*), while others vary according to the literature (i.e., effect size) or due to limited resources (i.e., sample size and design).

The standard approach for estimating any one of these parameters is the analytical method such that mathematical functions are applied to estimate the missing parameter based on the values provided for the other parameters (e.g., GPower; Erdfelder et al., 1996). While this method may be suitable for some research questions, Paxton et al. (2009)

suggested that “finite sample properties of structural equation model estimators are often beyond the reach of the established asymptotic theory”. Moreover, the analytical approach may not be adequate in cases where the type of continuous probability distribution is unknown a priori as well as in the context of complex statistical designs (e.g., mixed models).

To circumvent these issues, I have implemented scripts relying on the empirical Monte Carlo randomization approach, separately for each RRs. The core principle of the Monte Carlo method is that “properties of the distributions of random variables are investigated by use of simulated random numbers” (Gentle, 1985). In other words, large numbers of samplings are randomly drawn from a data distribution shaped by given parameters.

In my case, large numbers of datasets were generated by randomly drawing data from a simulated data distribution given fixed parameters (i.e., sample size, distribution type, within- and between-subjects SD and mean). Then, statistical tests were computed on thousands of generated datasets (i.e., usually at least 5000 randomizations). The estimated power corresponded to the percentage of significant results issued from these statistical tests. Since sample size is amongst the biggest limitations to well-powered studies, my script enabled to determine, step-by-step, the smallest sample size needed to reach the expected 90% statistical power given the other parameters (**Figure 18**).

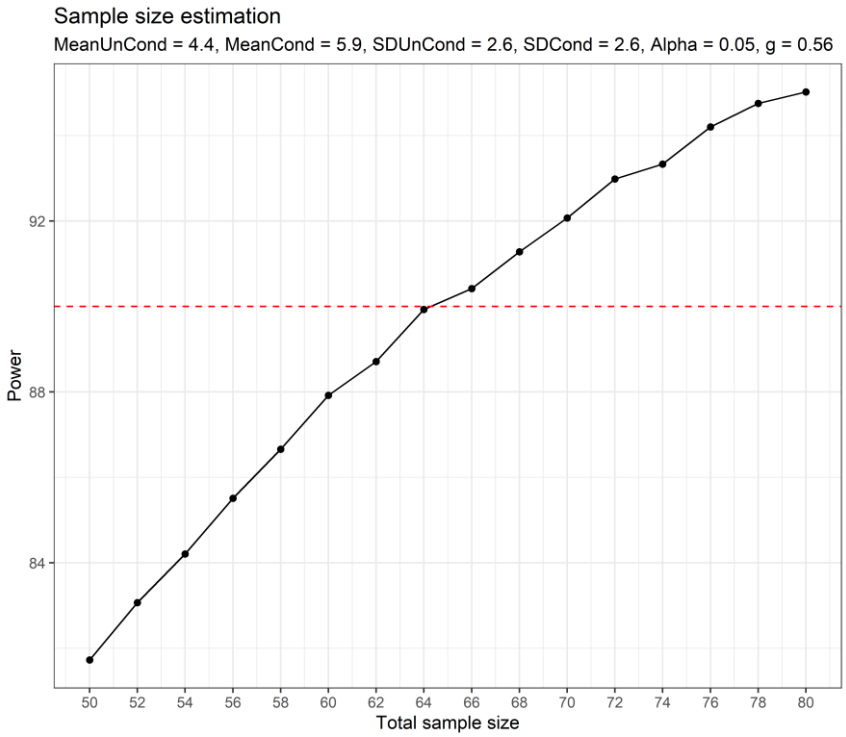

Figure 18. Power estimates for Study 2 using Monte Carlo randomization approach. I estimated the statistical power (y-axis) for my contrast of interest (difference in EEG voltage amplitude measured in μV) for each sample sizes (i.e., from 52 to 80 by steps of 2; x-axis) on data distributions simulated for each of the two groups (Cond and UnCond). The final sample size of 66 participants was required to provide statistical results with a power of at least 90%. Alpha=Significance Threshold; Cond=conditioned expectations group; EEG=Electroencephalography; g=Effect size (Hedges' *g*); UnCond=Unconditioned Expectations group; SD=Standard Deviation.

Chapter 3: Summary of Results

3.1 Study 1: Neural correlates of expectations-induced effects of caffeine intake on executive functions

Wicht, C.A., De Pretto, M., Mouthon, M., Spierer, L. 2021. *Cortex*, *submitted for Stage 2*.

3.1.1 Contribution

The candidate contributed to the elaboration of the task and experimental design, data collection and analyses, as well as the writing of the paper.

3.1.2 Abstract

Placebo effects (PE) are defined as the beneficial psychophysiological outcomes of an intervention that are not attributable to its inherent properties; PE thus follow from individuals' expectations about the effects of the intervention. The present study aimed at examining how expectations influence neurocognitive processes.

We addressed this question by contrasting three double-blinded within-subjects experimental conditions in which participants were given decaffeinated coffee, while being told they had received caffeinated (condition i) or decaffeinated coffee (ii), and given caffeinated coffee while being told they had received decaffeinated coffee (iii).

After each of these three interventions, performance and EEG was recorded at rest as well as during sustained attention RVIP and a Go/NoGo motor inhibitory control task.

We first aimed to confirm previous findings for caffeine-induced enhancement on these executive components and on their associated electrophysiological indexes (The Attention-P3 component, response conflict NoGo-N2 and inhibition NoGo-P3 components (ii vs iii contrast);

and then to test the hypotheses that expectations also induce these effects (i vs ii), although with a weaker amplitude (i vs iii).

We did not confirm any of our hypotheses for caffeine-induced behavioral improvements and thus did not test the effect of caffeine-related expectations. At the electrophysiological level, however, we confirmed that caffeine increased the Attention-P3 and NoGo-P3 components amplitude but did not confirm an effect on the response-conflict N2 component. We did not confirm that expectations influence any of the investigated electrophysiological indices, but we confirmed that the Attention-P3 GFP values were larger for the caffeine compared to the expectations conditions.

We conclude that previously identified behavioral effect sizes of caffeine and of the related expectations for sustained attention and inhibitory control may have been overestimated, and that caffeine primarily influences the ERP processing steps and brain areas supporting attention allocation. Finally, we confirm that caffeine-related expectations induce smaller effects than the substance itself.

Keywords: Caffeine; expectations; executive functions; EEG; ERP

3.2 Study 2: Experience with opioids does not lead to the recruitment of distinct brain network during placebo analgesia

Wicht, C.A., Mouthon, M., Nsimire Chabwine, J., Gaab, J., Spierer, L. 2021. *European Journal of Neuroscience*, *submitted for Stage 2*.

3.2.1 Contribution

The candidate contributed to the elaboration of the task and experimental design, data collection and analyses, as well as the writing of the paper.

3.2.2 Abstract

Placebo analgesia (PA) is defined as a psychobiological phenomenon triggered by the information surrounding an antalgic drug instead of its inherent pharmacological properties. PA is hypothesized to be formed through either verbal suggestions or conditioning. The present study aims at disentangling the neural correlates of expectations effects with or without conditioning through prior experience using the model of PA.

We addressed this question by recruiting two groups of individuals holding comparable neutral to positive expectations regarding morphine analgesia but either (i) with or (ii) without prior experience with opioids. We then contrasted the two groups' neurocognitive response to acute heat-pain induction following the injection of sham morphine using EEG. Topographic ERP analyses of the N2 and P2 pain evoked potential components allowed to test the hypothesis that PA involves distinct neural networks when induced by expectations with or without prior experience.

First, we confirmed that expectations of morphine analgesia did not differ by more than a *g* of 0.4 (actual difference: *g* = 0.37) and that our intervention induced a PA of at least g_{av} >= 0.5 (actual PA: g_{av} = 0.6). We then tested our hypothesis on the recruitment of different PA-

associated neural networks in individuals with vs without prior experience with opioids and found no evidence for a difference between the two groups at the level of topographic ERP analyses for the N2 and P2 components. Our results thus suggest that in the presence of verbal expectations, modifications in the neural mechanism of PA by conditioning is either absent or very small.

Keywords: Placebo; pain; expectations; EEG; ERP topography

Chapter 4: General Discussion

This thesis was dedicated to broadening the scope of the neural mechanisms underlying PEs triggered by expectations or conditioning, either in the context of the cognitive enhancing properties of psychostimulants such as caffeine (Study 1) or in relation to the analgesic features of painkillers (Study 2).

The current chapter will first provide a summary of the studies' conclusions and discuss their limitations considering recent findings. Then, I will provide evidence that my data advocate for updating current neurobiological models of expectations effects in favor of the Reactivation Hypothesis. Finally, I will offer my thoughts about strengths and weaknesses of preregistration and provide a conclusion as well as suggestions regarding future perspectives.

4.1 A unified neurobiological model of expectations effects

As mentioned in Chapter 1.4, according to the Kirsch et al. (2016) Cognitive Model of PEs, expectations can be formed and later recalled with classical conditioning (i.e., conditioned expectations) or verbal suggestion (i.e., verbally-induced expectations; **Figure 2**). The Dual-Process model (Schafer et al., 2018) provides an elegant way to disentangle the neurobiological correlates of those different types of expectations.

As such, the model distinguishes between neurobiological mechanisms that seem to be i) shared by both conditioned and verbally-induced expectations from ii) those solely involved in conditioned expectations. On the one side, the former relies on the Reactivation Hypothesis, namely the assumption that placebos reactivate the neural networks of the active compound they substitute to produce comparable effects. On the other side, the latter, according to the Placebo-Reward Hypothesis, requires the additional involvement of the dopaminergic reward pathway because of conditioning mechanisms.

While the theoretical background regarding conditioned and verbally-induced expectations' neurobiological mechanisms are already well defined, there is a lack of evidence to support their claims. Hence, the two studies conducted as part of this thesis aimed at providing empirical data in support of the Dual-Process model and its distinction between neural mechanisms governing the two types of expectations.

4.1.1 Neurobiological correlates of conditioned expectations

In Study 1, the goal was to demonstrate that the cognitive enhancing properties usually attributed to caffeine such as enhanced attentional focus or increased inhibitory control may, at least partially, stem from their mere expectations. Moreover, I aimed to provide evidence to support the Reactivation Hypothesis such that caffeine expectations would reactivate the same neural networks as pure caffeine to produce comparable behavioral results. In that sense, I first aimed at i) replicating previous evidence for caffeine's enhancing behavioral and neurophysiological effects on sustained attention (Deslandes et al., 2005; Martin and Garfield, 2006; Diukova et al., 2012; Foxe et al., 2012; Kahathuduwa et al., 2017; Wilhelmus et al., 2017; Saville et al., 2018) and inhibitory control (Barry et al., 2007, 2014, 2016; Foxe et al., 2012; Dodd et al., 2015; Pasman et al., 2017) to validate the experimental paradigm. Would the replication be successful, only then was I allowed to explore the hypotheses that ii) expectations induce effects that are comparable to those induced by caffeine (Oei and Hartley, 2005; Harrell and Juliano, 2009; Elliman et al., 2010; Dawkins et al., 2011; Denson et al., 2012; Heinz et al., 2013), iii) though to a weaker extent, since expectations generally account for a third of the substance effect (Schedlowski et al., 2015).

No replication of caffeine cognitive enhancing effects

Contrary to the first hypothesis and to previous findings, there was no evidence for an effect of caffeine on behavioral performance either on sustained attention or inhibitory control. Correspondingly, the sample composed of moderate coffee consumers did not display faster RT or higher response accuracy after having received 360mg of caffeine in less than an hour.

One presumptive explanation for the absence of caffeine behavioral effects may be related to discrepancy in genotypes. Recent evidence has highlighted that caffeine effects may be modulated by genetic variants in the Cytochrome P450 1A2 (CYP1A2) gene. Carswell and al. (2020) have demonstrated that caffeine effects on RT to a vigilance task are larger for CYP1A2 "fast" (AA genotype) compared to "slow" metabolizers (AC or CC genotype). Similarly, Guest and al. (2018) have shown that beneficial caffeine effects on sport performance only manifest in AA genotype individuals while having no impact on AC and even impairing CC genotypes performance. These discrepancies in performance may be better explained by differences in baseline cardiovascular activity across genotypes and especially by the way caffeine intake affects blood pressure (*see for more information* Soares et al., 2018). Of note, carriers of the "slow" AC and CC metabolizing variants represent more than half of the population (Cornelis et al., 2006). Consequently, I cannot preclude that the absence of caffeine effects on behavioral measures may be interpreted as resulting from heterogeneity in caffeine metabolism in my sample which would in turn have lessened the already weak caffeine effects (McLellan et al., 2016).

In addition, while my sample was evenly balanced in terms of gender distribution (56% females), I cannot entirely exclude a gender effect on the behavioral results. Correspondingly, Temple and Ziegler (2011) have demonstrated that gender has an impact on subjective and cardiovascular responses to caffeine which is mediated by the concentration of circulating steroid hormones. Furthermore, a recent study identified that females who drink caffeine daily have a higher tendency to consume alcohol, nonprescription drug, and tobacco (Dillon et al., 2019). In such a case, craving symptoms related to substances known to interact with caffeine effects (Gilbert et al., 1995, 2000; Martin and Garfield, 2006; Bailey et al., 2016b, 2016a) may have been stronger in females. Most importantly, I provided each participant with the same caffeine dosage, independent of their weight. Hence, lighter individuals and thus specifically females (e.g., in the United States, males are 16.5% heavier than females; Ogden et al., 2004), may have been more prone to experience caffeine side-effects. Indeed, evidence has demonstrated that side-effects start to increase exponentially when the dosage exceeds 6mg/kg body weight (Howell et al., 1997; Mora-Rodriguez and Pallarés, 2014). With the

dosage that was used, an individual weighing around 50kg would have exceeded the 6mg/kg limit, contrary to someone weighing 80kg. Thus, related to my findings, since in the caffeine condition participants were deceptively instructed that they had received a decaffeinated coffee, females (and lighter individuals in general) may have been more prone to unblind the deception due to increased subjective and physiological responses to caffeine as well as craving symptoms related to chronic use of other psychoactive substances. Thus, gender as well as individuals‘ weight may have impacted the behavioral results such that lighter individuals were more biased to guess which conditions they were assigned to.

Related to the electrophysiological measurements, I was able to replicate past evidence for a caffeine effect on the P3 ERP component. Accordingly, after having consumed caffeine, individuals displayed larger Attention-P3, and NoGo-P3 components' voltage amplitudes and larger GFP values related to either of the cognitive functions. Specifically related to inhibitory control, I demonstrated that caffeine increased brain activity in the Middle Frontal Gyrus (MFG). Since the MFG is a substrate for top-down attentional control mechanisms (Hong et al., 2017), my data suggest that caffeine tends to modulate brain areas related to attentional mechanisms instead of inhibitory control processes per se.

Interpreting electrophysiological effects without corresponding behavioral changes can sometimes be a puzzling mystery. In my case, I postulate that the caffeine effects that was reported on the neurophysiological correlates of attention did not translate into behavioral changes because the latter, if any, were too small to be detected. Since the sample of 38 participants was solely dedicated to detecting effect sizes of small magnitude (Hedges'*g* = 0.3) or higher, it is likely that with a larger sample I would have observed behavioral changes of even smaller magnitude. As such, Roberts et al. (2020) have demonstrated along a wide range of psychostimulants that their cognitive enhancing effects on executive functions were of smaller magnitude than my study's target effect size (*see also* Sinkeviciute et al., 2018). Nevertheless, such small effect sizes, especially in the case of cognitive enhancement, may often be deemed negligible. The principle of practical significance will be discussed in greater details in later sections.

No cognitive enhancing effects of caffeine expectations

Contradicting the second hypothesis as well as past empirical findings, I did not provide evidence for an effect of caffeine expectations either at the behavioral or the neurophysiological level regarding either the sustained attention or inhibitory control tasks.

The absence of behavioral findings comes as no surprise knowing that PEs are usually of smaller magnitude than the active drug effects (Schedlowski et al., 2015) and that I found no support for caffeine effects. A larger sample than was included might have enabled to detect a significant effect of caffeine expectations but of much smaller magnitude than I expected.

Of note, criticisms have been raised towards the BPD regarding the risk of unblinding in deceptive conditions due to its vulnerability to internal validity threats (George et al., 2012). In my experiment and in the case of caffeine expectations effects, participants were deceptively instructed to have received a caffeinated drink while they were, in fact, administered a decaffeinated coffee. Hence, my sample composed of daily caffeine drinkers may simply not have experienced the effects they are used to feel, which may have raised the risk of them unblinding conditions assignment. These criticisms are even more relevant towards pharmacological studies such as the one we conducted in a population of conditioned daily consumers who are accustomed to experiencing the drug's psychophysiological effects and are familiar with related sensory stimulation (e.g., smell, taste, color of the drug, etc.).

Finally, echoing the gender confounding effects raised in the previous section, Adan et al., (2008) highlighted that decaffeinated coffee produced larger arousing effects in females compared to males. This may suggest that females may be more sensitive to PEs than males. More specifically, a recent review found that females are more sensitive to PEs induced through conditioning procedures while males display larger PEs when induced through verbal suggestions (Vambheim and Flaten, 2017). Hence, since the present study design solely examined conditioned expectations, one cannot exclude that the sample's male-female ratio led to weaker PEs than what would have been observed in an all-female sample.

Caffeine expectations support the Reactivation Hypothesis

Supporting the third hypothesis, I uncovered that caffeine effects were stronger than expectations effects at the level of GFP and in relation to the Attention-P3 component. More specifically, since GFP is a measure of the strength of activation of the same brain electrical generators, the difference in GFP indicates that identical neural networks were activated in both conditions, though to a different intensity (Brunet et al., 2011). Hence, while this electrophysiological result did not result in differences at the behavioral level, it does provide consistent support for the Reactivation Hypothesis.

I provide here, to the best of my knowledge, the first electrophysiological evidence that caffeine and expectations seem to trigger the same neural networks underlying attentional mechanisms though to a different extent. This finding also suggests that caffeine leads to higher level of neural synchrony or recruits a larger neuronal population compared to expectations (*see* Brunet et al., 2011).

Methodological limitations

Since the study could not replicate past behavioral findings, I provide here an alternative hypothesis according to which the cognitive enhancing effects usually attributed to caffeine may in fact solely emerge when combined with expectations. To support my assertion, Elliman et al. (2010) highlighted that caffeine can enhance vigilance but only when individuals are accurately informed that they are receiving caffeine. In the same vein, Oei and Hartley (2005) demonstrated that participants perform better at a signal detection task under caffeine only when informed accordingly. In fact, in real life situations, coffee drinkers are conscious of their behavior and as such, expectations of benefits are triggered.

This remark relates to the long-time debate between the additive and interactive hypotheses of combining PEs and active substance effects (**Figure 19**). Regarding my experiment, if the additivity principle held true, adding up expectations and caffeine effects should not have resulted in a significant behavioral improvement since neither intervention enhanced cognitive performance separately. On the contrary, if the interactivity principle

were true, then the added value resulting from the interaction between expectations and caffeine effects would in turn have led to cognitive enhancement. Nevertheless, since Study 1's design lacks the fourth condition of the BPD where participants would have received a caffeinated coffee and been instructed in accordance, I am not able to provide support for this assertion and it should be the scope of future investigations.

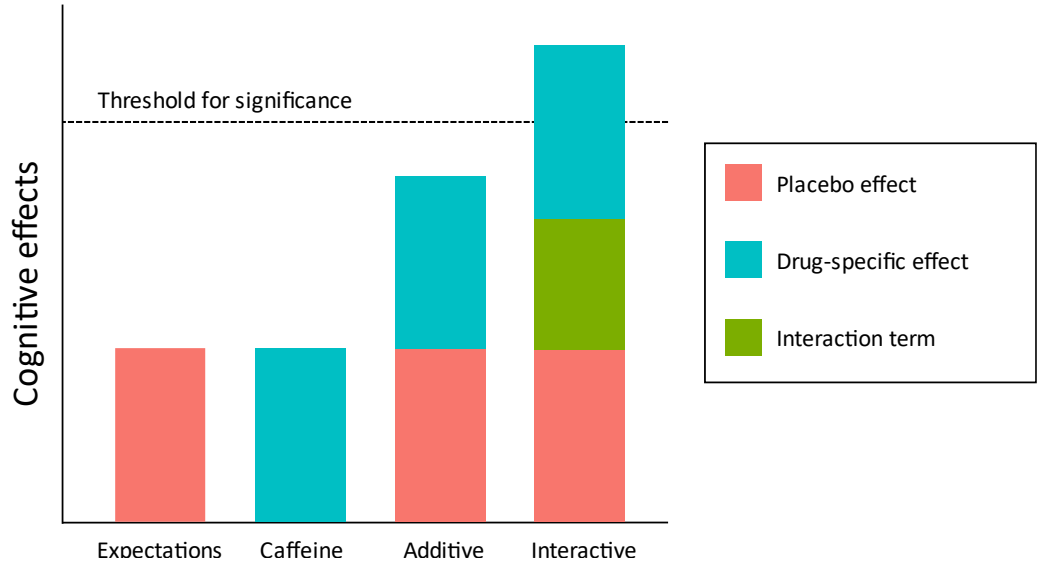

Figure 19. Hypothetical representation of the additivity and interactivity principles in relation to Study 1. On one side, the additive hypothesis implies that the combined effect of expectations and caffeine is not larger than the addition of their individual terms. On the other side, the interactive hypothesis stipulates that expectations and caffeine effects, when combined, result in an interactive term. Regarding Study 1, would the additive hypothesis be true, the added effects of expectations and caffeine would not have led to significant effects on cognitive performance. On the contrary, if the interaction hypothesis held true, it is possible that the interaction term added to each individual term would have led to a significant cognitive effect.

In conclusion, though I could not replicate previous evidence for behavioral effects of caffeine and expectations, I could successfully demonstrate, using the model of caffeine, that expectations in a group of conditioned individuals (i.e., moderate coffee drinkers) rely on the same neural networks as the active substance they are based on.

While this finding is highly relevant to the current project, it does not yet enable to determine whether the Dual-Process model assumption, according to which two neural

systems distinguish conditioned and verbally-induced expectations, holds true. This was thus the purpose of Study 2.

4.1.2 Comparable neural networks underlying conditioned and verbally-induced expectations

In Study 2, I aimed at providing evidence supporting differences in the brain networks recruited to induce PEs through conditioned or verbally-induced expectations. For that purpose, I relied on the extensively studied model of acute pain and PA in healthy individuals. Based on past evidence (Colloca et al., 2009; Carlino et al., 2015), I postulated that individuals with or without prior experience with morphine (i.e., which had built respectively conditioned and verbally-induced expectations) would rely on different brain mechanisms to produce comparable PA. Importantly, I ensured that all participants shared common neutral-to-positive expectations of morphine analgesic properties. Hence, since the magnitude of expectations was kept constant across groups, contrasting the two groups enabled to isolate the mechanisms specific to each type of expectations.

Contrary to my hypothesis, while I ensured that the procedure was able to induce PA of medium effect size (Hedge's g_{av} = 0.6), I could not provide support for a difference in neural networks recruited between the two types of expectations. Hence, the evidence indicates that the Dual-Process model and the Placebo-Reward hypothesis may be wrong in postulating that conditioned expectations would additionally trigger neural circuitry processing reward mechanisms.

Neurochemical differences between types of expectations

Alternatively, I could postulate that, instead of different brain structures, conditioned and verbally-induced expectations may differ in terms of the neurotransmission systems they recruit. Accordingly, using functional molecular imaging techniques, evidence indicated that not only dopaminergic but also opioidergic neurotransmissions are triggered in the NAc to elicit PEs (Scott et al., 2007, 2008). Relying on PET and the model of psychostimulants, Volkow

et al. (2006) showed that expectations related to methylphenidate administration increased brain glucose metabolism in the NAc but in a group of unconditioned, non-abusing individuals. Moreover, the same first author demonstrated, this time in a group of conditioned, cocaine abusers, that methylphenidate increased brain glucose metabolism in the thalamus and the cerebellum but solely when expected (Volkow et al., 2003). In the same vein, Wang et al. (2019), comparing unconditioned and conditioned individuals, demonstrated that expectations of methylphenidate increased dopamine release in caudate and midbrain but only in the unconditioned group. Finally, Kaasinen et al. (2004) highlighted in a group of conditioned habitual coffee drinkers that expectations enhanced the release of dopamine in the thalamus.

Consequently, while these experiments are supporting my findings by largely calling into questions the Placebo-Reward Hypothesis, they are also advocating for potential molecular differences between types of expectations. Moreover, since evidence did not unanimously point towards the same brain areas, it is very likely that the neural substrates supporting expectations are not transferable across different types of modalities. In other words, the neural networks that expectations rely on may depend on contextual information that accompany the active intervention substituted with the placebo, as suggested by the Reactivation Hypothesis.

Overall, my findings as well as evidence from molecular imaging studies would warrant a replication of the study using PET and specific radioligands that may inform on putative neurochemical differences in the same brain areas between the two types of expectations.

Methodological limitations

Even if Study 2 provides robust findings using state-of-the-art electrophysiological measurements, I would still like to highlight a few methodological limitations.

Even though I relied on robust estimators of electrophysiological topography differences (i.e., the GMD index), I cannot preclude that small differences arising from deep brain

structures (e.g., the NAc) may have remained undetected with EEG. Nevertheless, speaking in the favor of Study 2's findings, recent evidence highlighted that scalp EEG can accurately detect and locate electrical activity stemming from deep brain structures including the NAc (Seeber et al., 2019) and as efficiently as intracranial EEG (Hnazaee et al., 2020). Consequently, my results provide strong evidence that conditioned expectations may in fact not rely on different brain structures than verbally-induced ones to produce comparable PA.

I could then speculate that the neural distinction I was seeking between conditioned and verbally-induced expectations may have manifested elsewhere than in the N2 and P2 ERP component's time window that I focused on. Yet, contradicting this claim, Zhang and Luo (2009) highlighted that expectations can modulate N2 and P2 amplitudes, but exclusively in the case of conditioned expectations and not with verbal suggestions alone. Similarly, two experiments demonstrated, in the case of non-noxious tactile stimulation, that the amplitude of the P2 component is again influenced solely in the case of conditioned expectations (Fiorio et al., 2012), but not with verbal suggestion alone (Fiorio et al., 2014). These findings suggest that the components of interest I focused on are appropriately indexing the brain differences I sought between conditioned and verbally-induced expectations.

Moreover, previous findings have highlighted that the order of acquisition as well as the congruency between verbal suggestion and conditioning can have an influence on PA. Accordingly, Bajcar et al. (2021) showed that larger PA is expected when verbal suggestion precedes conditioning. Also, when the content of verbal suggestion and conditioning is incongruent, the magnitude of PA was in line with the direction of the last-used procedure. In the same vein, evidence demonstrated that prior experience with analgesic treatments can mitigate both later placebo response (Colloca and Benedetti, 2006) and subsequent experiences with different therapeutic approaches through a modulation of insular and DLPFC activity (Kessner et al., 2013). On this matter, Finniss et al. (2010) stated that conditioning will follow from expectations depending on the success of the initial encounter, strictly speaking the higher the expectations regarding the efficacy of a treatment, the larger the conditioning effect associated with subsequent drug intake. Since I do not know in Study 2 whether

individuals conditioned with prior experience with morphine may have been influenced by the i) order of acquisition of verbal suggestion and conditioning as well as by ii) the congruency between past experiences, I cannot rule out that these confounds may have increased the heterogeneity of the CondExp group.

Finally, uncontrolled psychological factors may have biased the electrophysiological measurements. While expectations are entangled in a meaning and emotional significance scheme (*see* Moerman & Jonas, 2002), Lyby *et al.* (2011) highlighted that fear of pain, which is the tendency to fear and be stressed during pain or by pain anticipation, can reduce PA effects on P2 amplitude. In the same vein, Aslaksen *et al.* (2011) uncovered a gender discrepancy in the strength of PA and in PA-mediated reduction in P2 amplitude, following from the fact that men were less subject to anticipatory stress. Speaking in favor of the mediation effect of emotional state in the placebo response, past evidence highlighted that fear and anxiety are negatively correlated with the magnitude of PA (Scott et al., 2007; Colagiuri and Quinn, 2018). Thus, in relation to the last paragraph, I cannot rule out that individuals in the CondExp group may have experienced larger fear of pain due to negative past experiences compared to individuals with no prior experience (*see for a review of the Fear-Avoidance Model* Leeuw et al., 2007). However, since I ensured that both groups shared comparable neutral to positive expectations regarding morphine analgesia, I excluded individuals displaying large prior negative experiences and thus minimized the risk of fear of pain confounding the results.

4.2 An updated neurobiological model of expectations effects

Schafer et al. (2018) suggested in their Dual-Process model that PEs are supported by two distinct neural structures: System 1 which recruits reward mechanisms to support conditioned, pre-cognitive learning and System 2 engaging cortical structures involved in top-down processes to support conscious learning. On this basis, I hypothesized that System 1 provides the neural substrates for the Placebo-Reward Hypothesis (de la Fuente-Fernández, 2009) while System 2 encompasses the neurobiological mechanisms behind the Reactivation

Hypothesis (Haour, 2005; Pacheco-López et al., 2006; Benedetti et al., 2011; Meissner et al., 2011; Benedetti, 2013, 2014; Enck et al., 2013; Colloca, 2014; Wager and Atlas, 2015; Atlas, 2021).

Since the aim of the thesis project was to highlight differences between two types of expectations as suggested in Kirsch et al. (2016) Cognitive Model of PEs (*see* **Figure 2**), I hypothesized that their neurobiological correlates would be delineated as suggested by the Dual-Process model. Hence, I postulated that, because of the conditioning process, only conditioned expectations would trigger System 1 whereas System 2 would be activated by the two types of expectations since they are both conscious top-down beliefs (Gu et al., 2016).

To my surprise, the data contradicts the Dual-Process model and provides support solely for the Reactivation Hypothesis. I found that, no matter if expectations were acquired through verbal suggestion or conditioning procedures, they all tended to trigger the same neurobiological mechanisms as the substance they are based on. More specifically, Study 1 suggested that conditioned, caffeine expectations trigger the same neural network as pure caffeine while Study 2 indicated that conditioned and verbally-induced expectations do not differ in the neural network they activate.

The Reactivation Hypothesis also stipulates that expectations will reactivate the same neural network to produce behavioral effects that are comparable to that of the active intervention. Correspondingly, I also provide support for this assertion such that, in Study 1, neither caffeine or expectations improved cognitive performance, and in Study 2, PA was comparable across the two expectations groups.

My findings would call into question the idea according to which expectations may be represented by a global neurobiological model (*see on this topic* Benedetti, 2014). On the opposite, and in accordance with the Reactivation Hypothesis, contextual information accompanying the active intervention substituted by the placebo may determine the neural networks that get recalled to support expectations effects. In other words, I would stipulate

that if the same placebo were to be presented either as a psychostimulant or as a pain-relieving pill it would trigger neural networks which are specific to either cognitive enhancement or pain management, respectively. Most importantly, my data indicate that this domain-specific brain mechanism is not influenced by prior experiences with the active intervention since conditioned expectations led to the same effects as verbally-induced ones.

While the results contradict the Dual-Process model, I only provide little evidence in regard to the Reactivation Hypothesis which is further restricted to a population of healthy young adults while relying on two pharmacological models. Though the conclusions may be limited and might not extend to clinical contexts or to non-pharmacological interventions, I provide strong evidence that expectations are a reliable top-down phenomenon deeply rooted in our brain that is able to mimic the neural mechanisms of pharmacologically active compounds.

4.3 A genuine report on preregistration

In this last section, I am offering my thoughts and experience about RRs, considering that the two thesis projects strictly followed the publication policies of preregistration and open access (*see section 2.5 for technical details)*.

Preregistration allows for the publication of null results and thus enables to counteract publication bias responsible for the inflation of effect sizes in the scientific literature. Accordingly, Schäfer and Schwarz (2019) have demonstrated that there is a dramatic inflation in published effect sizes such that the reported effect sizes for publications without preregistration is two-fold bigger than in RRs. Hence, the fact that I could not replicate caffeine and caffeine expectations effects in Study 1 may, at least partially, stem from the fact that I built the hypotheses and power calculations upon inflated effect sizes.

4.3.1 Practical significance

Since in the case of null results, frequentist analyses (i.e., null hypothesis significance testing) as opposed to Bayesian statistics, cannot inform as to whether the targeted phenomenon is likely true, but with a smaller magnitude, I may have missed in Study 1 the true caffeine and expectations effects simply because the effect size of interest was too large.

Based on this assertion, one can always wonder about the practical significance of very small effect sizes, even in the presence of statistically significant differences. A famous study on emotional contagion demonstrated that reducing the number of positive posts in people's social network news feed significantly diminished the number of positive words and increased the negative contents in participants' status updates (Kramer et al., 2014). Of relevance, this experiment included the data from nearly 700'000 participants and, as such, the reported effect sizes were extremely small, respectively Cohen's $d = 0.02$ and $d = 0.001$. In practice, this means that the intervention led people to include one additional negative word every 3570 words. This study perfectly illustrates a case where small effects, even though statistically significant, are in fact practically insignificant. In the same vein, a study including 569 advanced pancreatic cancer patients showed that combining two existing treatments significantly improved their survival rate (Moore et al., 2007). Nonetheless, the actual benefit was a mere 10 days, which is considered clinically irrelevant by oncologists, especially in regards of the incremental toxicity associated with the combination of the two treatments.

As a result, regarding Study 1, even if I may have missed caffeine and expectations true effects because the effect size of interest was not small enough, it does not necessarily mean that such modest effects would have any practical significance. Indeed, would caffeine or expectations hypothetically enhance cognitive performance by making thousands of daily consumers 1% more efficient, this would have, in the majority of cases, no practical impact on their daily functioning.

4.3.2 Limitations

From my experience, one of the main limitations of RRs is the number of participants that I needed to recruit to satisfy the positive controls and data exclusion criteria validated as part of the stage-1 RR. Positive controls are anticipatory strategies that ensure the reliability of the collected data. For example, in Study 2, I included a statistical criterion that determined whether PA across all subjects was large enough to be considered practically significant (i.e., larger than Hedges' g_{av} = 0.5). While positive controls doubtlessly improved the quality of the collected data, I had to recruit many more participants than initially planned to satisfy them. As a consequence, I recruited 55 instead of 38 participants in Study 1 and 75 instead of 66 in Study 2, which necessarily led to extended experimental timelines and costs.

A second constraint refers to the very limited space dedicated to exploratory analyses. The latter are authorized in RR as long as they are small, conducted in a separate section and that the conclusions do not essentially rely on their results. In the case where the actual results are not confirming the hypotheses (such as in Study 2), it may feel frustrating that the acquired datasets cannot be intensively explored. The reasoning lies in the fact that exploratory analyses may be largely underpowered and, thus, their conclusions may be less reliable if not misleading. Nevertheless, researchers recently advocated in the sense of a better consideration of exploratory research in preregistration in order to increase the reliability and robustness of novel theories and to avoid the pitfall of fallacious publication practices (Dirnagl, 2020). On this matter, *Cortex* launched in 2017 a new publication format, Exploratory Reports (McIntosh, 2017), which is dedicated to non-confirmatory research that ought to lay solid foundations for subsequent hypothesis testing research (Scheel et al., 2021).

Despite these few limitations, I am firmly convinced that preregistration currently represents the most suitable mean through which robust and reliable confirmatory findings can be published.

Chapter 5: Conclusion and Future Perspectives

5.1 Conclusion

The present work aimed at deepening the understanding of the electrophysiological correlates underlying PEs, especially focusing on the distinction between expectations and conditioning mechanisms as suggested in the Dual-Process model. More specifically, my goal was first to provide evidence supporting the Reactivation Hypothesis in that placebos tend to reactivate the neural networks of the active substance they replace to produce comparable PEs (Study 1). Then, building on this first evidence, I aimed to test the hypothesis that the neural networks underlying different types of expectations may slightly differ to produce comparable PA, according to the Placebo-Reward Hypothesis (Study 2).

Regarding Study 1, while the results failed to replicate previous evidence for a cognitive enhancing effect of caffeine and expectations at the behavioral level, I demonstrated that expectations and caffeine differed in how strongly they recruited the same neural network. Hence, I have met my goal of providing support for the Reactivation Hypothesis in that expectations, in the case of conditioned individuals (i.e., moderate coffee consumers), activate the same neural network as the substance they are based on to produce comparable effects (i.e., no behavioral effects in either case).

Concerning Study 2, the results indicated that a saline injection framed as morphine (i.e., sham morphine), independent of prior experience with opioids, was able to induce PA of medium magnitude. Nonetheless, because the two groups did not differ at level of EEG topography (i.e., GMD index), I could not provide support for the Placebo-Reward Hypothesis according to which conditioned expectations would recruit different brain networks compared to verbally-induced ones. Hence, even when ensuring that participants share common neutral to positive expectations regarding the analgesic properties of morphine, individuals with or without prior experience with opioids do not rely on different neural networks to produce comparable PA.

In conclusion, the findings challenge the assumption of the Dual-Process model that there are two neural systems supporting different types of expectations and, correspondingly, the assumption of the Placebo-Reward Hypothesis regarding the involvement of reward mechanisms in conditioned expectations. I speculate instead that the differences I sought may still manifest at two different stages. First, there may be distinctions between conditioned and verbally-induced expectations that manifest in the same neural network but at the molecular level (i.e., differences of neurotransmission systems). Secondly, it is also likely that conditioned and verbally-induced expectations rely on the same neural network but that the brain areas composing the network are modality specific, which is in compliance with the Reactivation Hypothesis. In other words, the contextual information accompanying the active intervention that the placebo substitutes would define which brain network gets reactivated, independently of the types of expectations.

5.2 Future perspectives

Since the findings appear to raise more questions than they solve, I hereby provide suggestions that may serve as food for thought.

For Study 1 and Study 2 I exclusively relied on robust estimators, respectively, GFP and GMD indexes which are orthogonal measures of the strength and topography of neural electrical generators. Since I did not find a GMD difference in Study 2, I could speculate that verbally-induced and conditioned expectations may have differed in how strongly they activate the same brain network, similarly to what I found in Study 1. Unfortunately, since the GMD index solely informs about differences in configuration of underlying electrical generators, additional investigations relying on the GFP index would be warranted.

Most importantly, relying on molecular imaging evidence of expectations effects (Volkow et al., 2003, 2006; Kaasinen et al., 2004; Wang et al., 2019), I postulate that the differences I was seeking between different types of expectations may better be highlighted at the level of neurotransmission systems. Accordingly, evidence demonstrated that placebos can activate not only dopaminergic but also μ-opioid neurotransmission systems in the NAc

(Zubieta et al., 2005; Wager et al., 2007), which is considered a crucial node of the mesolimbic dopaminergic pathway (Tu et al., 2020) and the scope of the Placebo-Reward hypothesis (de la Fuente-Fernández, 2009). Hence, it is likely that conditioned and verbally-induced expectations rely on the same brain network but by triggering different neurohormonal pathways. I could thus postulate that conditioned and verbally-induced expectations may differently recruit the NAc, in that the former would specifically activate the dopaminergic pathway while the second may solely rely on the opioidergic neurotransmission system (*see for a review* Benedetti, 2014). Thus, to evaluate this assumption, it may be of interest to replicate Study 2 using PET imaging technique as well as dopamine and μ-opioid radioligands.

Moreover, based on Kirsch et al. (2016) Cognitive Model, there is a third lead that was left unexplored, namely that PEs may also be elicited through unconscious conditioning procedures. In such paradigms, after completing a conditioning phase, the same conditioned cues are presented subliminally, hence without awareness. I could thus stipulate that differences in awareness of the recalled stimulus may drive conscious and unconscious conditioned expectations to activate different brain areas. Contradicting this claim, Jensen et al. (2015) indicated that unconscious, compared to conscious activation of previously conditioned PA lead to a stronger recruitment of the same orbitofrontal cortex. Additionally, Tu et al. (2021) highlighted using magnetoencephalography and machine learning decoding algorithms that expectations produced by either unconscious or conscious conditioned cues relied on the same brain structures, i.e., the Medial Prefrontal Cortex (mPFC) and ACC. These few findings suggest that differences in neural networks that I expected to observe in Study 2 are also unlikely to emerge when contrasting expectations derived from conscious or unconscious conditioning procedures.

Finally, to improve the overall generalizability of placebo findings to public applications, especially in the case where the therapeutic alliance plays a crucial role (Blease et al., 2016), it would be relevant to conduct additional experiments on designs that do not heavily depend on the ethical dilemmas inherent to deception (*see section 1.6*). Correspondingly, non-deceptive designs such as the OLP design, in which transparently prescribed placebos are

used, have emerged in the past decades. Even if laypersons tend to have higher outcome expectations regarding deceptive placebos (Haas et al., 2020), OLP has been shown to offer promising treatment opportunities in a variety of clinical conditions (*see for a meta-analysis* von Wernsdorff et al., 2021). Importantly, OLP effectiveness seems to depend on the plausibility of the rationale that accompanies the openly inactive intervention (Locher et al., 2017). In Study 2 I demonstrated that, independent of prior experience, a unique injection of saline framed as morphine was able to effectively reduce acute pain ratings. It would thus be relevant to determine whether this PE may persist in populations suffering from chronic pain diseases by testing, for example, newly branded sham placebo pills accompanied by different rationales in an OLP framework. Overall, there remain considerable efforts as to translate fundamental research like the ones I ran into practical applications by maximizing the healing benefits and public acceptance of placebo medicine.

Though both studies provided robust evidence regarding the neural correlates of expectations, much work is to be undertaken as to determine whether expectations recruit the same brain network but in a modality-specific manner or if a general model can be established, providing distinctions between expectations solely manifest at the level of neurotransmission systems.

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Neural correlates of expectations-induced effects of caffeine intake on executive functions

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ABSTRACT

Placebo effects are defined as the beneficial subjective or behavioral outcomes of an intervention that are not attributable to its inherent properties; Placebo effects thus follow from individuals' expectations about the effects of the intervention. The present study aimed at examining how expectations influence neurocognitive processes.

We addressed this question by contrasting three double-blinded within-subjects experimental conditions in which participants were given decaffeinated coffee, while being told they had received caffeinated (condition i) or decaffeinated coffee (ii), and given caffeinated coffee while being told they had received decaffeinated coffee (iii).

After each of these three interventions, performance and electroencephalogram was recorded at rest as well as during sustained attention Rapid Visual Information Processing task (RVIP) and a Go/NoGo motor inhibitory control task.

We first aimed to confirm previous findings for caffeine-induced enhancement on these executive components and on their associated electrophysiological indexes (The Attention-P3 component, response conflict NoGo-N2 and inhibition NoGo-P3 components (ii vs iii contrast); and then to test the hypotheses that expectations also induce these effects (i vs ii), although with a weaker amplitude (i vs iii).

We did not confirm any of our hypotheses for caffeine-induced behavioral improvements and thus did not test the effect of caffeine-related expectations. At the electrophysiological level, however, we confirmed that caffeine increased the Attention-P3 and NoGo-P3 components amplitude but did not confirm an effect on the response-conflict N2 component. We did not confirm that expectations influence any of the investigated electrophysiological indices, but we confirmed that the Attention-P3 Global Field Power values were larger for the caffeine compared to the expectations conditions.

We conclude that previously identified behavioral effect size of caffeine and of the related expectations for sustained attention and inhibitory control may have been overestimated, and that caffeine primarily influences the cognitive processes and brain areas supporting attention allocation. Finally, we confirm that caffeine-related expectations induce smaller effects than the substance itself.

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1. Introduction

Placebo effects (PE) are defined as the beneficial subjective or behavioral outcomes of an intervention that are not attributable to its inherent properties (Benedetti, Carlino, & Pollo, 2011; Wager & Atlas, 2015). PE thus only result from the administration of the intervention, which is thought to influence psychophysiological state via learning-based expectations about the effects of the actual intervention (Benedetti et al., 2011; Finniss, Kaptchuk, Miller, & Benedetti, 2010; Haour, 2005; Kirsch, 1985). According to the Expectancy Theory (Kirsch, 1985, 1997), Pavlovian conditioning indeed constitutes one of the main mechanism by which PE-triggering expectations are formed. In such context, classical conditioning has been redefined as the process of learning of relations between events (Robert, 1988). Conditioning, whose fulfillment is based on the information that the conditioned stimulus (CS, e.g. smell, taste, popular knowledge regarding a substance) provides about the unconditioned stimulus (US, the actual substance) and not on contiguity (Kirsch, 1997), will engender expectations that certain events will follow other events ultimately leading to a conditioned pharmacological response (Siegel, 1983).

Yet, while many studies examined the effects of expectations, most of them focused on behavioral or physiological outcomes, leaving largely unresolved the underlying neurophysiological mechanisms (for reviews, see e.g. Benedetti, 2014; Enck, Bingel, Schedlowski, & Rief, 2013; Wager & Atlas, 2015).

We addressed this question by investigating the neurocognitive PE of caffeine. This substance constitutes an advantageous model to study PE because i) it displays reliable cognitive enhancing and (neuro)physiological effects (Dance, 2016; Einöther & Giesbrecht, 2013; Franke, Lieb, & Hildt, 2012; Glade, 2010); and ii) it is the most widely used psychostimulant, with its effect thus well-known and widely shared among the general population (Ludden, O'Brien, & Pasch, 2017; Schreiber, Maffeo, Robins, Masters, & Bond, 1988; Turton, Piché, & Battram, 2016).

As for most substance-related PE, the literature reviewed in Table 1 indicates that expectations about the effects of caffeine lead individuals to experience the behavioral effects of caffeine when they think to have but have actually not ingested caffeine (for a review see Shabir, Hooton, Tallis, & Higgins, 2018). Accordingly, we tested the general hypothesis that since caffeine PE enhance behavioral performance as would the actual substance intake, they do so via an enhancement of the supporting neurophysiological processes.

To examine the neurocognitive effects of expectations, we focused more specifically on the effects of caffeine on sustained attention and inhibitory control. Executive functions have indeed been shown to be particularly sensitive to caffeine and given the large literature on the topic (Einöther & Giesbrecht, 2013; Glade, 2010), it constitutes an advantageous model to address our questions.

Caffeine-induced executive function enhancements are hypothesized to be mainly driven by striatal adenosine A_{2A}-dopamine D_2 receptor heteromers, which are mostly represented in the dopamine-rich putamen (Bauer et al., 2003; Ferré, 2016; Mishina & Ishiwata, 2014), and by adenosine neurons of the Locus Coeruleus, the major noradrenergic nucleus (Grant & Redmond, 1982; Samuels & Szabadi, 2008). By increasing noradrenergic and dopaminergic activity, caffeine influences the functional activity in brain areas regulated by these subcortical nuclei, which notably include the key inhibitory-control areas (i.e. the right inferior frontal gyrus (Chamberlain et al., 2009; Li & Kubota, 1998), internal globus pallidus (Pan et al., 2018) and subthalamic nucleus (*for a review see* Jentsch & Pennington, 2014; Bakhtiari, Altinkaya, Pack, & Sadikot, 2020) and the areas supporting sustained attention (i.e. the right medial frontal and dorsolateral prefrontal cortex (Sarter, Givens, & Bruno, 2001), temporo-parietal junction (Langner & Eickhoff, 2013; Strange & Dolan, 2007) and parahippocampal gyrus (Filbey, Russell, Morris, Murray, & McDonald, 2008; *for a review see*; Logue & Gould, 2014). This neurophysiological mechanism is considered as underlying the cognitive enhancing effects of caffeine on executive performance (Einöther & Giesbrecht, 2013).

To test the effects of caffeine and caffeine-related expectations on executive control and attention neurocognitive processes, we used i) the Rapid Visual Information Processing task (RVIP), a sustained attention detection task and ii) the Go/NoGo motor inhibitory control task. At the behavioral level, these two neurocognitive executive components were indexed by response times (RT) and accuracy. Neurophysiologically, they were indexed by the ERP components underlying the key sustained attention and inhibitory processes: The Attention-P3 for the RVIP, as well as the NoGo-N2 and NoGo-P3 ERP components for the Go/NoGo task.

These components represent ideal candidates to examine caffeine expectations in our setting because they have been associated with sustained attention and inhibitory control performance (Barry, Steiner, & De Blasio, 2016; Folstein & Van Petten, 2008; Patel & Azzam, 2005), have a demonstrated sensitivity to caffeine (Bailey et al., 2016b; Barry et al., 2007, 2014; Deslandes et al., 2004, 2005; Diukova et al., 2012; Kahathuduwa, Dassanayake, Amarakoon, & Weerasinghe, 2017; Martin & Garfield, 2006; Saville, de Morree, Dundon, Marcora, & Klein, 2018), and in line with these results, their neural generators partly overlap with the areas known to be modulated by caffeine.

The Attention-P3 is a central positive ERP component manifesting 300–500 ms post-stimulus onset (Key, Dove, & Maguire, 2005; Hoyniak, Petersen, McQuillan, Staples, & Bates, 2015) arising from the temporo-parietal junction (Smith et al., 1990; Ragazzoni et al., 2019), the superior temporal gyrus (Rogers et al., 1991; Mangalathu- Arumana et al., 2012) and the precuneus (Justen & Herbert, 2018). The amplitude of this component increases and its latency decreases when task-relevant attended (infrequent) stimuli are detected (Herrmann & Knight, 2001; Barry et al., 2016), suggesting that the Attention-P3 indexes active stimulus evaluation, discrimination and response preparation (Herrmann & Knight, 2001; Key et al., 2005) with its latency reflecting the duration of stimulus evaluation (Donchin & Coles, 1988). As for the inhibitory control components, consistent with the sustained attention improvement with caffeine (Glade, 2010; Einöther & Giesbrecht, 2013, Table 1) and the sensitivity to caffeine of partly overlapping areas, doses from 250 to 400 mg, induce a reduction of

Table 1 – Current literature on the effect of actual and placebo caffeine administration on inhibitory control and attentional executive functions and baseline brain activity.

	Tasks	Behavior	Electrophysiology
Effect of actual caffeine intake	**Sustained attention** *Behavior:* Foxe et al., 2012; Wilhelmus et al., 2017 *EEG:* Deslandes et al., 2005; Martin & Garfield, 2006; Diukova et al., 2012; Kahathuduwa et al., 2017; Saville et al., 2018	**↑ Correct sequence detection (HITS) & ↓ Reaction times (RT)**	**↓ latency & ↑ amplitude** of ERP components indexing stimulus evaluation, discrimination and response preparation (P3)
	Inhibitory control *Behavior:* Foxe et al., 2012; Barry et al., 2014; Dodd, Kennedy, Riby, & Haskell-Ramsay, 2015; Pasman et al., 2017 *EEG:* Barry et al., 2007, 2014, 2016	**↑ Correct Rejections (CR), ↓ Omission (MISS) and Commission errors (False Alarms, FA) & ↓ RT**	**↑ amplitude** of ERP components indexing i) conflict detection (N2) and iii) response inhibition and evaluation (P3)
Effects of caffeine-related expectations	**Sustained attention** *Behavior:* Elliman, Ash, & Green, 2010; Harrell & Juliano, 2009; Oei & Hartley, 2005	**↑ HITS & ↓ RT**	*Unknown*
	Inhibitory control *Behavior:* Dawkins, Shahzad, Ahmed, & Edmonds, 2011; Denson, Jacobson, Von Hippel, Kemp, & Mak, 2012; Heinz, de Wit, Lilje, & Kassel, 2013	**↑ CR & ↓ RT**	*Unknown*

the Attention-P3 latency (Deslandes et al., 2004, 2005; Diukova et al., 2012; Saville et al., 2018), and an increase of its amplitude (Kahathuduwa et al., 2017).

Related to inhibitory control, the NoGo-N2 is a fronto-central negative ERP component manifesting 200–400 ms after stimulus onset (Hayashi et al., 2018) and arising from the middle frontal, cingulate and precentral gyri (Stock, Popescu, Neuhaus, & Beste, 2016). The amplitude of this component increases when a conflict between a stimulus-driven response tendency and task demands is detected, as it is the case when a NoGo stimulus prompts for the suppression of a prepotent motor response in Go/NoGo tasks (Sehlmeyer et al., 2010; Wessel, Danielmeier, Bruce Morton, & Ullsperger, 2012). The NoGo-P3 is a fronto-central positive ERP component manifesting 300–500 ms after stimulus onset (Hayashi et al., 2018) arising from the middle frontal and anterior cingulate gyri (Stock et al., 2016). The amplitude of this component increases when the motor response to a NoGo stimulus is successfully suppressed (Ramautar, Kok, & Ridderinkhof, 2004; Wessel & Aron, 2015), suggesting that it indexes the implementation of motor suppression processes and its evaluation (Huster et al., 2011; Gajewski & Falkenstein, 2013; Wessel & Aron, 2015). Consistent with the inhibitory control performance improvement with caffeine (Glade, 2010; Einöther & Giesbrecht, 2013, Table 1), and the overlap between the neural generators of these components and the network sensitive to caffeine, doses from 120 to 250 mg have been shown to enhance the N2 (Bailey, Amlung, et al., 2016) and P3 amplitudes (Barry et al., 2007, 2014).

Based on the literature reviewed above, we first aimed at replicating previous findings about the neurocognitive effects of caffeine on executive functions; our hypothesis was:

Ha) In an administration condition where participants expected to receive a decaffeinated coffee (DECA), those actually receiving a caffeinated coffee (CAF) would show enhanced executive performance and electrophysiological markers of executive functions compared to those drinking a DECA.

We then tested the prediction that expectations effects would manifest as those of the caffeine in Ha (*see for details* section 2.10), though with a weaker amplitude:

Hb) In a placebo administration condition where participants drink a DECA, those being told it was a CAF would show enhanced executive performance and electrophysiological markers of executive functions compared to those being told they have received DECA.

Hc) Since expectations effects are hypothesized to correspond to roughly 1/3 of the actual substance effect size (*see for a review on clinical data* Schedlowski, Enck, Rief, & Bingel, 2015), the effects when participants received DECA but think to have been administered a CAF would be smaller than effects when they have received a CAF but believe they have received a DECA.

To address these hypotheses, we used the following experimental conditions: i) Give-DECA/Told-CAF (GD/TC), ii) Give-CAF/Told-DECA (GC/TD) and iii) Give-DECA/Told-DECA (GD/TD). Contrasting these conditions at the behavioral and electrophysiological level allowed assessing our three hypotheses (Table 2):

Ha) to isolate the effects of caffeine: GD/TD vs. GC/TD.

Hb) to isolate the effects of expectations: GD/TD vs. GD/TC.

Hc) to determine whether caffeine effects were actually stronger than expectations effects, we compared the following cells: GD/TC vs. GC/TD.

2. Methods

2.1. Participants and screening

2.1.1. Sample size

The sample size was determined for each dependent variable (DV) by Monte Carlo power analyses (Muthén & Muthén, 2009; Paxton, Curran, Bollen, Kirby, & Chen, 2009) conducted using custom R 3.5.2 scripts. For that purpose, we proceeded as follows:

1. First, we estimated for each contrast of interest the smallest absolute effect size of interest for caffeine effects (SESOI CAF) based on principle ground. We did not rely on previous literature to estimate relative effect sizes of interest since they are dependent on each study's parameters (e.g. within- and between-subject variance, number of trials, etc.; Fern & Monroe, 1996; Baker et al., 2019), and may be over-inflated due to publication biases (*see* Button et al., 2013; Nuijten, Van Assen, Veldkamp, & Wicherts, 2015).
2. For each investigated dependent variable (DV), we estimated the between- and within-subject variance based on datasets from our previous studies with the same tasks.
3. For each DV separately, we generated 10′000 simulated datasets per conditions for sample sizes ranging from 16 to 50 participants by steps of 2. For each simulation, we randomly drew data from normal distributions generated using the SESOI and the within- and between-subject variance parameters identified in 1) and 2).
4. We then computed the power of each sample size to detect our effect of interest by extracting the percentage of *p*-values for each of the three contrasts separately (Ha, Hb, Hc) that fell below our target alpha threshold of .02.
5. Finally, we identified the minimal sample required to detect our smallest SESOI with a .9 power and an alpha of .02.

Step 1). Absolute SESOI for the expectations and caffeine effects

The 240 mg (and additional 120 mg 45min later) dosage of caffeine we administered is considered a moderate dose and corresponds to the dosage chosen to induce minimally relevant phenomenological and cognitive improvements (*see* McLellan, Caldwell, & Lieberman, 2016).

On this basis, the associated SESOI of each contrast were determined on principled grounds. We still compared our decisions with previous literature on the psychopharmacological effects of caffeine and related substances because it helped establish links between the caffeine dose, its perceived enhancing effects in daily living and the related changes in performance/brain activity in laboratory tasks (notably Martin and Garfield (2006) and Haskell, Kennedy, Milne, Wesnes, and Scholey (2008) for the behavioral and electrophysiological measures of the RVIP task; Barry et al. (2014) and Bailey et al. (2016) for the behavioral and electrophysiological measures of the Go/NoGo task).

Since expectations' effects sizes are generally estimated to be ca. 1/3 of those of the actual substance (*see* Schedlowski et al., 2015), the expectation contrast (Hb, GD/TD < GD/TC) required the highest power; our power calculation were thus based on this contrast.

Step 2). Task-specific within- and between subject variance

For the RVIP task, we measured the task within-subject variance to be 30 ms and the between-subject variance to be 50 ms (Ribordy Lambert, Wicht, Mouthon, & Spierer, 2020).

For the Go/NoGo, we identified the task within-subject variance to be 33 ms (De Pretto, Hartmann, Najberg, Mouthon, & Spierer, *in preparation*) and the between-subject variance to be 60 ms (De Pretto, Rochat, & Spierer, 2017).

For the ERP P3 peak amplitude, we estimated for both RVIP and Go/NoGo tasks the within-subject variances to be 1.2 μV (Martin & Garfield, 2006) and the between-subject variances to be 2 μV (Kompatsiari, Candrian, & Mueller, 2016). We differentiated between sustained attention and inhibitory control P3 components amplitude although they did not differ in terms of variance/amplitude (see Martin & Garfield, 2006; Barry et al., 2007, 2014). Regarding the P3 latency, we estimated the within-subject variance only for the RVIP task to be 50 ms (Ouyang, Hildebrandt, Sommer, & Zhou, 2017) and the between-subject variance to be 90 ms (Diukova et al., 2012). We conservatively focused on the P3 component because late latency ERP components are more heterogeneous (Ouyang et al., 2017) and display higher variability (i.e. resulting in less power) than early latency components (e.g. N2; *see* Luck, Steven, 2015; Ouyang, Sommer, & Zhou, 2016).

Step 3). Contrast-specific simulations

The results of each simulation accompanied with Step-by-step explanations of the procedure can be found on the Open Science Framework page (https://osf.io/hcy69/) as well as the R scripts (https://osf.io/sfwqy/).

Based on 1) and 2), the contrast with the smallest SESOI was the RVIP RT. We thus identified the minimal sample size based on this DV and we reported the power for the other DV based on this sample size (Table 3).

Hence, our final sample corresponded to the most conservative sample size (i.e. $N = 38$ participants per condition to detect a small effect, Hedge's g_{av}=˙3 with a power of .9 and an alpha threshold of .02). Drop-outs and other excluded participants were replaced to maintain this sample size in the final analyses.

2.1.2. Recruitment and screening

Participants were recruited with public advertisement at the University of Fribourg, Switzerland.

Inclusion criteria included: Moderate daily caffeine drinkers (from 1 to 4 cups of coffee or 4 energy drinks or 8 cups of tea or 8 cans of soda/day), non-smokers, right-handed, between 18 and 30 years old, French speakers, no history of substance-related addictive or misuse disorders (alcohol or other drugs), no personal history of diagnosed neurological or psychiatric disorders and of heart and circulation disease, and regular consumption of less than or equal to 21 units of alcohol/week.

Exclusion criteria included: Pregnancy as assessed by a pregnancy test; cardiovascular readings at baseline outside the acceptable range for caffeine studies (i.e. Systolic Blood

Table 2 – Operational behavioral and electrophysiological predictions. The contrasts of interest were: for Ha (GD/TD Vs. GC/TD), Hb (GD/TD Vs. GD/TC) and Hc contrasts (GD/TC Vs. GC/TD). Our hypotheses predicted the same directions for the effects in the three hypotheses.

Tasks	Expected effects	
	Behavioral	Electrophysiology
Rapid Visual Information processing (RVIP)	↑ Hits ↓ RT	**Attention-P3** ~400 ms post stimulus onset at central electrodes and localized in the TPJ, STG and the Precuneus: ↑ Voltage amplitude, peak latency ↑ GFP ↑ CSD
Go/NoGo	↓ False Alarms (FA) to NoGo stimuli ↓ RT to Go stimuli	**NoGo-N2**~300 ms after CR at NoGo stimuli at fronto-central electrodes and localized in the MFG, Cingulate Cortex, Precentral Gyrus: ↑ Voltage amplitude ↑ GFP ↑ CSD **NoGo-P3** ~400 ms after CR at NoGo stimuli at fronto-central electrodes and localized in the MFG, ACC: ↑ Voltage amplitude ↑ GFP ↑ CSD

Note: ACC = Anterior Cingulate Cortex; FA=False Alarms; CR=Correct Rejection; CSD = Current Source Density; GC = Give-CAF; GD = Give-DECA; GFP = Global Field Power; MFG = Middle Frontal Gyrus; STG=Superior Temporal Gyrus; TC = Told-CAF; TD = Told-DECA; TPJ = Temporo-Parietal Junction.

Pressure (SBP) < 140 mmHg; Diastolic Blood Pressure (DBP) < 90 mmHg; Heart Rate (HR) < 100 beats per minutes; *see* Flaten & Blumenthal, 1999); consumption of caffeine in the last 12h and/or alcohol, chewing-gum in the last 24h before testing; performing sporting activity in the last 24h; tooth brushing, major meal and/or high sugar foods in the last 60min.

All eligible participants provided informed consent before beginning the experiment. Participants were allowed to withdraw their participation anytime without needing to provide explanations. We compensated participants for their participation (20 CHF/hour; including transportation costs) even in case of withdrawal.

2.1.3. *Experimental design*

We used a three cells within-subjects design:

- Give-Decaffeinated/Told-Caffeine (GD/TC)
- Give-Decaffeinated/Told-Decaffeinated (GD/TD)
- Give-Caffeine/Told-Decaffeinated (GC/TD)

With these conditions, we addressed our three effects of interest:

- Caffeine effects were captured by the contrast: GD/TD < GC/TD (**Ha**), in which the effects of caffeine are not contaminated by the presence of expectations.
- Placebo effects were captured by the contrast: GD/TD < GD/TC (**Hb**), in which the effects of expectations are not contaminated by the actual presence of caffeine.
- Caffeine Vs Placebo effects were captured by the contrast: GD/TC < GC/TD (**Hc**), allowing to directly assess our hypothesis on the differences between the effects of caffeine vs expectations.

2.2. *Procedure*

The three experimental sessions took place from 9 a.m. to 12 p.m. and at least 1 week apart (*for comparable procedure see* Campbell, Chambers, Allen, Hedge, & Sumner, 2017) at the Neurology Unit of the University of Fribourg, Switzerland. Each experimental session lasted around 2.5 h. The procedure of the sessions is summarized in Table 4 and the timing of events was matched to simulated caffeine pharmacokinetics in Fig. 3.

The procedure of the sessions consisted of the following steps:

2.2.1. *Session 1 only*

- Participants gave their written consent for the study prior to entering any procedure or collection of data related to the study. In the informed consent document, participants' beliefs in the cognitive enhancing effects of caffeine had been reinforced with the following paragraph:

"Scientific studies agree that caffeine enhances cognitive performance and more specifically executive functions (attention, motor control). Moreover, many articles published by different types of media (e.g. newspapers, internet) appropriately highlight the health benefits of a moderate coffee consumption (between 1 and 4 cups/day)". (*Informed consent original text in French:* https://osf.io/wnc5q/).

2.2.2. *Sessions 1,2 and 3*

- Participants were screened regarding the inclusion and exclusion criteria and required to stay quietly seated so that the cardiovascular readings could be taken (*see details in* section 2.7.2).

Table 3 – Power estimation for all DV in the Hb contrast.

Task	Dependent Variables (DV)	Absolute SESOI Caffeine	Absolute SESOI Placebo	SD Within	SD Between	Power	Sample size
Go/NoGo	RT (Hit stimuli) [ms]	60	20	33	60	.95	38
	Accuracy (NoGo FA) [%]	5.5	1.8	3	7	.93	38
	P3 peak amplitude [μV]	2.2	0.7	1.2	2.2	.92	38
RVIP	**RT (Target stimuli) [ms]**	**50**	**16.7**	**30**	**50**	**.90**	**38**
	Accuracy (Target Hit) [%]	20	6.7	10	40	.98	38
	P3 peak amplitude [μV]	2.2	0.7	1.2	2.2	.93	38
	P3 latency [ms]	90	30	50	90	.93	38

Note: the sample size of 38 participants was identified as the minimal sample size require to reach a .9 power in the condition requiring the more power (i.e. RVIP RT Hit). The power for the other condition was then estimated with this sample size.

Table 4 – Procedure of each session[3]

	SESSIONS 1, 2, 3		
	Screening	Experimentation	
Time (HH:MM)	0:00 0:20 0:40	1:00 1:20 1:40 2:00 2:20 2:40 3:00	
Steps	1 2 3	4,5 6,7 9 8 10	
	1 **Ethics** : Informed consent **Incl/excl criteria, medical history**: GHQ *Pregnancy test*	**4** **Questionnaires** : B-CaffEQ	**Cognitive (behaviour + ERP)**: **7** Sustained attention (RVIP) **8** Inhibitory control (Go/NoGo)
	2 Cardiovascular readings	**5** Intervention (CAF/DECA)	**9** Intervention (CAF/DECA)
	3 EEG cap positioning	**6** Salivary sampling	**10** **Debriefing**: Next session reminder (session 1) DPEQ (session 3) Debriefing & 2nd informed consent (session 3)

Note: In session 1, regarding steps 1 & 4, respectively, all incl/excl criteria, medical history and the B-CaffEQ questionnaire were administered. For sessions 2 and 3, only the Pregnancy test (in *italic*) were administered. Thus, the 2nd and 3rd sessions should last around 30min less than the 1st session. Since the order of cognitive tasks were randomized, the example above only covers one of the scenarios where the RVIP would start before the Go/NoGo task.

- The electrodes for the EEG recording system were positioned on participants' head (duration ~15 min).
- Participants were given either the CAF or DECA beverages (i.e. first two large coffee cups), depending on condition assignment (*see* section 2.5.2), and be required to drink it in less than 5min.
- Participants were instructed to complete two computerized cognitive tasks. Twenty minutes after the first coffee administration, before beginning the first cognitive task, a salivary sample was collected which was used for the cover procedure (*see* section 2.5.4). Then, participants were given a third large coffee cup (i.e. half the caffeine content) exactly 45min[1] after the first one, while again be required to drink it in less than 5min.
- Once the cognitive tasks were completed, Participants were reminded about the following session (session 1 and 2) or filled in the debriefing questionnaire (DPEQ; session 3).
- Finally, at the end of session 3, participants received a debriefing form disclosing the deception involved in the study and enabled them to react to it. This disclosure was recommended to comply with ethics requirements regarding placebo studies (*see recommendations from* George, Gilmore, & Stappenbeck, 2012; Rohsenow & Marlatt, 1981). Participants further provided a second informed consent, necessary to ensure that they maintained their consent after having received all information on the study.[2]

[1] We corrected a typo regarding delay between coffees from 60 min to 45 min (i.e. emails exchange on the 17.02.2020).

[2] We removed the follow-up session (i.e. End of the study subsection) and disclosed all study information at the end of session 3 to avoid additional dropouts (i.e. emails exchange on the 17.02.2020).

[3] Table 4 header was missing.

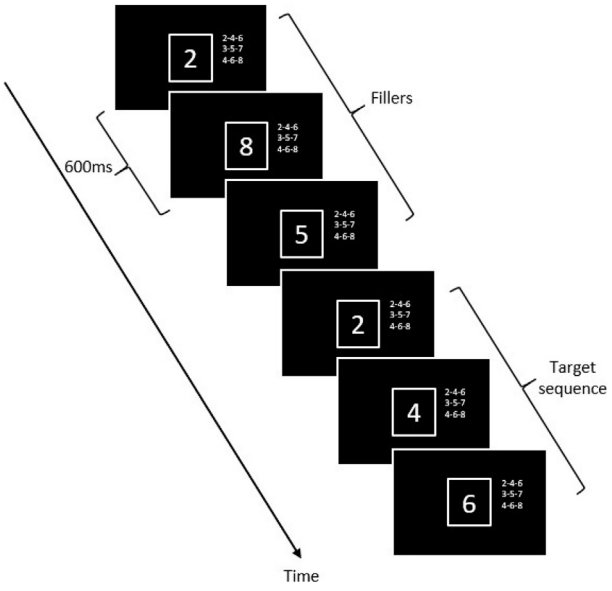


Fig. 1 – Schematic representation of the RVIP task.

2.3. *Tasks*

The following cognitive tasks (i.e. RVIP and Go/NoGo) were developed using E-Prime 3.0 software (Psychology Software Tools, Inc., Sharpsburg, PA). The scripts are freely available on Open Science Framework (https://osf.io/zv67j/).

Participants responded with their right-hand index finger on the Chronos response box (Psychology Software Tools, Inc., Sharpsburg, PA).

2.3.1. *Rapid Visual Information Processing (RVIP)*

The task was adapted from the RVIP task in the Cambridge Neuropsychological Test Automated Battery (CANTAB; Sahakian & Owen, 1992). Participants underwent, first, a training session before starting the main testing session. The only difference between both sessions is that the training session was shorter (i.e. two blocks of 38 digits each) and we did not record resulting behavioral data. The testing session included sixteen blocks each lasting 90 s. The amount and position of stimuli within each block were counterbalanced.

Before the first block, participants were presented with written instructions and received an additional oral instruction. They were instructed to respond as fast as possible to target sequences while withholding their responses to fillers stimuli. One-minute breaks were proposed between each two-blocks. Hence, they had to detect three target sequences (i.e. "2–4–6", "3-5-7" or "4-6-8") and press a button on the response box when the last number of a target sequence appeared. In each block, 12 target sequences (i.e. 4 of each 3-digits sequence) and 114 fillers (i.e. random white numbers from 0 to 9, except 1) appeared on screen, for a total of 150 digits/blocks (*for similar parameters see* Hilti et al., 2010). The target sequences in both blocks were written on the top-right corner of the screen during the whole session to reduce participants' memory load. In each trial, numbers appeared in pseudo-random order for 600 ms at the center of the screen and at a rate of 100 digits per minutes, with a response window of maximum 1800 ms after the last digit of a target sequence and ending at participant's response (Fig. 1).

We recorded RT for correctly detected sequences and the number of correct sequences detection (Hits).

2.3.2. *Go/NoGo*

The Go/NoGo version was adapted from Hartmann and al. (2016). Participants underwent first a training session before starting the main testing session. The only difference between both sessions is that the training session was shorter (i.e. one block of 16 trials) and we did not record resulting behavioral data. The testing session included four blocks of ca. 5 min each and consisted of 70 trials: 50 Go and 20 NoGo trials presented randomly. Contrary to previous findings that relied on an equiprobable Go/NoGo task (Barry et al., 2007, 2014), our version involving a predominance of go trials has been shown to induce stronger inhibitory control demands (e.g. higher FA rate; Young, Sutherland, & McCoy, 2018).

Before the first block, participants were presented with written instructions and received an additional oral instruction. They were instructed to respond as fast as possible to Go stimuli while withholding their responses to NoGo stimuli. One-minute breaks were proposed between each block. The stimuli consisted of white letters (i.e. A, E, O, M, S or T) presented in the center of a screen. For each block of trials, one letter was randomly picked to be used as the NoGo stimulus, to avoid repetition. Go stimuli were all the remaining letters. Thus, for example, in the first block, the letter "E" would be the NoGo stimulus, presented 20 times and each of the remaining letters (i.e. A, O, M, S and T) would represent the Go stimuli each presented 10 times.

Participants were presented with, first, a grey fixation cross centered on the screen for 1500–2200 ms, followed by the stimulus (either Go or NoGo) for 500 ms and a response window ending at participant's response (1500 ms), with a minimal duration of 250 ms. Finally, a performance feedback was provided for 500 ms: a "✓" symbol for Hits with RT < RTt and a "Tard!" feedback (i.e. late) for Hits with RT > RTt; and a "✗" symbol for misses or for FA (Fig. 2).

A reaction time threshold (RTt) was computed to increase time pressure and in turn, response prepotency and inhibition during NoGo trials: The RTt was calculated as the median of the RT to the last five Go trials and was multiplied by 110%, with an initial RTt of 800 ms. The RTt was dynamically adjusted throughout the experiment and individually for each participant, which helped maintaining the same level of difficulty across conditions and individuals.

We recorded RT for Go trials and accurate (i.e. CR) and failed rejections (i.e. False Alarms rate, FA) for NoGo trials.

2.3.3. *Outcome neutral controls*

The estimations in Table 5 were used as controls to ensure the reliability of the data collected (e.g. no floor or ceiling effects, etc.). They were based on previous evidence from our laboratory and from others using comparable tasks (*RVIP*: Dodd et al., 2015; Wilhelmus et al., 2017; *Go/NoGo*: De Pretto, Sallard, & Spierer, 2016; Hartmann, Sallard, & Spierer, 2016). These estimations were checked for the Give-DECA/Told-DECA experimental condition, where the smallest effect of

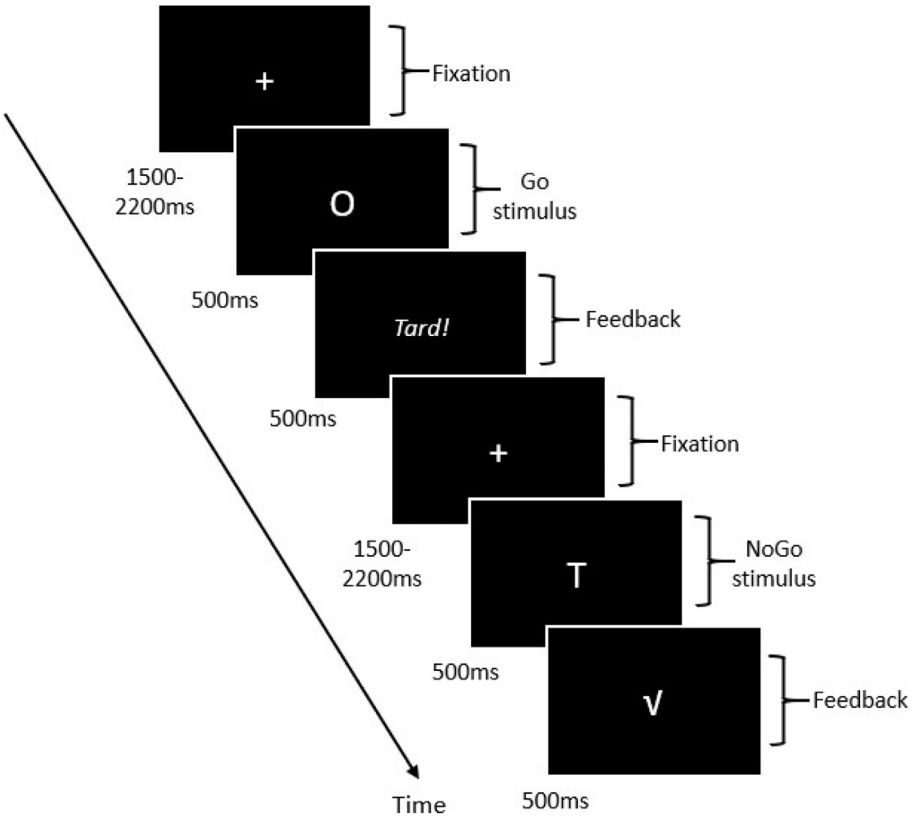


Fig. 2 – Schematic representation of the Go/NoGo task.

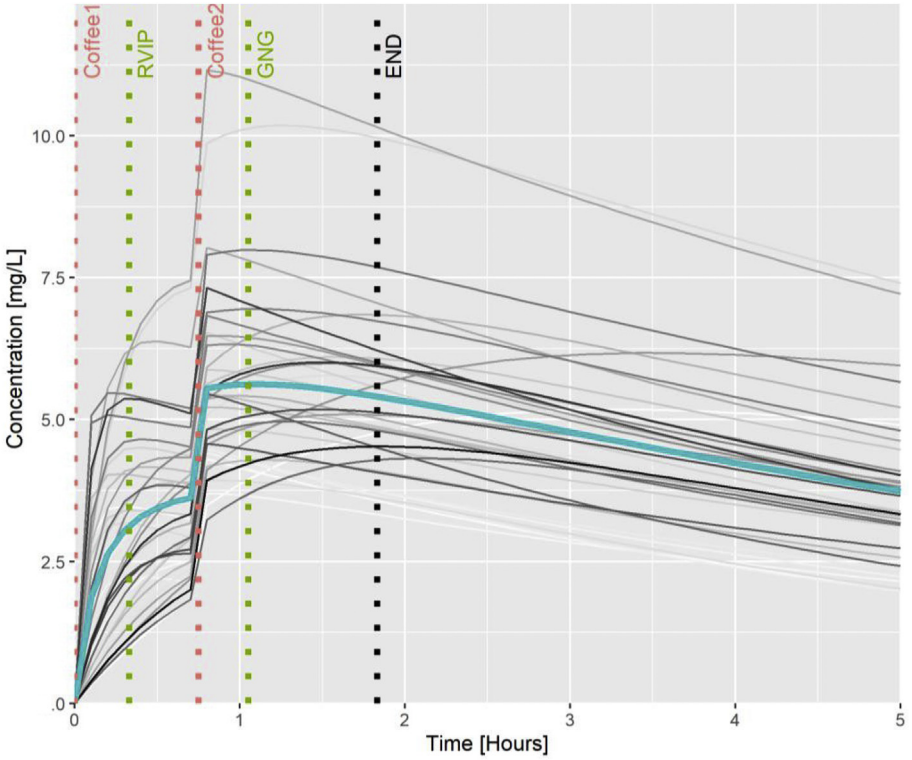


Fig. 3 – Caffeine pharmacokinetics simulations. Note: We used the following parameters: Population Mean Weight ±SD = 73,6 ± 15 kg, Dose = 240 mg + 120 mg, simulated subjects N = 38, interval of dosing Tau = 1 (hour), number of dosing Repeat = 2.

Table 5 – Summary of the outcome neutral criteria separated by tasks.

Tasks	Behavioral	Electrophysiology
RVIP	Accuracy >30% 350 ms < RT < 750 ms	Presence of central positivity at 400 ms (Attention-P3 component) after onset of the first digit of target sequences (Hits condition).
Go/NoGo	NoGo FA > 10% 170 ms < RT < 570 ms	Presence of fronto-central negativity at 300 ms and fronto-central positivity at 400 ms (resp. NoGo-N2 and -P3) after NoGo (CR condition)
B-Caff Questionnaire	Mean score >3 on subscales: i) Withdrawal/Dependence, ii) Energy/Work Enhancement iii) Physical Performance Enhancement	

caffeine or caffeine-related expectations on performance was expected (*see power analyses in* section 2.1.1).

2.4. *Questionnaires*

Demographics, questions related to the efficacy of our deceptive procedure and measures of caffeine expectations were assessed with:

- A custom-made General Health Questionnaire (GHQ): 40 items, self-assessment of overall health, sport activities and drug consumption habits, substance use, abuse (e.g. cigarettes, alcohol, etc.).
- A custom-made Debriefing Post-Experimental Questionnaire (DPEQ), only given at the end of session 3: 5 items, self-assessment of beliefs regarding the experimental protocol. This questionnaire enabled us to assess the efficacy of our deceptive procedure, ensuring that our participants were adequately tricked into believing they were administered different types of coffee in each session.
- The Brief-Caffeine Expectancy Questionnaire (B-CaffEQ): 20-items, self-assessment of expectations regarding the effects of caffeine (Kearns et al., 2018).

2.5. *Blinding procedures and cover story*

2.5.1. *Randomization*

The order of the three session and the order of cognitive tasks administration and of blocks within the cognitive tasks were randomized for each participant, based on pseudorandom lists of numbers.

2.5.2. *Coffee preparations*

Participants reached the caffeine peak concentration after 40–50min (Teekachunhatean, Tosri, Rojanasthien, Srichairatanakool, & Sangdee, 2013; White et al., 2016). Based on simulations run with the Caffsim R package (Fig. 3; Han, Cho, Yoon, Kim, & Bae, 2017) and Swiss population statistics (Marques-Vidal et al., 2008), to reach a meaningful long-lasting caffeine blood concentration (*see* Bailey et al., 2016) and elicit the expected ergogenic effects (McLellan et al., 2016), we administered participants with two cups of coffee (R script available here: https://osf.io/f7zwa/).[4] The first contained two pods and the second one pod of either caffeinated coffee, Nespresso Kazaar© (i.e. each pod containing ~120 mg of caffeine; Desbrow, Hall, & Irwin, 2018) or of decaffeinated coffee, in one session Nespresso Ristretto Decaffeinato© and in the other Arpeggio Decaffeinato© (i.e. each pod containing 2–3 mg of caffeine; Desbrow et al., 2018). Hence, the first coffee contained either 240 mg (Give-CAF) or ~6 mg (Give-DECA) of caffeine and the second one 120 mg (Give-CAF) or ~3 mg (Give-DECA). The second coffee was given to compensate for the decline in caffeine concentration that can be observed after ~1.5h (White et al., 2016), while the overall dosage (i.e. 240 + 120 mg 45min later) doesn't elicit noticeable side effects (Howell, Coffin, & Spealman, 1997; Mora-Rodriguez & Pallarés, 2014). As can be seen in Fig. 3, participants' caffeine concentration was expected to remain high enough throughout the experiment and especially during the two cognitive tasks (RVIP and GNG), while also staying well below the 15–25 mg/L blood concentration threshold which is considered safe (Banerjee, Ali, Levine, & Fowler, 2014; Cannon, Cooke, & McCarthy, 2001).

Coffee was always poured in the same large, opaque, coffee cup (*see* Desbrow et al., 2018). Moreover, to control for variations in temperature and liquid ingestion due to varying rates of consumption, we asked our participants to drink their coffee within maximum 5min, even if previous evidence did not indicate that it would significantly influence caffeine pharmacokinetics (White et al., 2016).

Regarding the type of the coffee proposed to participants, we exclusively administered "black coffee" for two reasons:

- To avoid putative interaction with another substance (e.g. sugar) that we wouldn't have been able to control in our experiment.
- To ensure that all our participants were comparable in terms of the substance that was administered.

There might have been between-subject variations in the coffee preference but such effects should not have confounded our results since we used a fully within-subject design and thus our three experimental conditions were similarly affected by participants preferences.

2.5.3. *Control for blinding*

To preclude participants' attempt to guess which condition they were currently assigned to and to ensure that they believed they have received in one session the CAF and in the two others the DECA, a second experimenter prepared the beverages in front of the participants. Hence, the first

[4] The caffeine concentration simulation script was updated to match the typo correction regarding delay between coffees from 60min to 45min (i.e. emails exchange on the 17.02.2020).

experimenter remained blind to condition assignment. To ensure that participants remained naive to the manipulation, the experimenter drew each coffee pod from their respective box in front of the participant and prepared the beverage in his office, with open doors so as to hear the sound of the machine. Importantly, the second experimenter swapped coffee cups in his office when necessary (depending on condition assignment). For e.g., in the GC/TD condition, the second experimenter drew a decaffeinated coffee pod from its box in front of the participant and swapped it for a caffeinated coffee pod when preparing the beverage in his office. We further asked participants to wash their mouth with water before drinking the beverage to reduce taste acuity (George et al., 2012; Rohsenow & Marlatt, 1981).

2.5.4. *Cover story*

We also implemented a deceptive protocol (i.e. cover story) to enhance the credibility of our procedure as well as participants' expectations regarding the intervention. The method was the same as in Elkins-Brown et al., 2018 for which a complete description is available at the following address: https://osf.io/mg5dc/. The procedure was adapted to our paradigm as follows: participants provided saliva samples on a cotton-tipped applicator which was mixed with a small test tube of water and 3–4 drops of iodine (i.e. yellow solution). If the participant was in the Told-CAF condition, the saliva-containing Q-tip was exchanged out of the view of the participant for a Q-tip that was placed in a test tube of water and potato starch. Then, the experimenter came back to the participant while mixing the potato starch Q-tip inside the test tube of water and iodine which changed the solution's color to dark-blue. If the participant was in the Told-DECA condition, the procedure was identical except that a clean Q-tip was used instead of the potato starch Q-tip and the solution remained yellow. Beforehand, participants were informed that if the solution turned dark-blue it would mean that caffeine concentration was high (i.e. Told-CAF condition) and if it stayed yellow that caffeine concentration was so low that it could not be detected (i.e. Told-DECA condition).[5]

2.6. *Timeline*

Estimation of the timeline for the completion of the study starting from the Stage 1 in-principle- acceptance (IPA) date can be found in Table 6. Stage 2 submission was estimated to occur at the end of January 2021.

2.7. *(Neuro-) physiological recordings and preprocessing*

2.7.1. *Electroencephalography (EEG)*

The EEG data was recorded at 1024Hz using a 64 electrodes EEG Biosemi ActiveTwo® system referenced to the common mode sense-driven right leg (CMS-DRL) ground (Biosemi, Amsterdam, Netherlands), during the RVIP and Go/NoGo tasks. Offline preprocessing and further statistical analyses were performed using custom MATLAB R2018b (MathWorks, Natick, Mass) scripts based on the EEGLab 14.1.2b Toolbox (Delorme & Makeig, 2004) coupled with Cartool 3.70 (Brunet, Murray, & Michel, 2011), Ragu (Koenig, Kottlow, Stein, & Melie-García, 2011a) and STEN 2.0 (developed by Jean-François Knebel and Michael Notter: http://doi.org/10.5281/zenodo.1164038).

2.7.2. *ERP preprocessing*

Regarding tasks-dependent EEG recordings, we used first, a semi-automated, custom MATLAB script relying on EEGLab. The pre-processing of the raw data was done accordingly:

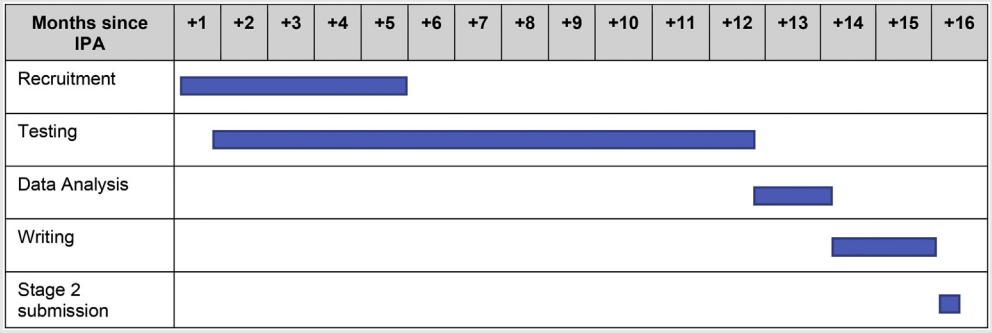
- Re-referencing to Cz electrode and band-pass filtering (.5–40Hz).
- Artifacts removal on continuous data with the EEGLab plugins, i) CleanLine (sinusoidal, line noise frequencies removed: 50/100 Hz (*see* Mullen, 2012); ii) Artifact Subspace Reconstruction (ASR: non-stationary signals >10SD from mixing matrix calculated on a clean "reference" section of the recording; *see* Mullen et al., 2015; Chang et al., 2018) and iii) BLINKER with default settings (detection of eye blinks; *see* Kleifges, Bigdely-Shamlo, Kerick, & Robbins, 2017).
- Epochs' segmentation time-locked to stimulus onset (100 ms pre-to 700 ms post-stimulus onset).
- Baseline correction on the whole epoch window.
- Interpolation of bad channel(s) using multiquadric interpolation relying on radial basis functions (*see* Jäger, Klein, Buhmann, & Skrandies, 2016; Janin, 2018; Buhmann & Jäger, 2019). Electrodes were selected based on identification from the averaged ERPs.
- Epochs averaging for each participant across the following conditions: for RVIP: detected sequences (Hits) and for the Go/NoGo task: successfully not-responded NoGo trials (correct rejection (CR; *see statistics in* section 2.10).
- Re-referencing to common average reference.

2.7.3. *ERP analyses*

After the ERP pre-processing, we determined the period of interest (POI) for the condition-level analyses. The POI was defined based on the N2 and P3 ERP components on the condition-averaged Global Field Power (GFP) waveform. GFP is a measure of the strength of electrical field potentials computed as the standard deviation of the mean voltage amplitude over all electrodes at a given time point (Michel & Murray, 2012). The GFP peak during the component-specific POI corresponds to the time point during which each component displays maximal neuronal synchronization, and thus the highest signal-to-noise ratio (Michel & Murray, 2012). Each component was identified at the individual recording level based on the latency and topography of each GFP peak (i.e. GFP peak around 300 ms with fronto-central negativity for the Nogo-N2 and around, respectively 400 ms with fronto-central and with central positivity for the Nogo-P3 and Attention-P3 components). Once each component had been identified, the POI was determined as the component peak latency of the mean GFP + - 1SD of the individual GFP peaks. Individual subjects' component amplitude was then calculated as the average voltage over the POI for each component's specific cluster of electrodes of interest (i.e. FCz, Cz, FC1, C1, FC2, C2 electrodes for the NoGo-N2 and NoGo-P3; Wessel &

[5] The Cover Story has been updated to the latest version of the procedure (PMID: 30316113) and the description was enhanced (i.e. emails exchange on the 17.02.2020).

Table 6 – Estimated timeline for the completion of the study since Stage 1 IPA



Aron, 2015; Cz and Pz electrodes for the Attention- P3 component; Segalowitz, Bernstein, & Lawson, 2001). In addition, the GFP amplitude were averaged for each participant separately over the POI for each component to compute analyses of the variation in GFP across experimental conditions. The scripts used to determine the POI are freely available following this address: https://github.com/CorentinWicht/GFPPeaks(Wicht, 2020). The analysis of the GFP provides interpretative advantage over the analyses of local ERP waveforms: GFP takes into account the whole electrode montage, is reference-independent and is insensitive to spatial (i.e. topographic) changes in the ERP. GFP was analyzed with robust randomization statistics (see Habermann, Weusmann, Stein, & Koenig, 2018; Koenig, Kottlow, Stein, & Melie-García, 2011b) using 5000 permutations per data point with an alpha threshold of $P < .02$[6] to estimate the significance of GFP differences. For each POI showing either a local ERP and/or GFP effect, distributed electrical source estimation was then computed on the whole brain with Cartool using a local autoregressive average (LAURA) distributed linear inverse solution (Grave De Peralta Menendez, Murray, Michel, Martuzzi, & Gonzalez Andino, 2004). The solution space (i.e. the lead field matrix) was computed on a realistic head model comprising nodes uniformly distributed in the grey matter of the Montreal Neurological Institute (MNI) average brain. The current source density (CSD) at each node was averaged within each predefined ROI of the AAL Atlas (*see* Table 2; Tzourio-Mazoyer et al., 2002). The single ROI CSD values was then compared between conditions using planned test statistics (*see* section 2.10).[7]

2.7.4. *Cardiovascular readings*

Cardiovascular readings (i.e. Systolic (SBP) and Diastolic Blood Pressure (DBP), Heart Rate (HR)) were measured once at the beginning of each session (*see* Table 4) to assess exclusion criteria, using an Omron M7 Intelli IT device (Omron Healthcare, Inc., Lake Forest, IL, US). Data was collected according to Flaten and Blumenthal (1999), namely three assessments were performed in a row, each separated by 2-min rest. Then only the last two assessments were averaged to compute a mean score.

2.7.5. *Saliva biomarkers*

Saliva collection for the cover story (see section 2.5.4) was performed throughout the experiment using the SalivaBio Oral Swab (Salimetrics, CA, USA). Ten minutes prior to saliva collection, participants were asked to rinse their mouth thoroughly with water to prepare for saliva sampling (*see recommandations from* Salimetrics, 2016).

2.8. *Data removal summary*

We rejected trials if they met the following criteria:

- Intra-subject level behavior:
  - RT $\leq$ 100 ms (Gabay & Behrmann, 2014).
  - Trial associated with task disengagement, as defined by False Alarms (FA) and MISS rates within and between task blocks (*see* section 2.3 *for block length*), separately for each participant and each task:
    - Intra-block task disengagement was defined as any block of trials with more than 70% FA and/or 20% MISS.
    - Between-blocks task disengagement was defined as any block with FA rate 20% and/or with MISS rate 10% above the between-blocks median. Blocks exceeding these thresholds were excluded from the analyses.
- Inter-subject level behavior:
  - We used the median absolute deviation (MAD) to detect univariate outliers with default parameters (i.e. MAD range around the median of 1.4826).[8]

[6] Since the power calculations were based on an alpha threshold set at 2%, all our statistical tests should have de facto the same probability value.

[7] We had to change the method we implemented (i.e. using resting-state EEG as the clean data reference provided to the ASR algorithm for ERP preprocessing) since this method was found to be flawed, see https://github.com/sccn/clean_rawdata/issues/22. Instead, we used ASR algorithm defaults, namely leaving the algorithm detect clean reference sections from the ERP files directly. Thus, any mention of resting-state data has been removed since they were only used for the ASR algorithm initially.

[8] We have removed the Mahalanobis-MCD method for multivariate outliers detection since we didn't run any multivariate statistical model (i.e. only dependent samples t-test were preregistered).

- After detecting outliers, if they were considered random (i.e. belonging to the distribution of interest) we left them in the dataset. If they were considered interesting outliers (i.e. influenced by an unknown moderator), we applied the Winsorization approach (Tukey & Mclaughlin, 1963; percentile observation $k = 5$) to avoid as much as possible rejecting data points that would have resulted in loss of power.

- EEG:
  - For ERPs, trials with i) at least one time frame (TF) at one electrode with voltage ±80 μV (*see* Hartmann et al., 2016) or ii) jump of more than 30 μV at one electrode from one TF to the next.

We took the decision of removing the entire data of one participant if it met the following criteria:

- Behavior
  - 80% of the behavioral data contained RT < 100 ms.
  - Evidence of computer errors.
  - More than 60% of the total amount of blocks within a task, for each participant, was above the thresholds defined above.
  - Evidence of task instructions misunderstanding evaluated in an open question following each cognitive task. Participants were prompted to write down the task instructions within maximum 2 min and we were looking for presence of key instructions in their response (e.g. which keyboard button for response, which stimuli needed to be inhibited in the GNG task, etc.).
  - Evidence of unblinding based on sum of scores >18 at the DPEQ questionnaire for items 1 (*"Do you think to have guessed the goal of the study?"*) + 2 (*"Did you have any doubts regarding* the *instructions provided by the experimenters* (e.g. *type of coffee, the saliva collection for caffeine concentration, etc.)"*) + 6 (*"Have you already heard of the placebo effect?"*).
- EEG:
  - The minimum number of EEG trials for each task was lower than 40[9] trials for each to-be-averaged ERPs (*see* Boudewyn, Luck, Farrens, & Kappenman, 2018). The limit of 40 was based on percentage of missed trials (i.e. ~30% in RVIP, ~10% in Go/NoGo, *see* Section 2.3.3), rejection of trials due to the presence of artifacts (~20% of trials) and an additional security margin (~10%).

2.9. Analysis procedures

For all analyses, normality was assessed with Shapiro–Wilks tests[10] together with the criteria of skewness and kurtosis within a ±2 range for the parametric analyses (Gravetter & Wallnau, 2013). In case of non-normality, we used equivalent non-parametric tests.

For all statistical tests, effect sizes were reported using Hedges' g_{av} (for correlated groups, *see* Lakens, 2013).

2.10. Summary of statistical tests

To control for the effectiveness of our experimental procedure, we performed statistical tests on our cognitive tasks. Since the Ha contrast aimed at confirming previously identified cognitive enhancing effects of caffeine, all the DV listed in Table 7 were tested. Nevertheless, DV for Hb and Hc contrasts depended on Ha results, namely only the caffeine effects that we were able to replicate in Ha were investigated in Hb and Hc. This limited the number of tests and remained in accordance with our hypothesis that expectations rely on the mechanisms underlying caffeine effects.

Correction for multiple comparison were addressed by means of the False Discovery Rate correction (FDR; Benjamini & Hochberg, 1995). Accordingly, FDR correction was applied a posteriori on ordered *P*-values across the three contrasts, for each DV separately. FDR was favored over Bonferroni corrections to minimize inflation of Type-II errors (i.e. false negatives due to overpowered comparisons) while efficiently controlling for Type-I errors (Fiedler, Kutzner, & Krueger, 2012).

2.11. Data availability

Coded study data, digital materials and analysis codes were uploaded to a public archive and can be downloaded at the following address: http://doi.org/10.5281/zenodo.4500849.

Additionally, the approved and published Stage 1 protocol can be downloaded at the following address: https://osf.io/2vabk.

3. Results

Regarding the behavioral measures, data were analyzed with Paired-samples *t*-tests or Wilcoxon Signed-rank tests and we report for each measures the test statistic, degree of freedom, *p*-value and effect size. Concerning the ERP, voltage amplitudes are analyzed with the same univariate tests as for the behavioral measures while the GFP measures are analyzed with robust randomization statistics for which only the *p*-value should be reported (see Janssen, 1997; R-Package "MKinfer: Inferential Statistics"). Thus, data averages in the results section were formatted as mean ± SD (i.e. Paired-samples *t*-tests) or median/IQR (i.e. Wilcoxon Signed-rank tests). We additionally computed Bayes factors (BF) for each effect not reaching significance ($P < .02$) since frequentist analyses do not provide information on the likelihood of the null hypotheses. More specifically, the BF_{01} represents the likelihood of the data given H0 relative to H1 (Jarosz & Wiley, 2014). We considered a $BF_{01} > 6$ to provide substantial evidence for H0.

3.1. Study population

Between March 2020 and July 2021, we recruited 55 participants of whom 7 withdrew from the experiment before the

[9] The initial number of 45 trials had to be revised due to a lower CR rate than expected in the GNG task. To ensure that the data were as reliable with 40 trials compared to 45, we have run a Reliability Analysis (see Supplementary Figure XXXVIII).

[10] We have replaced the Kolmogorov–Smirnov (K–S) test by the Shapiro–Wilks test since it is more powerful specifically for small samples (<50; Razali, 2011).

Table 7 – Summary table of all statistical tests.

Hypotheses	Statistical test	Contrast	Dependent Variable	
			Behavior	Physiology
Ha: Caffeine effects & Hb: Expectations effects & Hc: Caffeine Vs. expectations effects	Paired-samples *t*-tests[1]	**Ha:** GD/TD < GC/TD **&** **Hb:** GD/TD < GD/TC **&** **Hc:** GD/TC < GC/TD	**RVIP**: Hits	**RVIP** (Hits P3) and **Go/NoGo** (CR N2 & P3) components: - Voltage amplitude -GFP -**RVIP**: Attention-P3 TPJ, STG and Precuneus CSD -**Go/NoGo**: NoGo-N2 MFG, Cingulate Cortex and Precentral Gyrus CSD & NoGo-P3 MFG and ACC CSD
		Ha: GD/TD > GC/TD **&** **Hb:** GD/TD > GD/TC **&** **Hc:** GD/TC > GC/TD[a]	**RVIP**: RT **Go/NoGo**: FA & RT	
Outcome neutral contrasts (on the GD/TD condition)	One-sample t- tests[1]	**RVIP**: 1) **Accuracy**: Hits >30% 2) **RT**: 350 ms < RT < 750 ms		Presence of central positivity at 400 ms (Attention-P3 component) after onset of the first digit of target sequences (Hits condition).
	One-sample t- tests[1]	**Go/NoGo**: 1) **Accuracy**: NoGo FA > 10% 2) **RT:** 170 ms < RT < 570 ms		Presence of fronto-central negativity at 300 ms and fronto-central positivity at 400 ms (resp. NoGo-N2 and -P3) after NoGo (CR condition)
	One-sample t- tests[1]	**B-Caff questionnaire:** Mean score >3 on subscales: i) Withdrawal/Dependence, ii) Energy/Work Enhancement iii) Physical Performance Enhancement[b]		

Note: ACC = Anterior Cingulate Cortex; Beg = Beginning; CR=Correct Response; CSD=Current Source Density; FA=False Alarms; GC = Give-CAF; GD = Give-DECA; GFP = Global Field Power; MFG = Middle Frontal Gyrus; STG=Superior Temporal Gyrus; TC = Told-CAF; TD = Told-DECA; TOST = Two-One-Sided *t*-Tests; TPJ = Temporo-Parietal Junction; [1] = One-sided test.

[a] Since we expected an increase in performance in each of the contrast, we corrected conceptual mistakes such that RT and FA rates should be smaller in GD/TC and GC/TD compared to the GD/TD condition (and not larger as initially written).

[b] We corrected a typo here, namely the B-Caff questionnaire line from Table 7 was not supposed to be associated with the GD/TD condition. The B-Caff questionnaire was provided during the 1st session and the conditions order was randomized such that only few participants filled it while in the GD/TD condition. Moreover, the questionnaire could not have been influenced by conditions, since participants had to fill it at the beginning of the session (i.e. before even beig informed on the condition assignment).

last session (Fig. 4 and Supplementary Table V). Hence, our final sample was composed of 48 participants (57.45% females) aged 23.15 ± 2.51 years and who consumed on average 167.8 ± 63.2 mg of caffeine daily.

The local ethics committee (*Commission cantonale d'éthique de la recherche sur l'être humain*, CER-VD) approved the protocol (#2019–02075). All recruited participants provided a first written informed consent prior to inclusion, while participants included in the final sample provided a second informed consent at the end of the last session. They were all compensated for their participation.

3.2. *Outcome neutral controls*

Except for the RVIP RT criteria (i.e. 350 ms < RT < 750 ms), all outcome neutral controls were validated (Supplementary Figures XII-XVI and Tables VI–VIII). Regarding the RVIP, while our estimates were based on previous evidence relying on corresponding tasks (Dodd et al., 2015; Wilhelmus et al., 2017), our participants replied ca. 200 ms (~40%) faster than expected. Importantly, the RT did not exhibit any floor effects (Supplementary Figure XVIII): the skewness (respectively .323, .340 and −.398 for the Give-CAF/Told-DECA (GC/TD), Give-DECA/Told- CAF (GD/TC) and Give-DECA/Told-DECA (GD/TD)) and the kurtosis (respectively .089, 1.115 and .519) were within a ±2 range for normal distribution (Gravetter & Wallnau, 2013), while the Shapiro–Wilk tests were all non-significant (respectively $P = .977$, $P = .977$ and $P = .979$; Supplementary Table II).

3.3. *Data removal*

After outliers' exclusion according to the criteria listed in section 2.8, we completed the sample so that each of the contrasts for each DV included at least 38 participants to comply with our minimum sample size calculations (see section 2.1.1). Details of data removal steps can be found in the Supplementary Material (Supplementary Figures IV-XI and Tables IV–V).

We applied the Winsorization approach for 4 datapoints identified as interesting outliers, namely on the i) Go/NoGo RT

variable for Participant P14 in the GD/TC condition (546.50 ms–445.99 ms), ii) RVIP RT variable for P900 in the GD/TC condition (451.58 ms–408.27 ms) and iii-iv) GNG N2 voltage amplitude for P24 in the GD/TD condition and P8 in the GD/TC condition (resp. 4.86 μV to 3.06 μV and 4.86 μV–1.38 μV).

3.4. Behavioral results

The behavioral results are summarized below. Importantly, as specified in section 2.10, only the caffeine effects that we were able to replicate in Ha were investigated in Hb and Hc. Hence, we do not consider nor report the results of the Hb and Hc contrasts for which the Ha contrast did not reach our significance threshold. All negative results and related figures are reported in the.

Supplementary Material (Supplementary Figures XVII-XX and Tables IX–XX). Data distribution parameters are summarized in Table 8.

3.4.1. RVIP

3.4.1.1. Caffeine effects (Ha contrast). The Ha hypothesis was not confirmed: the GC/TD group did not perform better compared to the GD/TD group, both at the level of HITS ($W = 417$, $z = -1.15$, $P = .291$, $r = -.10$, BF_{01}=2.59) and at the level of RT ($t(43)$=1.794, $P = .120$, $g_{av} = .27$, BF_{01}=.74). Since we could only test Hb and Hc for contrasts showing a significant effect of caffeine (Ha), we do not report the results of the Hb and Hc contrasts (Supplementary Tables X-XI for HITS and **XIII-XIV** for RT).

We would note, however, that we detected signs of ceiling effects for the RVIP HITS index (Supplementary Figure XVII), which may have contributed to our negative result at this level.

3.4.2. Go/NoGo

3.4.2.1. Caffeine effects (Ha contrast). The Ha hypothesis was not confirmed: the percentage of FA and the RT were not lower in the GC/TD compared to the GD/TD conditions, respectively $t(43)$=.688, $P = .372$, $g_{av} = -.10$, BF_{01}=3.29 and $t(43)$=2.425, $P = .029$, $g_{av} = -.36$, BF_{01}=.23. For the same reason as above, we did not report the results of the Hb and Hc contrasts (Supplementary Tables XVI-XVII for FA and **XIX-XX** for RT).

3.5. ERP results

As for the behavioral analyses, the ERP results for Hb and Hc are reported only for the contrasts showing a significant Ha result. All negative results and related figures are found in the Supplementary Material (Supplementary Figures XXII-XXXVII and Tables XXI-LXII), and data distribution parameters and summarized in Table 9 and Table 11.

As specified in section 2.7.3, the POI for each of the investigated ERP component was determined as the average of individual GFP peaks + - 1SD for each condition (Table 10). While the Attention-P3 component related to the RVIP task was expected to occur 300–500 ms post-stimulus onset (Hoyniak et al., 2015; Key et al., 2005), it actually manifested at 208–277 ms (Supplementary Figure XXI). The component manifested ca. 200 ms earlier than expected because our participants were also ca. 200 ms faster than expected at the behavioral level (*see* section 3.2).

3.5.1. RVIP

3.5.1.1. Attention-P3 component. Caffeine effects (Ha contrast).

First, confirming the Ha hypothesis, voltage amplitudes and GFP for the P3 component were larger in the GC/TD than in the GD/TD conditions, respectively $t(46)=-3.021$, $P = .006$, $g_{av} = -.43$ and $P = .001$ (Fig. 5A and B).

Regarding the source estimation analyses, the conditions did not differ either in the STG, $W = 470$, $z = -1.40$, $P = .244$, $r = -.14$, in the TPJ, $W = 588.5$, $z = -.52$, $P = .906$, $r = .04$, BF_{01}=6.11, or in the Precuneus, $W = 443$, $z = -1.63$, $P = .306$, $r = -.19$, BF_{01}=2.22.

Expectations effects (Hb contrast).

The Hb hypothesis was not confirmed: voltage amplitudes and GFP for the P3 component were not larger in the GC/TC than in the GD/TD conditions, respectively $t(46)=-2.059$, $P = .034$, $g_{av} = -.29$, BF_{01}=.47, and $P = .416$ (Fig. 5A and B).

Caffeine Vs expectations effects (Hc contrast).

Partly confirming our Hc hypothesis, the effects of caffeine and expectations did not differ at the level of voltage amplitudes, $t(46)=-.335$, $P = .369$, $g_{av} = -.05$, BF_{01}=4.77, but caffeine effects were larger in the GC/TD than in the expectations conditions (GD/TC) at the level of the GFP, $P = .001$ (Fig. 5A and B).

Regarding the source estimation analyses, there was no difference between the GC/TD and the GD/TC conditions either in the TPJ, $W = 511$, $z = -1.06$, $P = .873$, $r = -.08$, BF_{01}=2.10, the Precuneus, $W = 501$, $z = -1.14$, $P = .384$, $r = -.10$, BF_{01}=2.34, or in the STG, $W = 407$, $z = -1.97$, $P = .073$, $r = -.24$, BF_{01}=.89.

3.5.2. Go/NoGo

3.5.2.1. NoGo-N2 component. Caffeine effects (Ha contrast).

The Ha hypothesis was not confirmed: voltage amplitudes and GFP for the N2 component were not larger in the GC/TD than in the GD/TD conditions, respectively $t(37)=.370$, $P = .965$, $g_{av} = -.06$, BF_{01}=7.44 and $P = .086$ (Supplementary Figures XXVIII-XXIX).

3.5.2.2. NoGo-P3 component. Caffeine effects (Ha contrast).

Confirming the Ha hypothesis, voltage amplitudes and GFP were larger in the GC/TD than in the GD/TD conditions, respectively $t(37)=-2.888$, $P = .010$, $g_{av} = .46$ and $P = .009$ (Fig. 6A and B).

Regarding the source estimation analyses, the MFG was more activated in the GC/TD than in the GD/TD conditions, $W = 195$, $z=-2.81$, $P = .015$, $r = -.41$ (Fig. 6C and D), while the conditions did not differ in the ACC, $t(37)=-1.927$, $P = .046$, $g_{av} = .31$, $BF01=.56$.

Expectations effects (Hb contrast).

The Hb hypothesis was not confirmed: voltage amplitudes and GFP levels were not larger in the GD/TC compared to the GD/TD conditions, respectively $t(37)=-1.273$, $P = .105$, $g_{av} = -.20$, BF_{01}=1.53 and $P = .059$ (Fig. 6A and B).

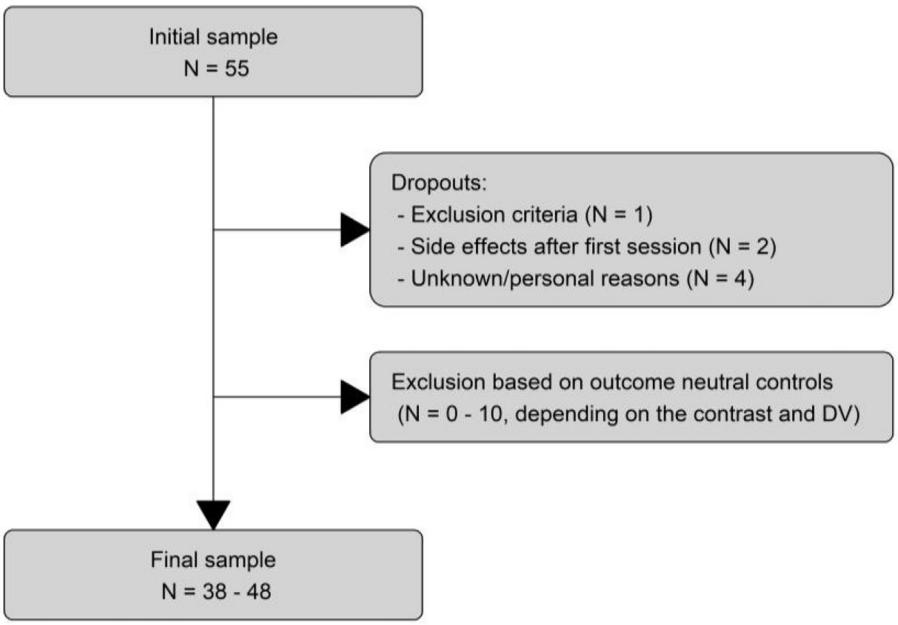


Fig. 4 – Study flow diagram.

Table 8 – Summary table of descriptive statistics for behavioral data.

Task	DV	Condition	Mean	SD	Median	IQR	N
RVIP	HITS (%)	GD/TD	94.648	3.546	95.210	4.167	45
		GD/TC	95.057	3.944	96.354	6.290	44
		GC/TD	95.180	3.884	96.354	5.587	45
	RT (ms)	GD/TD	316.636	31.677	316.894	39.646	45
		GD/TC	313.263	30.912	309.461	38.228	44
		GC/TD	307.761	35.945	312.134	44.082	45
GNG	FA (%)	GD/TD	29.186	14.170	26.250	23.125	47
		GD/TC	29.433	13.645	28.750	18.750	47
		GC/TD	27.926	14.685	27.500	20.625	47
	RT (ms)	GD/TD	360.387	33.576	359.175	39.102	47
		GD/TC	356.254	31.990	351.085	43.068	47
		GC/TD	351.472	33.337	348.445	41.675	47

Note: DV = Dependent Variable; FA=False Alarms; GC/TD = Give-CAF/Told-DECA; GD/TC = Give-DECA/Told-CAF; GD/TD = Give-DECA/Told-DECA; GNG = Go/NoGo; IQR=Interquartile Range; RT = Reaction Time; RVIP = Rapid Visual Information Processing.SD=Standard Deviation.

3.6. *Caffeine vs expectations effects (Hc contrast)*

Finally, the Hc hypothesis was not confirmed, voltage amplitudes and GFP levels were not larger in the GC/TD compared to the GD/TC conditions, respectively $t(39)=-2.284$, $P = .021$, $g_{av} = -.25$, $BF_{01}=.35$, and $P = .044$ (Fig. 6A and B).

4. Discussion

The aim of the study was to replicate previously identified performance-enhancing effects of caffeine and of caffeine-related expectations on inhibitory control and sustained attention at the behavioral level, and to further investigate their electrophysiological correlates. Neither caffeine nor caffeine-related expectations influenced any of the investigated behavioral dependent variables (correct Go trials (HITS) and response time (RT) for the Rapid Visual Information Processing task (RVIP), and false alarms (FA) and RT for the Go/NoGo task (GNG)). At the electrophysiological level, we confirmed our hypothesis that as compared to the control condition (Give-DECA/Told- DECA (GD/TD)), the caffeine condition (Give-CAF/Told-DECA (GC/TD)) induced larger RVIP Attention-P3 component voltage amplitude and Global Field Power (GFP). We also found that the caffeine condition (GC/TD) induced stronger GFP values compared to the expectations condition (Give-DECA/Told-CAF (GD/TC)) for that same Attention-P3 component. Finally, the caffeine condition (GC/TD) induced larger GNG NoGo-P3 component voltage amplitude, GFP values and Middle Frontal Gyrus (MFG) current source density (CSD) compared to the control condition (GD/TD).

Table 9 – Summary table of descriptive statistics of ERP Voltage amplitude (μV) and GFP data.

Task	Component	Voltage amplitude					GFP				
		Condition	Mean	SD	Median	IQR	Mean	SD	Median	IQR	N
RVIP	Attention-P3	GD/TD	.62	.49	.55	.88	1.32	.51	1.26	.69	47
		GD/TC	.75	.58	.69	.75	1.33	.48	1.34	.74	47
		GC/TD	.78	.60	.63	.83	1.50	.53	1.33	.84	47
GNG	NoGo-N2	GD/TD	−2.20	1.69	−2.04	2.03	2.73	1.05	2.66	1.37	40
		GD/TC	−3.07	1.94	−2.84	3.06	2.78	1.02	2.63	1.15	44
		GC/TD	−2.37	1.77	−2.47	1.81	2.92	1.03	2.81	1.05	42
	NoGo-P3	GD/TD	5.14	2.49	5.35	3.59	3.87	1.26	3.67	1.57	40
		GD/TC	5.30	2.90	5.00	2.82	4.00	1.39	3.90	2.27	44
		GC/TD	5.92	2.34	5.59	4.06	4.27	1.19	4.18	1.33	42

Note: GC/TD = Give-CAF/Told-DECA; GD/TC = Give-DECA/Told-CAF; GD/TD = Give-DECA/Told-DECA; GFP = Global Field Power; GNG = Go/NoGo; IQR=Interquartile Range; RVIP = Rapid Visual Information Processing; SD=Standard Deviation.

Table 10 – Condition averages and SD of individual GFP peak, in milliseconds.

Component	Condition	Peak	SD
RVIP Attention-P3	GD/TD	218.36	35.32
	GD/TC	216.41	33.85
	GC/TD	229.10	34.07
GNG NoGo-N2	GD/TD	287.69	46.81
	GD/TC	273.05	37.68
	GC/TD	285.74	36.81
GNG NoGo-P3	GD/TD	402.93	35.60
	GD/TC	405.86	35.28
	GC/TD	397.07	31.44

Note: GC/TD = Give-CAF/Told-DECA; GD/TC = Give-DECA/Told-CAF; GD/TD = Give-DECA/Told-DECA; GNG = Go/NoGo; RVIP = Rapid Visual.
Information Processing; SD=Standard Deviation.

4.1. *Caffeine effects*

We could not replicate previous behavioral evidence that caffeine enhances sustained attention (Cooper et al., 2021; Foxe et al., 2012; Wilhelmus et al., 2017) and inhibitory control performance (Barry et al., 2014; Dodd et al., 2015; Pasman, Boessen, Donner, Clabbers, & Boorsma, 2017). In our study, the ingestion of a total of 360 mg of caffeine had no effect on RT nor on accuracy (respectively HITS and FA) at the RVIP or at the Go/NoGo task.

The following discrepancies between previous findings and ours may explain our diverging findings. First, the smaller sample sizes in previous studies may have resulted in over-estimated effect size (i.e. between 12 and 31 subjects/group in Foxe et al., 2012; Barry et al., 2014; Dodd et al., 2015; Cooper et al., 2021; *see for discussion* Button et al., 2013b; Lakens, 2013; Schäfer & Schwarz, 2019). Since our experiment had a 90% power to detect an effect of at least Hedge's $g_{av} = .3$ with an $\alpha = 2\%$, our results indicate that caffeine effects, if any, may actually be smaller than $g_{av} = .3$. There were also differences between previous well-powered studies and ours (i.e. between 41-53 subjects/group in Pasman et al., 2017; Wilhelmus et al., 2017): Wilhelmus and al. (2017) recruited low or non-caffeine consuming individuals between 40-60 years old, a population in which caffeine may have larger effect than in our moderate-consumers sample. Pasman et al. (2017) focused on a more heterogenous sample than ours: young-to-older adults (Age: *Mean* = 36, *SD* = 14) which were mainly women (77%), and most importantly the coffee consumption habits differed widely between individuals (i.e. from <7 cups/week to >14 cups/week). Hence, part of this sample with the lowest consumption habits may have driven their effects since evidence indicate that low consumers tend to benefit more from the cognitive enhancing effects of caffeine compared to heavier consumers (Haskell, Kennedy, Wesnes, & Scholey, 2005). As part of the inclusion criteria, we ensured that all our participants were moderate caffeine drinkers (i.e., on average 167.8 ± 63.2 mg/day) which considerably reduced the heterogeneity regarding consumption habits in our sample.

Importantly, the majority of studies cited above relied on caffeine dosage lower than ours (i.e. 50-85 mg of caffeine in Foxe et al., 2012; Dodd et al., 2015; Pasman et al., 2017; Wilhelmus et al., 2017; 250 mg in Barry et al., 2014; and up to 3 mg/kg in Cooper et al., 2021). The fact that these studies with lower dosage found larger effects support the idea of an inverted-U shaped relationship between caffeine concentration and its cognitive-enhancing effect. High dosage of caffeine (roughly 400 mg) may indeed negatively impact cognitive performance (*see for a review* Caviola & Faber, 2015). Zhang, Liu, Wang, Deng, and Zheng (2020) have demonstrated in a dose–response study that their lowest caffeine concentration of 3 mg/kg (i.e. 210 mg for a 70 kg individual) had greater effects on cognition and prefrontal cortex activity compared to higher dosages. While we administered 240 mg with another 120 mg of caffeine 45min later regardless of weight, we cannot exclude that our strong dosage may have led to detrimental effects on performance or to interfering side-effects in lighter individuals compared to heavier ones.

While the literature cited above mainly relied on caffeine capsules, we favored brewed coffee (see for similar approach Elliman et al., 2010; Fukuda & Aoyama, 2017; Pasman et al., 2017; Haskell-Ramsay et al., 2018) since sensory contextual information are key ingredients in our caffeine-related placebo effects of interest (Flaten & Blumenthal, 1999; Mikalsen, Bertelsen, & Flaten, 2001). We used Switzerland's most frequent coffee pods (Statista, 2018) to ensure that our participants were familiar with the coffee brand and in turn to maximize expectations. Our choice is supported by

Table 11 – Summary table of descriptive statistics of ERP CSD data, in μA/mm³.

Task	Component	ROI	Condition	Mean	SD	Median	IQR	N
RVIP	Attention-P3	Precuneus	GD/TD	.00063	.00021	.00058	.00020	47
			GD/TC	.00063	.00021	.00061	.00028	47
			GC/TD	.00066	.00027	.00061	.00034	47
		STG	GD/TD	.00086	.00026	.00078	.00024	47
			GD/TC	.00086	.00026	.00081	.00039	47
			GC/TD	.00089	.00025	.00083	.00037	47
		TPJ	GD/TD	.00074	.00022	.00068	.00030	47
			GD/TC	.00070	.00022	.00070	.00028	47
			GC/TD	.00074	.00029	.00065	.00038	47
GNG	NoGo-N2	Cingulate Cortex	GD/TD	.00143	.00051	.00131	.00069	40
			GD/TC	.00144	.00055	.00136	.00072	44
			GC/TD	.00150	.00047	.00139	.00048	42
		MFG	GD/TD	.00172	.00065	.00156	.00081	40
			GD/TC	.00169	.00054	.00163	.00082	44
			GC/TD	.00178	.00049	.00164	.00078	42
		Precentral Gyrus	GD/TD	.00146	.00050	.00137	.00059	40
			GD/TC	.00149	.00043	.00138	.00050	44
			GC/TD	.00150	.00037	.00140	.00048	42
	NoGo-P3	ACC	GD/TD	.00184	.00076	.00176	.00107	40
			GD/TC	.00186	.00079	.00176	.00110	44
			GC/TD	.00203	.00069	.00207	.00121	42
		MFG	GD/TD	.00220	.00076	.00202	.00094	40
			GD/TC	.00229	.00080	.00217	.00089	44
			GC/TD	.00237	.00059	.00221	.00075	42

Note: ACC = Anterior Cingulate Cortex; GC/TD = Give-CAF/Told-DECA; GD/TC = Give-DECA/Told-CAF; GD/TD = Give- DECA/Told-DECA; GFP = Global Field Power; GNG = Go/NoGo; IQR=Interquartile Range; MFG = Middle Frontal Gyrus; ROI = Region of Interest; RVIP = Rapid Visual Information Processing; SD=Standard Deviation; STG=Superior Temporal; Gyrus; TPG = Temporo-parietal Junction.

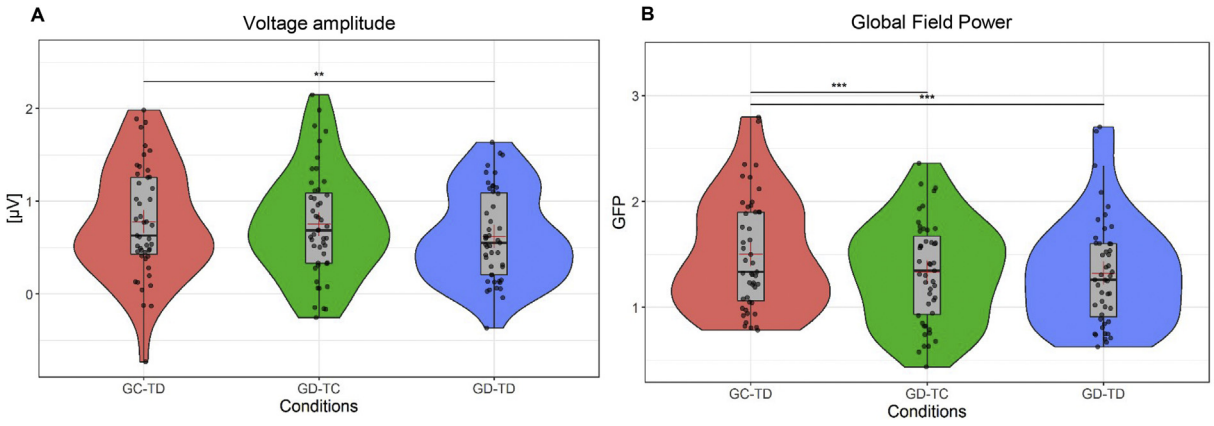


Fig. 5 – Violin plots for the RVIP Attention-P3 component measures. Note: Violin plots representing the three conditions' effects on the RVIP P3 component at the level of (A) voltage amplitude and (B) GFP. The horizontal grey line in each boxplot symbolizes the median while the red cross represents the mean. * = *P* < .02; ** = *P* < .01; * = *P* < .001.**

experiments reporting that, although caffeine absorption varies between caffeine capsules and brewed coffee, they do not differ at the level of subjective measures (Liguori, Hughes, & Grass, 1997). Irwin, McCartney, Khalesi, and Desbrow (2018) also highlighted that consumption of coffee brewed from different coffee pods influenced mood and cognitive performance, irrespective of caffeine content. Nevertheless, even though we controlled for coffee absorption parameters (see section 2.5.2), coffee is a complex beverage constituted of more than a thousand compounds with unique effects (see for reviews O'Keefe et al., 2013; Cappelletti, Daria, Sani, & Aromatario, 2014) whose concentration in brewed coffee may have abolished the caffeine effects we expected to observe. This difference between caffeine capsule vs coffee delivery may account for part of the discrepancies between our findings and previous results, and our study may be better referred to as a coffee instead of a caffeine experiment.

Another aspect to consider is that the studies discussed above relied on traditional double-blind randomized designs, in which participants were instructed that they had a 50% chance of receiving either caffeine or a placebo. Such designs cannot disentangle whether the reported effects are due only

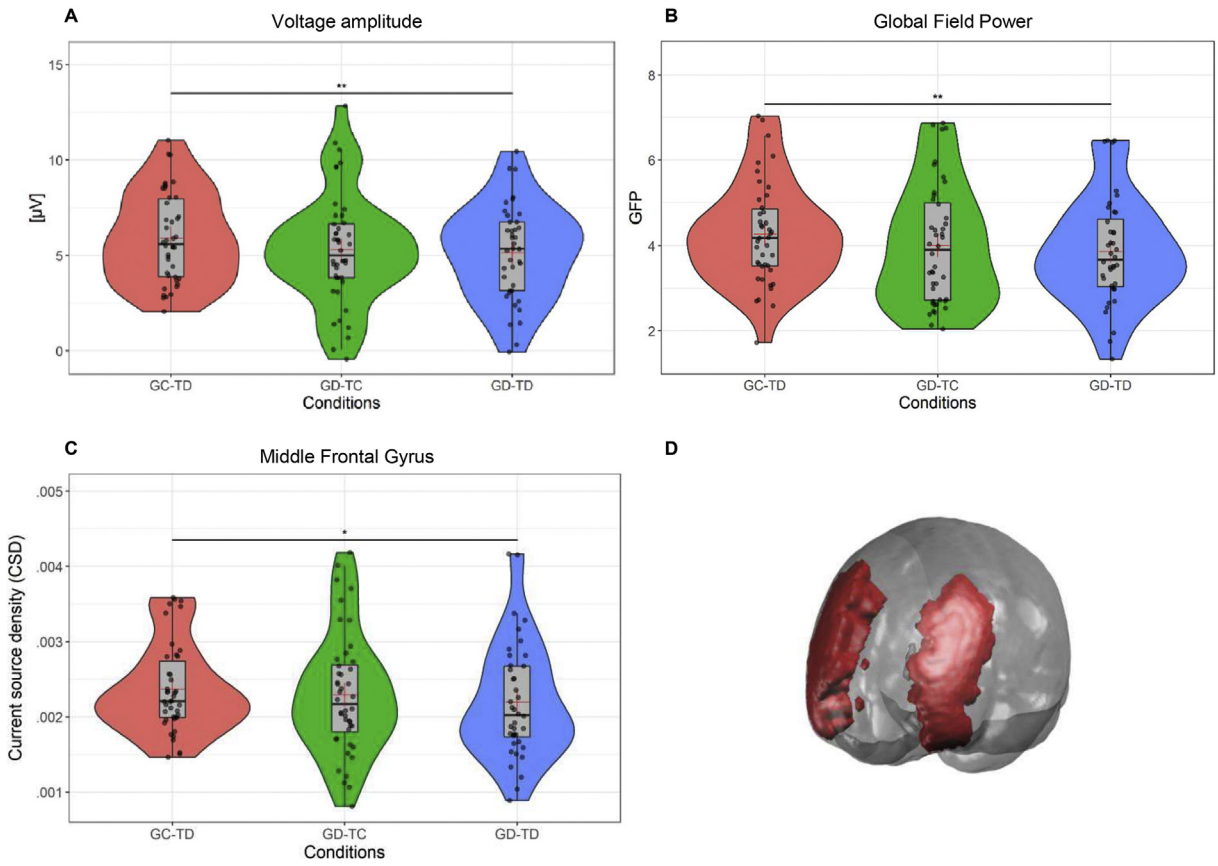


Fig. 6 – Violin plots for the GNG NoGo-P3 component measures. Note: Violin plots representing the three conditions' effects on the GNG P3 component at the level of (A) voltage amplitude (B) GFP and (C) CSD in the MFG. (D) 3D representation of the bilateral MFG Region of Interest (ROI), in red, based on the AAL atlas. The horizontal grey line in each boxplot symbolizes the median while the red cross represents the mean. * = $P < .02$; ** = $P < .01$; *** = $P < .001$.

to caffeine (without expectations) or to a combination of caffeine and expectations effects; expectations are indeed not controlled for and may vary greatly across individuals (*see for reviews* Enck et al., 2013; Justman, 2013). Supporting this hypothesis, Elliman et al. (2010) have demonstrated with a balanced placebo design that caffeine indeed enhanced sustained attention performance but only when individuals were expecting to receive it. The fact that we did not find any effect when investigating exclusively the pure effects of caffeine (i.e. when individuals were not expecting it) suggests that caffeine effects may only manifest when also expecting to receive caffeine. Accordingly, Elliman et al. (2010) have demonstrated that caffeine enhanced sustained attention performance only when subjects were told that they were indeed receiving caffeine. On the opposite, when they were instructed that they had received a decaffeinated coffee their performance was as poor as when no caffeine was provided. Looby et al. (2021) also reported that individuals' performance at a working memory task reached their highest level when they were receiving caffeine and expected to have ingested a more potent drug than caffeine itself (i.e. Adderall). Since our design lacks a fourth GC/TC condition, where participants would have received a caffeinated coffee and instructed in accordance, the assumption could not be investigated. Together with our data, previous literature suggests that caffeine effects are small, and likely only manifest when reinforced with expectations.

Corroborating previous literature, we identified an enhancing effect of caffeine on the P3 ERP components (Sustained attention: Diukova et al., 2012; Kahathuduwa et al., 2017; and inhibitory control: Barry et al., 2007, 2014): compared to the GD/TD condition, individuals in the GC/TD condition showed a larger Attention-P3 voltage amplitude and Global Field Power (GFP) for the RVIP task, and in the NoGo-P3 voltage amplitude, GFP, and Middle Frontal Gyrus (MFG) activity for the Go/NoGo task. The finding that caffeine influenced both the Attention-P3 and NoGo-P3 components in the same direction while leaving the NoGo-N2 component unaffected suggests that caffeine's effects are restricted to attention processes and do not influence motor control processes implementation. The source estimation analyses support this interpretation by confirming a NoGo- P3 effect in the middle frontal gyrus, a region involved in top-down attentional control (Hong, Wang, Sun, Li, & Tong, 2017). Of note, fMRI evidence have also demonstrated that caffeine tends to modulate brain metabolism in regions that control vigilance and attention (Chang, Song, et al., 2018; Jin et al., 2015; Zhang et al., 2020).

4.2. *Expectations effects*

Since we could not replicate any of the previously identified caffeine effects at the behavioral level, our analytical strategy imposed not to investigate expectations effects at the behavioral level.

Expectations effects were indeed expected to be smaller than the caffeine effects and thus not worth investigating if the later were not detected.

At the electrophysiological level, there was no effect of expectations at any of the investigated tasks-related ERP components and associated measures. This absence of effects comes as no surprise, knowing that caffeine electrophysiological effects were already of small magnitude and expectations effects are typically smaller (*see for a review* Schedlowski et al., 2015).

4.3. *Caffeine versus expectations effects*

Similarly, since we did not find caffeine effects at the behavioral level, we did not investigate the difference between the effects of caffeine and expectations at the behavioral level.

At the electrophysiological level, we found larger GFP values in the GC/TD than in the GD/TC conditions for the RVIP Attention-P3 component. Since large GFP values indicate higher neural synchronization or number of involved neurons in the activated network (Brunet et al., 2011), compared to caffeine expectations, caffeine alone may induce response gains in brain areas underlying sustained attention in the P3 time window.

4.4. *Conclusions and future directions*

To conclude, our results do not corroborate previous literature for an improvement of sustained attention and inhibitory control performance by caffeine nor by caffeine expectations. While the NoGo-P3 modulation for the inhibitory control task indeed manifested in one of our pre-determined regions of interest, it was not the case for the sustained attention task. Future studies should thus focus on other areas or on whole-brain source analyses.

Although our inability to replicate previous evidence for caffeine effects at the behavioral level may be related to methodological discrepancies (age range, gender distribution or coffee consumption habits), our data suggest that the size of caffeine effect on behavioral performance in the current literature might have been overestimated (*see for a meta-analysis* Zhou et al., 2018), and the importance of the interaction between caffeine and the related expectations underestimated. Our data also suggest that future studies should focus on caffeine dose effects as well as consumption habits, two factors that may have a larger influence than currently considered.

Credit author statement

Wicht, Corentin Aurèle: Conceptualization, Methodology, Software, Formal Analysis, Investigation, Data Curation, Writing-Original Draft, Visualization, Funding Acquisition.

De Pretto, Michael: Conceptualization, Methodology, Writing-Review & Editing.

Mouthon, Michael: Data Collection, Methodology, Writing-Review & Editing.

Spierer, Lucas: Conceptualization, Methodology, Resources, Writing-Review & Editing, Supervision, Project Administration, Funding Acquisition.

Open Practices section

The study in this article earned Open Data, Open Materials and Preregistered badges for transparent practices. Data for this study is available at http://doi.org/10.5281/zenodo.4500849.

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Supplementary data

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Experience with opioids does not modify the brain network involved in expectations of placebo analgesia

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Abstract

Placebo analgesia (PA) is defined as a psychobiological phenomenon triggered by the information surrounding an analgesic drug instead of its inherent pharmacological properties. PA is hypothesized to be formed through either verbal suggestions or conditioning. The present study aims at disentangling the neural correlates of expectations effects with or without conditioning through prior experience using the model of PA.

We addressed this question by recruiting two groups of individuals holding comparable verbally-induced expectations regarding morphine analgesia but either (i) with or (ii) without prior experience with opioids. We then contrasted the two groups' neurocognitive response to acute heat-pain induction following the injection of sham morphine using electroencephalography (EEG). Topographic ERP analyses of the N2 and P2 pain evoked potential components allowed to test the hypothesis that PA involves distinct neural networks when induced by expectations with or without prior experience.

First, we confirmed that the two groups showed corresponding expectations of morphine analgesia (Hedges' $g_s < .4$ positive control criteria, $g_s = .37$ observed difference), and that our intervention induced a medium-sized PA (Hedges' $g_{av} \geq .5$ positive control, $g_{av} = .6$ observed PA). We then tested our hypothesis on the recruitment of different PA-associated brain networks in individuals with versus without prior experience with opioids and found no evidence for a

List of abbreviations: ASR, Artifact Subspace Reconstruction; CHEP(S), Contact Heat Evoked Potential (Stimulator); CMS-DRL, Common Mode Sense-Driven Right Leg; CondExp, Conditioned Expectations (group); DBP, diastolic blood pressure; EEG, electroencephalography; ERP, event-related potential; GFP, Global Field Power; GHQ, General Health Questionnaire; GMD, Global Map Dissimilarity; HR, heart rate; IPA, in-principle-acceptance; LEP, laser-evoked potential; LPP, late positive potential (component); MAD, median absolute deviation; MAEQ, Morphine Adverse Effects Questionnaire; MAExpQ, Morphine Analgesia Expectations Questionnaire; MFS, Medical Fear Survey; PA, placebo analgesia; PBO, placebo; POI, period of interest; PostInject, post-injection (phase); PreInject, pre-injection (phase); SBP, systolic blood pressure; SESOI, smallest effect size of interest; TF, time frame; UncondExp, Unconditioned Expectations (group); VAS, Visual Analogue Scale.

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topographic N2 and P2 ERP components difference between the two groups. Our results thus suggest that in the presence of verbally-induced expectations, modifications in the PA-associated brain activity by conditioning are either absent or very small.

KEYWORDS
EEG, ERP topography, expectations, pain, placebo

1 | INTRODUCTION

Placebo analgesia (PA; *see for comparable acronym use* Koban et al., 2012; Nakamura et al., 2012; De Pascalis & Scacchia, 2019) is a psychobiological reaction elicited by the contextual information associated with a non-active drug (i.e., placebo drug) rather than by any inherent active pharmacological properties. As for other placebo effects, PA is thought to result from expectations formed through verbal suggestions (unconditioned expectations) and conditioning (conditioned expectations). Yet, while verbal suggestions and conditioning induce corresponding behavioural placebo effects, indirect evidence suggest that they might involve different brain networks. The present study aims at confirming this hypothesis to deepen the fundamental understanding of the placebo effects.

Support for the assumption that distinct brain networks are involved in conditioned and unconditioned expectations notably comes from electrophysiological data. Colloca et al. (2009), for instance, showed that while PA induced by both conditioned and unconditioned expectations is associated with reduced N2-P2 event-related potential (ERP) complex amplitude, this effect is larger with conditioning. This pattern suggests a stronger involvement of early nociceptive brain mechanisms in conditioned than unconditioned expectations. In line with this finding, Carlino et al. (2015) report that PA -related reductions in N2-P2 amplitude occur when conditioning is associated with verbal information, but not when conditioning is engaged alone. Finally, psychopharmacological studies show that while conditioned PA depends on the drug's pharmacological effect, unconditioned PA mostly relies on the opioid system, further suggesting that different neurochemical pathways support each type of PA (*see for a review* Okusogu & Colloca, 2019; and for other investigation on this question: Amanzio & Benedetti, 1999; Bartels et al., 2014; Benedetti et al., 2003; Colloca et al., 2008; Colloca & Benedetti, 2009; De Jong et al., 1996; Montgomery & Kirsch, 1997; Reicherts et al., 2016; Voudouris et al., 1990).

Additionally, striatal regions of the reward system contribute to pre-cognitive anticipation of PA in conditioning (*see for reviews* de la Fuente-Fernández, 2009; Peciña et al., 2014). Since conditioning is by definition implicit (Bąbel, 2019; Benedetti et al., 2003), only implicit mechanisms would recruit this system. Hence, these evidence further suggest that different brain networks are involved in conditioned and unconditioned expectations.

We tested this hypothesis by focusing on the N2 and P2 ERP components during heat-evoked pain responses; The N2 and P2 components arise respectively 200–400 and 300–500 ms after the stimulation of Aδ fibers (Bromm & Treede, 1987) and originates from brain areas also involved in PA (Apkarian et al., 2005; *see for reviews* Benedetti, 2014; Wager & Atlas, 2015). These early components are sensitive to nociceptive stimulation (Wager et al., 2006) and are associated with the magnitude of pain perception (Colloca et al., 2009; Garcí-Larrea et al., 1997; Iannetti et al., 2005; *for reviews see* Colloca, 2014; Legrain et al., 2002). At the cognitive level, the N2 component is hypothesized to index top-down attentional mechanisms, while the P2 is more sensitive to bottom-up attentional orienting mechanisms as those modulated by the probability of stimulus occurrence (Legrain et al., 2002; Legrain et al., 2003; Legrain et al., 2005). We chose to focus on these components to compare the placebo effects induced by two types of expectations because even if they are not specific to PA, they are minimally involved in it (Carlino et al., 2015; Colloca et al., 2009). Current accounts for the neural bases of placebo effects indeed advance that placebos mimic the neurobiological action of the substituted drugs (*see for reviews* Benedetti, 2014; Benedetti et al., 2011; Colloca, 2014; Haour, 2005; Kirsch, 1997; Meissner et al., 2011; Pacheco-López et al., 2006; Stewart-Williams & Podd, 2004; Wager & Atlas, 2015). We thus expect placebo morphine to modulate the same brain markers that would be affected by real morphine, and in turn the N2 and P2 components, two reliable indexes of antinociceptive drugs-induced analgesia (Truini et al., 2010).

The literature reviewed, however, relies on methods with limited neurophysiological interpretability; they could notably not differentiate between purely

quantitative from qualitative modulation of brain activity. In addition, they focused on laboratory-induced non-pharmacological conditioning. They could thus not provide direct evidence that the brain networks mediating pre-established pharmacological conditioning effects differ from those involved in verbally-induced expectations.

To fill these gaps, we compared the neurocognitive responses to acute pain induction after the stimulation of Aδ fibers and after sham morphine administration between groups having the same verbally-induced expectations on the effects of morphine, but either with versus without an actual experience of opioids. This contrast enabled us to address our hypothesis because only the group with experience of opioids had formed conditioned expectations through prior experience. Specific questionnaires and inclusion criteria were used to control that morphine-related verbal suggestions were homogenous within- and between-group.

We identified whether each type of expectation engages distinct brain networks by comparing the spatial distribution of the N2-P2 scalp field potentials between the conditioned versus unconditioned expectations groups. We statistically compared the N2-P2 components topography with the so-called Global Map Dissimilarity (GMD), an index computed as the root mean square of the difference between the potentials measured at each electrode. This approach allowed to test our hypothesis because differences in ERP topography necessarily follow from alterations in the configuration of the underlying brain generators (Murray et al., 2008; Tzovara et al., 2012). Hence, if we observed different N2 and/or P2 ERP topographic maps (i.e., GMD differences) between the conditioned versus unconditioned group, our hypothesis that the two types of expectations involve different brain networks would be confirmed. Whether the topographic modulation manifest during the N2 and/or P2 component further provided information on whether each type of expectations differ at the level of the network involved in top-down or bottom-up attention to noxious stimulations.

2 | METHODS

2.1 | Participants

Participants were recruited with public advertisement.

Inclusion criteria include: Male or female, right-handed, 18 to 50 years old, French speakers, and a regular consumption of less than or equal to 21 units of alcohol/week to exclude individuals with a pathological relationship to alcohol.

To improve the homogeneity of the expectations in both groups, we controlled that they had neutral to positive prior experience with opioids (no severe adverse effects or intolerance), and thus that they had formed neutral to positive expectations regarding morphine analgesic properties (i.e., score > or = to 18 at the Morphine Analgesia Expectations Questionnaire, MAExpQ; *see* Section 3.5).

For the conditioned group, we controlled that they had comparable levels of PA conditioned expectations by ensuring that they had been treated with opioids as part of a medical treatment for a 1- to 6-month continuous duration per treatment course in the last 3 years maximum (several courses allowed during this period, provided there was a >1-month free time interval between them). Additionally, the pain-causing disease should not have been a cancer (unless completely healed) or a neurological disease (i.e., neuropathic pain). Yet, since pure conditioning (i.e., without verbal suggestions) is by nature implicit (*see* Bąbel, 2019) variation at this level may only have had a limited influence over our results, if any.

Exclusion criteria include: Needle phobia (score >8 on the Injections and Blood Draws subscale of the Medical Fear Survey, MFS; *see* Olatunji et al., 2012), history of substance-related addictive or misuse disorders (alcohol or other drugs), history of diagnosed neurological or psychiatric disorders (including acute and chronic pain syndromes), skin affliction of the forearms (*see* Schenk et al., 2014).

All eligible participants provided informed consent before beginning the experiment. Participants were allowed to withdraw their participation anytime without needing to provide explanations. We compensated participation to the study (at a rate of 25 CHF/hour; including transportation costs) even in case of withdrawal.

2.2 | Hypotheses and power analyses

We hypothesized that participants with prior experience with opioids (i.e., CondExp group) would recruit different neural networks to generate PA compared to individuals without prior experience with opioids (i.e., UncondExp group). This difference was expected to manifest during the N2 and/or P2 ERP components time windows, following the onset of heat-pain stimulations. Namely, if the effect manifested during the N2 time window we would have concluded that conditioning in PA influences attention towards noxious stimuli (i.e., top-down attentional mechanisms) while if it manifested for P2 we would have assumed that conditioning affects the way noxious

stimuli attracts attention (i.e., bottom-up attentional mechanisms; *see* Legrain et al., 2005, Legrain et al., 2003, Legrain et al., 2002).

2.2.1 | Power analysis

The sample was determined by computing a Monte Carlo power analysis (Muthén & Muthén, 2002; Paxton et al., 2001) on the contrast used to test our main hypothesis with a custom R script (R Core Team, 2020) relying on the 'Superpower' R package (Caldwell & Lakens, 2019).

For that purpose, we proceeded as follows:

1. First, we estimated the smallest absolute effect size of interest (SESOI) for our GMD contrast. Since GMD is a single value index of the differences in topography between two ERP fields (Brunet et al., 2011), the GMD group mean and standard deviation cannot be computed. We thus relied on the maximal single-electrode voltage difference across the whole montage at a given time frame, an index highly correlated with the GMD (correlation of $r = .79$ and $r = .81$ during the period of the N2 component in two independent datasets) (Najberg et al., 2020; Ribordy Lambert et al., 2020). On this basis, we identified the SESOI as 2.99 mV based on those observed in previous contrasts close to the present study in terms of the expected variation in network configuration (Colloca et al., 2009; Ribordy Lambert et al., 2020). We conservatively decided to take only half of the absolute effect size reported in Colloca et al. (2009) since this study included a small sample size (i.e., $N = 16$ per group) and may thus have detected an inflated effect size. Consequently, we restricted our SESOI as half of the 2.99 mV: 1.45 mV. Considering the adjusted SESOI and the SD of each group, the smallest relative effect size corresponded to a Hedge's $g_s = .56$.
2. We then calculated the between-subject variance of the voltage amplitude difference during the N2 component in Ribordy Lambert et al. (2020): 2.6 mV.
3. Based on the SESOI and variance parameters identified in steps 1 and 2, we generated 10,000 simulated datasets per conditions (conditioned and unconditioned groups) for total sample sizes ranging from 50 to 80 participants by steps of 2. For each simulation, we randomly drew data from the generated normal distributions and computed the power of each sample size to detect our effect of interest by extracting the percentage of p values that fell below our target alpha threshold of .05.
4. Finally, we identified the minimal sample required to detect our smallest effect size of interest with a .9 power.

The R script of the simulation can be found on Zenodo (https://doi.org/10.5281/zenodo.6043795).

To detect a moderate effect size of Hedge's $g_s = .56$ with a power of .9 and an alpha threshold of .05, a total sample of $N = 66$ (i.e., $n = 33$ per group) was considered (*see* Figure 1). Drop-outs and other excluded participants were replaced to maintain this sample size in the final analyses.

2.2.2 | Experimental design

We tested our hypothesis using the analgesic effects of placebo morphine after acute pain induction (i.e., PA). The target population was manageable to recruit because knowledge of morphine antalgic properties is largely shared (De Sola et al., 2018), with ~8% of individuals having actually experienced its effects (Wertli et al., 2017 for data in Swiss populations).

We used a two-cell between-subjects design: (i) Conditioned expectations group (CondExp): Individuals holding neutral or positive expectations of morphine analgesia and with prior positive experience with opioids, namely they had been treated with opioids as part of a

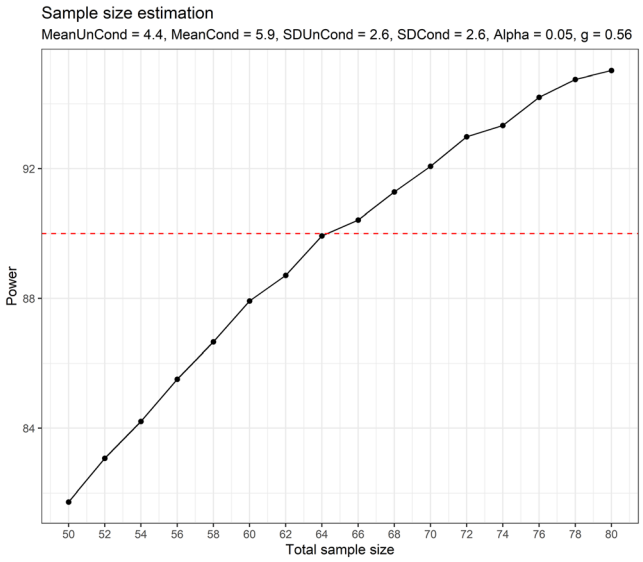


FIGURE 1 Representation of the power that can be reached according to each sample size, from $N = 50$ to $N = 80$ by steps of 2, based on data from Colloca et al., 2009 Hence, to reach a 90% power, a sample of $N = 66$ for both groups was required. MeanUnCond/SDUnCond = Mean/SD of UncondExp group; MeanCond/SDCond = Mean/SD of CondExp group; Alpha = Alpha threshold; g = Hedge's g_s

medical treatments according to criteria detailed in Section 3.1; and (ii) Unconditioned expectations group (UncondExp): Individuals holding neutral to positive expectations of morphine analgesia but without prior experience with opioids.

Due to the lack of a conditioning-only group, our design could not rule out the presence of a conditioning-by-expectations interaction effect in the CondExp versus UncondExp contrast. Hence, interpretations of our results solely went in the direction that adding conditioning with prior experience to expectations would recruit different neural networks than expectations alone to engender PA.

We were aware that our design remained less well-controlled than laboratory-based conditioning designs with administration of precise molecule, dose and number of runs (*see*, *for an example*, Amanzio & Benedetti, 1999). Nevertheless, our approach had the advantage of providing stronger ecological relevance while replicating earlier laboratory-based findings in an observational paradigm and extending them at the electrophysiological level.

2.3 | Procedure

The experimental session lasted around 1.75 h. The procedure of the session is summarized in Figure 2; it consisted of the following steps:

As part of a two-stage informed consent procedure, participants gave their initial written consent for the study before data collection (i.e., only partial information disclosure) while a second consent was provided as soon as the complete information was revealed at the end of the session. In the first informed consent document, participants' beliefs in the analgesic properties of Morphine were reinforced with the following paragraph: 'Opium, from which morphine is extracted, was cultivated and used by the Sumerians to treat pain already 5000 years ago. The extracted morphine was injected for the first time 150 years ago by the Irish surgeon Francis Rynd (1801-1861). It remains now the most widely used analgesic and is the standard against which new pain-relieving medicine are tested. From 33 to 100% of patients report that morphine can completely suppress their pain, depending on the route of administration (Walsh et al., 2006). Morphine is a very potent drug since, once injected, it reaches its peak concentration in the blood after roughly 15min and its analgesic effects can last up to 24hours'. Then, participants were screened regarding the inclusion and exclusion criteria (with the GHQ, MAExpQ and MFS questionnaires) and the electrodes for the electroencephalography (EEG) recording system were positioned on participants' head (duration ~15 min). Then, pain stimulation threshold was measured to determine the individual stimulation intensity that produces comparable pain feelings across participants (*see* Section 2.4.2).

Afterwards, participants' cardiovascular readings were assessed for the first time as part of the cover story (*see* Section 2.6.2) after which they underwent the pre-injection pain induction phase (i.e., PreInject phase) which lasted ~8 min. They were then administered the saline injection framed as containing morphine by licensed study personnel. They were instructed that the syringe contained a dose of 3.5-mg morphine (*see for a review* Sverrisdóttir et al., 2015) corresponding to half the dose that was routinely administered subcutaneously in a

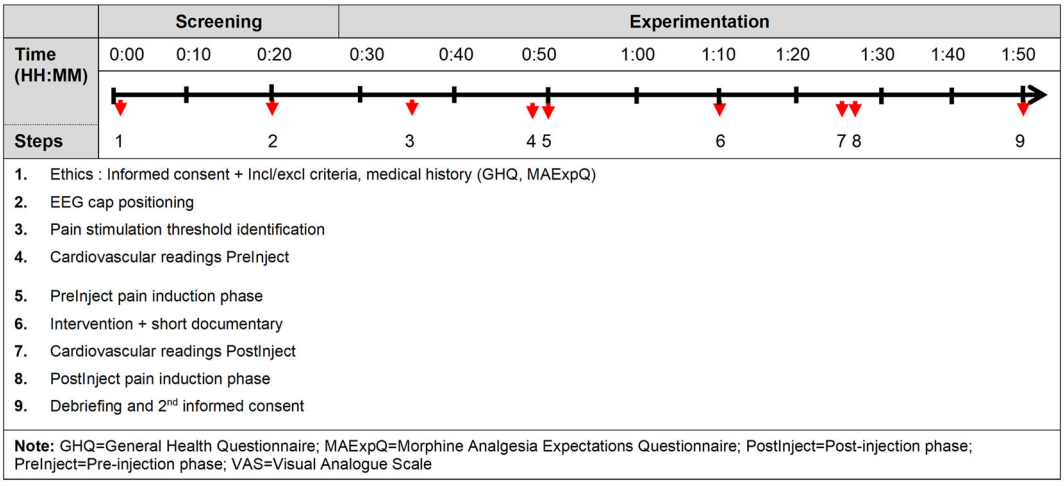


FIGURE 2 Summary of the procedure. GHQ = General Health Questionnaire; MAExpQ = Morphine Analgesia Expectations Questionnaire; PostInject = post-injection phase; PreInject = pre-injection phase; VAS = Visual Analogue Scale

hospital setting after a surgery or an injury, or to manage cancer pain or pain after a heart attack (National Health Institute, 2018). Fifteen minutes after the injection, participants had their cardiovascular function assessed for a second time again as part of the cover story (see Section 2.6.2) and then they underwent the post-injection pain induction phase (i.e., PostInject phase), again lasting ~8 min. Finally, participants received a debriefing information which disclosed the deception involved in the study and enabled them to react to it. They further provided a second informed consent, necessary to ensure that they maintained their consent after having received all information on the study.

2.4 | Task

2.4.1 | Pain stimulation device

Painful stimulations were performed with the PC-controlled PATHWAY CHEPS device (Medoc Advanced Medical Systems, Rimat Yishai, Israel). The thermofoil thermode had a surface of 27 mm in diameter (527.5 mm^2). The thermode was placed on the left volar forearm and held by the experimenter while the stimulation site was moved between one of three positions 5 cm apart[1] within the same dermatome after each trial to avoid sensitization and/or habituation after repeated pain stimuli (*for a similar procedure, see* Warbrick et al., 2009). The thermofoil temperature ranged between 32°C and 52°C with a heating rate of 70°C/s and was further cooled down with a rate of 40°C/sec (*for a similar procedure, see* Aslaksen et al., 2011).

2.4.2 | Identification of pain stimulation threshold

The intensity of the experimental stimulation trials was defined at the individual-subject level according to Schenk et al. (2014). In a first step, we relied on the methods of limits to assess the heat pain threshold and tolerance with temperature increasing at a rate of .3°C/s (Fruhstorfer et al., 1976). We applied two steadily increasing thermal stimulations until participants indicated orally when (i) they started to experience pain (i.e., transition from warm sensation to pain feeling) and (ii) when the pain was unbearable (i.e., pain tolerance). In a second step, 11 pain stimulations were applied to reach an individualized temperature eliciting a pain level of 8 or higher on the Visual Analogue Scale (VAS; 0–10) or 52°C (if the corresponding VAS rating was lower than 8). The stimulation temperatures ranged from 42°C to 52°C and the temperature increased by steps of 1°C after each trial. Correspondingly, the temperature equivalent to a level of pain of 8 or higher on the VAS scale[2] was then used to induce pain throughout the session.

2.4.3 | Experimental painful stimulation

The experimental painful stimulation paradigm was divided into two phases of two blocks of 12[3] trials (i.e., 24 trials in total; *for a comparable procedure, see* Aslaksen et al., 2011). Each block was separated by a 5-min break. The first phase happened before the saline injection (i.e., PreInject phase) while the second phase happened 15 min after the saline injection (i.e., PostInject phase), which corresponded to the time necessary to reach the peak concentration with real morphine (Mazoit et al., 2007). The post-injection scores were further used for statistical comparisons of our main contrast of interest (see Section 2.2.2) while both pre- and post-injection scores were used for the sanity checks to ensure that placebo analgesia indeed occurred (see Section 2.4.5).

The CHEPS software enabled the randomization of the interval between two stimulations which was set between 10 and 15 s to minimize the predictability of pain onset (*see for a similiar procedure* Schenk et al., 2014). Each block of 12 trials thus lasted roughly 3 min (including the inter-stimulus intervals). Stimulus onset was indexed by a TTL-pulse issued from the CHEPS software to the EEG-amplifier as soon as the temperature starts increasing (*see for a similar procedure* Aslaksen et al., 2011).

2.4.4 | Pain perception ratings

After the 6th and the 12th trial of each block, participants had to rate the perceived intensity of the stimulation on a

[1] *The anticipated sensitization process after repeated painful stimulations at the same skin location was stronger than expected and the signal-to-noise ratio was improved by moving the thermode within the same dermatome after each trial. The editorial approval for the deviation was obtained on the 27 October 2021, after the commencement of data collection but prior to data analysis.*

[2] *We adjusted this criterion as we realized that a VAS = 6 corresponded to a peak temperature of 46–48°C and was thus too low to reach an optimal signal-to-noise ratio in the ERPs. Hence, we increase it to VAS = 8 to reach a temperature of ~51–52°C.*

[3] *Since we increased the target VAS from 6 to 8, we also reduced by half the number of trials to shorten the duration of painful sensations.The editorial approval for these two deviations was obtained on 27 October 2021, after the commencement of data collection but prior to data analysis.*

0–10 VAS scale, labelled respectively as 'no pain at all' to 'unbearable pain'. The VAS was displayed on a computer screen and subjects had to move a cursor to indicate the value corresponding to the intensity of their pain. Global scores were computed as the average of the painful ratings over the four trials of each phase.

2.4.5 | Sanity checks

The following data sanity checks were used to control that our two groups shared common verbally-induced expectations and that the manipulation induced PA, which were a prerequisite for our key CondExp versu UncondExp GMD differences of interest to be interpretable.

A. First, we ensured that participants from both groups shared common positive verbally-induced expectations of morphine analgesia to ensure that this factor did not confound our contrast of interest. To this aim, we controlled that the difference at the MAExpQ global score was smaller than Hedges' $g_s < .4$.
B. We then ensured that a placebo effect indeed occurred after the injection and thus that we could interpret any electrophysiological effect in terms of PA. To this aim, we used one-sided differences of Hedges' $g_{av} \geq .5$ (.9 power and alpha threshold of .05 for this contrast with our planned sample size) on the mean of VAS trials after the injection (PostInject phase) compared to trials before the injection (PreInject phase), on the whole population sample.

If the first sanity check (i.e., A) was not fulfilled, participants with the value farther from the overall pooled median were successively excluded and replaced until the groups were balanced (i.e., since all participants should share the same expectations).

If the second sanity check (i.e., B) was not fulfilled, participants not showing placebo effects with the highest value compared to the difference score between the Δ VAS PreInject − VAS PostInject phases[4] were successfully excluded and replaced until we reached the expected difference of Hedges' $g_{av} \geq .5$ between the phases.

In the case where only one of the sanity checks was not fulfilled while the other one was, we will proceed to the exclusion and replacement of the participant.

2.5 | Questionnaires

- Demographics, measures of morphine analgesia expectations, as well as exclusion criteria were assessed with the following questionnaires:
- General Health Questionnaire (GHQ): custom-made 40-items questionnaire, self-assessment of overall health, sport activities, drug consumption habits and substance use and abuse (e.g., cigarettes and alcohol).
- Morphine Analgesia Expectations Questionnaire (MAExpQ): custom-made 9-items questionnaire, self-assessment of expectations regarding the analgesic properties of morphine and prior morphine or other opioids exposure.
- Morphine Adverse Effects Questionnaire (MAEQ): custom-made 12-items questionnaire, self-assessment of expectations of and prior experience with morphine or other opioids' side effects.
- Medical Fear Survey-Short Version (MFS): 25-items, self-assessment of medically related fears along five dimensions: Injections and Blood Draws, Sharp Objects, Blood, Mutilation and Examinations and Symptoms (*translated from* Olatunji et al., 2012). We exclusively focused on the Injections and Blood Draws subscale to exclude participants with needle phobia (*see* Section 3.1).

2.6 | Blinding procedures and cover story

2.6.1 | Saline injection

All subjects received a subcutaneous injection (i.e. better than intramuscular injection for morphine; Jin et al., 2015) of one bolus of saline (NaCl .9%) which was framed as containing real morphine, in the lower abdomen. The injection was performed by licensed study personnel.

2.6.2 | Cover story

We implemented a deceptive protocol (i.e., cover story) to maximize the credibility of our procedure as well as participants' expectations regarding the intervention. Previous evidence had demonstrated the usefulness of using cover stories when deceiving participants in placebo

[4]*The size of the placebo effect was initially calculated by comparing the individual's Post inject VAS to the group median VAS PostInject. Still, with this approach, individuals displaying a placebo effect but that have (by chance) a VAS PostInject close to the group VAS PostInject will be considered as not showing placebo effect. Thus, to efficiently exclude individuals experiencing no placebo effects, we instead computed a difference score between the Δ VAS PreInject – VAS PostInject.* (i.e. *emails exchange of the 19.11.2021).*

manipulation experiments (see Elkins-Brown et al., 2018). Participants were instructed that the study aimed at clarifying the physiological mechanisms underlying the effects of morphine on acute pain in healthy populations. They were informed that, among others, we expected to observe a significant decrease in their cardiovascular readings roughly 15 min after morphine injection.

First, the injection was performed by licensed study personnel who were wearing the local hospital official coat and badge. The personnel followed the hospital safety guideline before beginning the injection by asking participants about their medical history, allergies, medication intake and assessed their cardiovascular function for the first time. We ensured that the cardiovascular readings that participants saw on the device's screen were not their own, but a measurement that was preprogrammed to display readings which were in the upper norm (e.g., heart rate (HR) = 95 beats/min; Systolic Blood Pressure (SBP) = 138 mmHg; diastolic blood pressure (DBP) = 74 mmHg; *taken from* Rouby et al., 1981).

Obviously since we injected saline, the licensed personnel let each participant know that his/her results to the safety assessments were fine and that he could proceed with the injection. Beforehand, he warned the participant regarding the most common adverse events that can occur after injecting morphine (e.g., dizziness, drowsiness, sweating, low blood pressure and nausea; *see* Jamison et al., 1998). When the participant acknowledged the putative unpleasantness of receiving morphine, the study personnel told then participants that they were going to be injected with a dose of morphine of 3.5 mg which corresponded to half the dose that was routinely administered in a hospital setting. Moreover, he made sure to leave on the table a real morphine packaging in plain sight.

Then, after the injection of saline framed as morphine, the licensed personnel asked participants to remain seated and wait 15 min for morphine to reach its peak concentration. We carefully explained them that the choice of 15 min was grounded in the literature of morphine pharmacodynamics (*see for a review* Sverrisdóttir et al., 2015). During that time, we showed our participants a short documentary on anaesthesia in order to prime their verbally-induced expectations regarding morphine analgesic properties (https://youtu.be/UN4RNnIq7ds?t=699).

After 15 min, the licensed personnel assessed participants' cardiovascular function for the second time. We made sure that the readings displayed on the screen were lower than during the first measurement (e.g., HR = 88 beats/min; SBP = 119 mmHg; DBP = 65 mmHg; *taken from* Rouby et al., 1981). To do that, we preprogramed in advance a low measurement (performed on ourselves) that we again reloaded on the device's screen as soon as the second blood pressure measurement was done. Hence, the participants were not aware of their actual results and each of them saw the same blood pressure readings for the first and second measurements.

2.7 | Timeline

Estimation of the timeline for the completion of the study starting from the Stage 1 in-principle-acceptance (IPA) date can be found in Table 1. Stage 2 submission was estimated to occur at the end of February 2022.

2.8 | (Neuro-) physiological recordings and preprocessing

2.8.1 | Electroencephalography (EEG)

The EEG data was recorded at 1024 Hz using a 64 electrodes EEG Biosemi ActiveTwo® system referenced to

TABLE 1 Estimated timeline for the completion of the study since Stage 1 IPA

Months since IPA	+1	+2	+3	+4	+5	+6	+7	+8	+9	+10	+11	+12
Recruitment												
Testing												
Data Analysis												
Writing												
Stage 2 submission												

the common mode sense-driven right leg (CMS-DRL) ground (Biosemi, Amsterdam, Netherlands). Offline preprocessing and further statistical analyses were performed using custom MATLAB R2020b (MathWorks, Natick, Mass) scripts based on the EEGLab v2021.0 Toolbox (Delorme & Makeig, 2004) coupled with Cartool 3.91 (Brunet et al., 2011), Ragu (Koenig et al., 2011) and STEN 2.0 (developed by Jean-François Knebel and Michael Notter: https://doi.org/10.5281/zenodo.1164038).

2.8.2 | ERP preprocessing

We relied on a semi-automated MATLAB (MathWorks, Natick, Mass) toolbox, autoERP2.0 (Najberg & Wicht, 2021) relying on the EEGLab Toolbox (Delorme & Makeig, 2004). The pre-processing of the raw data was done accordingly:

- Re-referencing to Cz electrode and band-pass filtering (.5–40 Hz).
- Artifacts removal on continuous data with the EEGLab plugins, (i) CleanLine (sinusoidal, line noise frequencies removed: 50/100 Hz; *see* Mullen, 2012), (ii) Artifact Subspace Reconstruction (ASR: non-stationary signals > 10SD from mixing matrix calculated on a clean 'reference' section of the recording; *see* Mullen et al., 2015; Chang et al., 2018) and (iii) BLINKER with default settings (detection of eye blinks; *see* Kleifges et al., 2017).
- Epochs' segmentation time-locked to stimulus onset (100-ms pre- to 1000-ms post-stimulus onset; *see for similar parameters* Aslaksen et al., 2011).
- Baseline correction on the whole epoch window.
- Interpolation of bad channel(s) using multiquadric interpolation relying on radial basis functions (see Jäger, 2018; Jäger et al., 2016; Buhmann & Jäger, 2019). Electrodes were selected based on identification from the averaged ERPs.
- Epochs averaging for each participant and for the PreInject and PostInject phases separately.[5]
- Re-referencing to the common average reference.

[5]*We removed the step that excluded the four last trials of each block used for the VAS subjective pain ratings. Since we decreased the number of trials in each ERP from 48 to 24, rejecting four additional trials would result in a lower signal-to-noise ratio while these trials could safely be included in the ERP. The editorial approval for the deviation was obtained on 27 October 2021, after the commencement of data collection but prior to data analysis.*

2.8.3 | ERP analyses

After the ERP pre-processing, we determined the period of interest (POI) for the group-level analyses. The POI was defined based on the N2 and P2 ERP components on the group-averaged Global Field Power (GFP) waveform. GFP is a measure of the strength of electrical field potentials computed as the standard deviation of the mean voltage amplitude over all electrodes at a given time point (Michel & Murray, 2012). The GFP peak during the component-specific POI corresponds to the time point during each component with the highest signal-to-noise ratio (Michel & Murray, 2012). Each component was identified at the individual level based on the latency and topography of each GFP peak (i.e. GFP peak around 300 ms with vertex [fronto-central] negativity and 400 ms with vertex positivity, respectively for the N2 and P2 components; *see for reviews* Garcia-Larrea et al., 2003; Kakigi et al., 2004). Once the component was identified, the POI was determined as the component peak latency of the mean GFP ± 1SD of the individual GFP peaks. Then, the ERP was averaged for each participant separately over each component's POI. The scripts used to determine the POI are freely available following this address: https://github.com/CorentinWicht/GFPPeaks (Wicht, 2020). The resulting ERP topographic map were submitted to the GMD analysis. GMD indexes the differences in the underlying configuration of two distinct electric fields and is computed as the root mean square of the difference between the potentials measured at each electrode for the different experimental conditions normalized by instantaneous GFP (Brunet et al., 2011). Hence, GMD informs about distinct configuration of neural networks activated in each experimental condition. GMD was analysed with robust randomization statistics (*see* Habermann et al., 2018; Koenig et al., 2011) using 5,000 permutations per data point with an alpha threshold of $p < .05$ to estimate the significance of GMD differences.

The analysis of the GMD provides interpretative advantage over the analyses of local ERP waveforms since it takes into account the whole electrode montage and is reference-independent. Importantly, because GMD analyses are applied on strength-normalized electric field, we could rule out that any observed effect was confounded by quantitative variations in the response strength of the underlying generators.

2.8.4 | Cardiovascular readings

Cardiovascular readings (i.e., systolic (SBP) and DBP, HR) were performed (i) before the PreInject pain

induction phase and (ii) 15 min after the injection and before the PostInject pain induction phase (*see* Figure 2) to increase the credibility in our deceptive procedure (*see* Section 2.6.2), using an Omron M7 Intelli IT device (Omron Healthcare, Inc., Lake Forest, IL, USA).

2.9 | Data removal summary

We rejected trials if they met the following criteria:

2.9.1 | Behaviour (VAS)

- Intra-subject level behaviour:
  - To ensure a thorough filling of the VAS, trials with a RT shorter than 300 ms were excluded.
- Inter-subject level behaviour:
  - We used the median absolute deviation (MAD) to detect outliers participants (Leys et al., 2019), with default parameters (i.e. MAD range around the median of 1.4826).
  - After detecting outliers, if they were considered random (i.e. belonging to the distribution of interest) we left them in the dataset. If they were considered interesting outliers (i.e. influenced by an unknown moderator), we applied the Winsorization approach (Tukey & Mclaughlin, 1963; percentile observation $k = 5$) to avoid as much as possible rejecting data points that would have resulted in loss of power.

EEG:

- For ERPs, trials with (i) at least one time frame (TF) at one electrode with voltage ±80 μV (*see* Hartmann et al., 2016) or (ii) jump of more than 30 μV at one electrode from one TF to the next will be reject.

We removed the entire data of one participant if it met the following criteria:

- Behaviour[6]
  - Evidence of substantial computer errors (i.e., >80% of datapoints corrupted).
- EEG:
  - The minimum number of EEG trials for each task was lower than 16[7] trials for each to-be-averaged ERPs (*see* Boudewyn et al., 2018).

2.10 | Summary of statistical tests

The target alpha threshold for all statistical comparisons was set to 5% (see Table 2 for a list of contrasts).

For behavioural analyses, normality was assessed with the Shapiro–Wilks test together with the criteria of skewness and kurtosis within a ± 2 range for parametric analyses (Gravetter & Wallnau, 2013). In case of non-normality, we used equivalent non-parametric tests (i.e., Mann–Whitney U). Additionally, for all statistical tests, effect sizes were reported using Hedges' g_s *and* g_{av} (respectively for between- and within-subject designs, *see* Lakens, 2013).

For electrophysiological analyses (i.e., GMD), normality of data distribution was not assessed since we used non-parametric randomization statistics that are robust to asymmetrical distributions.

2.11 | Data availability

Coded study data, digital materials and analysis codes were uploaded to a public archive and can be downloaded at the following address: https://doi.org/10.5281/zenodo.6043795.

Additionally, the approved and published Stage 1 protocol can be downloaded at the following address: https://doi.org/10.5281/zenodo.4541048.

3 | RESULTS

Averages in the results section are reported as mean ± SD for parametric tests and as median/IQR for non-parametric tests.

3.1 | Study population

We recruited 75 participants, of whom (i) 2 were excluded at the beginning of the session based on inclusion/exclusion criteria and (ii) 3 were excluded from the analyses to comply with the quality checks (Figure 3). Our final sample was composed of 70 participants (65.7% females) aged 23.7 ± 5.2 years (see Figures S1 and S2).

[6] *In relation to the adjustments implemented in the Sanity Checks section (*i.e.*, further discussed in the emails exchange of the 19.11.2021), the second criterion was here removed. Since we are already controlling for the occurrence of the placebo effect in the sanity check, it was unnecessary to repeat it in this section.*

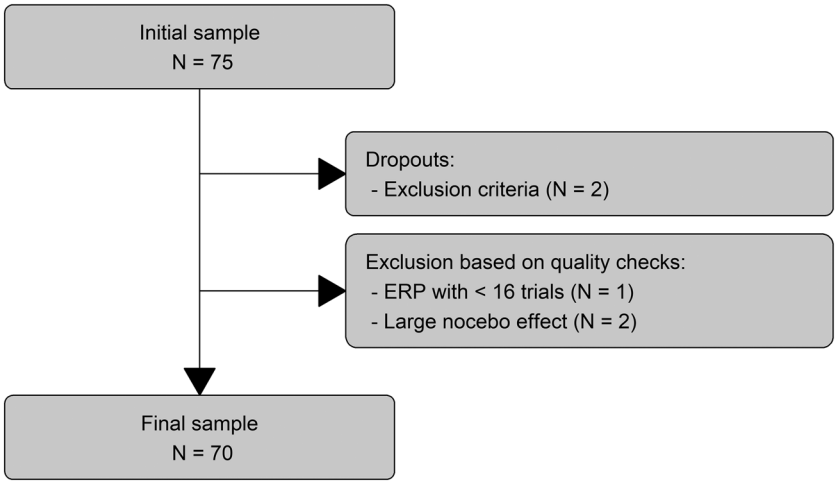
[7] *Since we decreased the number of trials in each ERP from 48 to 24 (*i.e.*, emails exchange of 27 October 2021), we adjusted this criterion.*

TABLE 2 Summary table of all statistical tests

			Dependent variable	
Hypotheses	**Statistical test**	**Contrast**	**Behaviour**	**Physiology**
Main contrast of interest				
PBO morphine effect	Independent-samples *t* test[a]	CondExp ≠[b] UncondExp		PostInject POI-averaged GMD values separately for: • N2 • P2

Note: GMD = Global Map Dissimilarity; PBO = Placebo; PostInject = Post-injection phase; VAS = Visual Analogue Score.
[a]One-sided test.
[b]The GMD index is not directional since it is a difference score between the two groups.

FIGURE 3 Study flow diagram



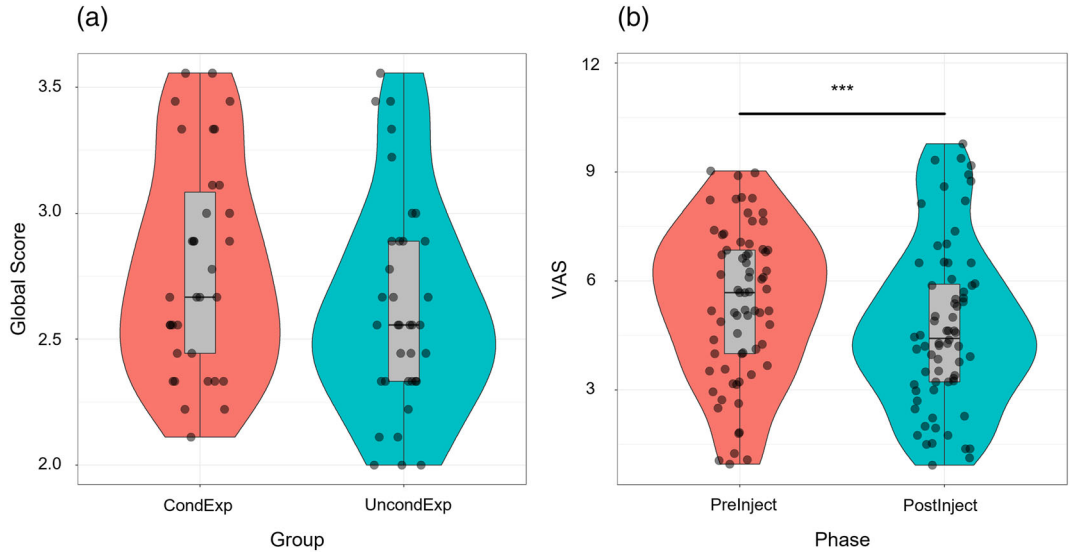


FIGURE 4 (a) Verbal expectations as measured with the morphine analgesia expectations questionnaire (MAExpQ) questionnaire averaged across groups. (b) Visual analogue scale (VAS) pain estimates averaged across phases. CondExp = Conditioned Expectations group; PreInject = pre-injection phase; PostInject = post-injection phase; UncondExp = Unconditioned Expectations group. *** = $p < .001$

The local ethics committee (*Commission cantonale d'éthique de la recherche sur l'être humain*, CER-VD) approved the protocol (#2021-00359). All recruited participants provided written informed consent prior to inclusion. They were all compensated for their participation.

3.2 | Sanity checks

Both sanity checks were validated (*see* Section 2.4.5): First, the groups difference in positive verbally-induced expectations of morphine analgesia was smaller than our criteria of $g_s < .4$ (actual difference of $g_s = .370$, Table S3 and Figure 4a). Second, we ensured that our intervention induced a PA of minimum $g_{av} \geq .5$ (actual PA of $g_{av} = .552$). To satisfy the second criteria, we had to replace four participants to ensure that a placebo effect indeed occurred after the injection (Table S4 and Figure 4b).

3.3 | Data removal

According to the rejection criteria in the Data Removal Summary section, no outliers were identified at the behavioural level. Regarding the EEG data, one participant (P1) was excluded for having <16 trials in one of the ERP. After its exclusion, we completed the sample so that each group included at least 33 participants, which corresponded to our minimum sample size (*see* Section 2.2.1).

TABLE 3 Group averages and SD of individual GFP peak, in milliseconds

Component	Group	Peak	SD
N2	UncondExp	456.86	40.01
	CondExp	450.47	51.66
	Overall	453.75	45.82
P2	UncondExp	589.45	50.42
	CondExp	585.06	43.30
	Overall	587.32	46.81

Note: GFP = Global Field Power; SD=Standard Deviation.

3.4 | ERPs results

As specified in the ERP analyses section, the Period of Interest (POI) for each of the investigated ERP component was determined as the average of individual GFP peaks ±1SD for each group (Table 3). While the N2 and P2 components were expected to occur respectively 200–400 and 300–500 ms post-stimulus onset (Bromm & Treede, 1987), they actually manifested in the 408- to 500- and 541- to 634-ms intervals (Figures S10 and S11).

3.5 | GMD

The GMD analyses did not confirm our hypothesis: we did not find evidence that participants with prior experience with opioids (i.e., CondExp group) recruit different brain networks during placebo analgesia compared to individuals without prior experience with opioids (i.e., UncondExp group) both during the N2 ($p = 0.951$, .61% explained variance, Figure 5a,b) and the P2 time windows, ($p = .605$, 1.07% explained variance, Figure 5c, d). Moreover, we computed the spatial correlation index to determine how strongly correlated the scalp topographies of the two groups were, separately for each component. As such, the two groups topographical maps were

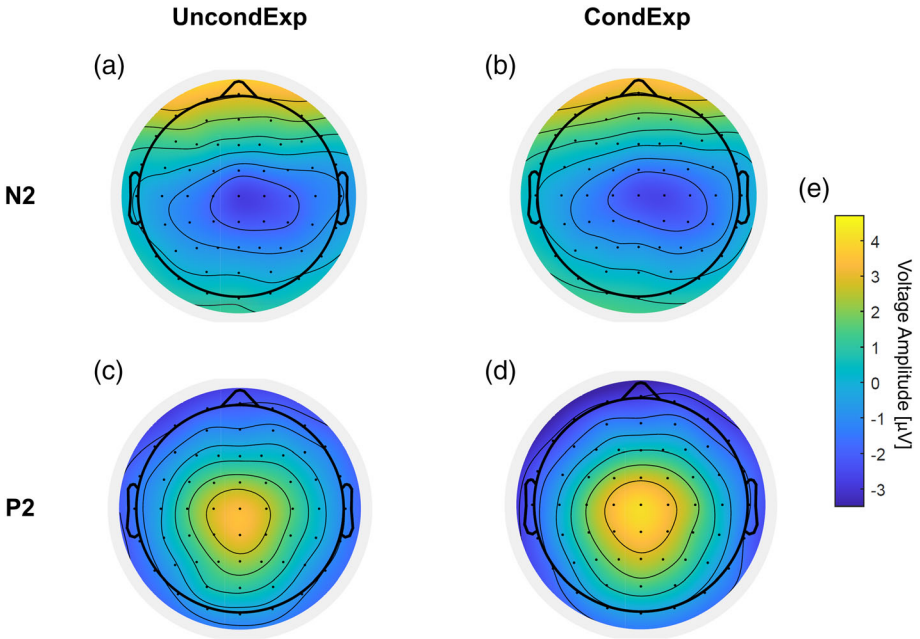


FIGURE 5 (a–d) topographical representations of voltage amplitudes (in μV) across groups (UncondExp and CondExp) and period of interest (POI) for each component of interests (N2 and P2). (e) Colour scale that was used to display the four topographies

strongly correlated both for the N2 ($r = .99$) and P2 ($r = .99$) components further supporting the assertion that the recruited brain networks were not different between groups.

3.6 | Exploratory findings

We conducted an exploratory GMD analysis using Ragu (Koenig et al., 2011) on the whole time-period to determine whether the ERP topographic group differences that we expected manifested outside our N2 and P2 POI or during short time periods.

We found two period of significant topographic modulations, namely 386 to 398 ms ($p = .035$, 3.02% explained variance) and 825 to 852 ms after the stimulus onset ($p = .022$, 3.5% explained variance; Figures 6a and 6c–g). The first significant period fell into the N2 time-window (Garcia-Larrea et al., 2003; Kakigi et al., 2004). The second significant period manifested during the

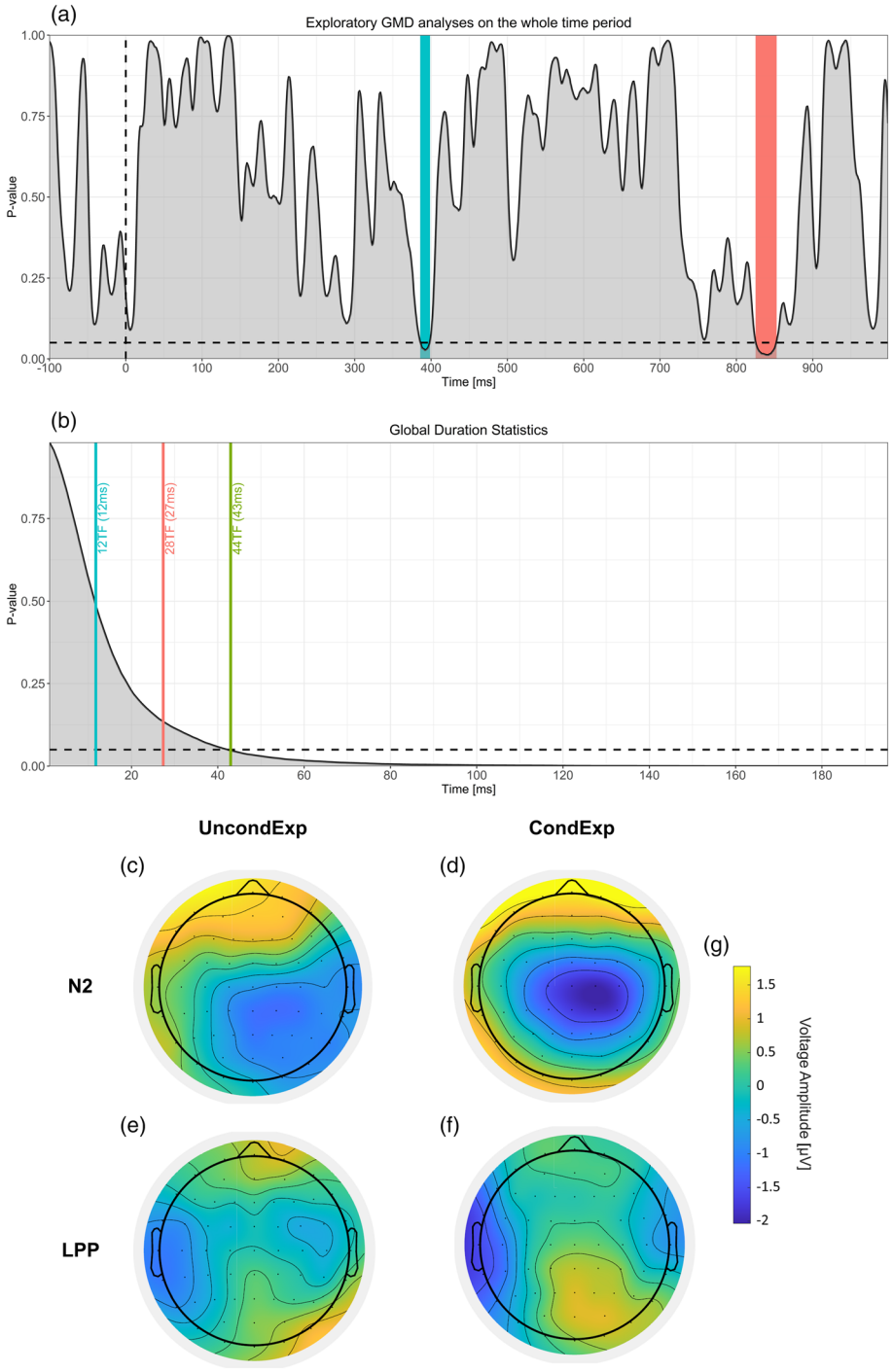


FIGURE 6 (a) *P* values of the Global Map Dissimilarity (GMD) differences between groups over time. The blue rectangle corresponds to the first significant time-period (N2) and the red one to the second (LPP). The dashed vertical line represents the stimulus onset. (b) *P* values of the global duration statistics over time. The vertical solid lines represent the length of each significant time-periods, namely 12 ms for N2 (blue), 27 ms for LPP (red) as well as the minimum duration needed to reach the 5% alpha level (43 ms in green). The *x* axis was shortened to improve visualization. (a,b) The dashed horizontal lines represent the 5% alpha level. (c–f) Topographical representations of voltage amplitudes (in µV) across groups (UncondExp and CondExp) and for the two significant time-periods (N2 and LPP). (g) Colour scale that was used to display the four topographies

centro-parietal late positive potential (LPP) component (usually 400- to 800-ms post-stimulus onset; Garland et al., 2015).

We additionally ran global duration statistics on the whole recording to identify the probability that for a N ms contiguous time-period of significant topographic modulation to occur under the null hypothesis (Figure 6b). We found that a minimum of 44 contiguous timeframes (i.e., ~43 ms) would have been required to reach a false positive rate of less than 5% (i.e., alpha level of $p < .05$). In our case, the first significant time-period lasted 12 ms while the second lasted 27 ms which corresponded to false positive rates of 48.59% and 13.48%, respectively. These short-lasting topographic modulations should thus be interpreted with much caution.

4 | DISCUSSION

The aim of the study was to test whether different types of morphine-related expectations would be supported by distinct brain networks during placebo analgesia (PA): We compared PA and the related electrophysiological activity between individuals with (CondExp group) vs without prior experience with morphine (UncondExp group) after being injected with a saline solution framed as being morphine. We posited that different brain networks would be recruited between the two groups over N2 and/or P2 ERP components after heat-pain stimulations. To test this hypothesis, we compared the ERP topography between the two groups. Topographic modulations indeed necessarily follow from alterations in the configuration of underlying brain generators (Murray et al., 2008; Tzovara et al., 2012).

Our positive control ensured that morphine analgesia was similar in the two groups ($g_s = .37$) and that PA indeed occurred following our sham morphine intervention ($g_{av} = .55$). In this context, however, our study could not contradict the assumption according to which ERP topographies are similar between the CondExp and UncondExp groups at the PostInject phase, neither during the N2 nor the P2 component. In the context of verbally-induced analgesia expectations, we did not find sufficient evidence to support the idea that prior conditioning to opioids leads to the recruitment of different brain networks to produce PA.

Assuming that our ERP analyses are sensitive to the differential recruitment of the dopaminergic and opioid systems, this finding is surprising since previous literature suggested that conditioned PA are supported by striatal regions of the dopaminergic reward system while the opioid system mainly underlie unconditioned PA (see for reviews de la Fuente-Fernández, 2009; Peciña et al., 2014; Okusogu & Colloca, 2019).

The absence of ERP topography effects on N2 and P2 components possibly originates from the fact that individuals in the CondExp group may have acquired expectations at first through verbal suggestions and then through conditioning, which may have led to a dominance of the former type of expectation in determining the underlying brain mechanisms. In a recent paper, Bajcar et al. (2021) indeed demonstrated that when verbal suggestions and classical conditioning coexist, the order of acquisition influences PA, with larger PA when verbal suggestions precede conditioning. Most importantly, Bajcar et al. (2021) have also found that when expectations were incongruent between verbal suggestions and conditioning, the magnitude of PA was in line with the direction of the last-used procedure. Since in clinical settings the experience of pain relief may precede suggestions provided by clinicians and follow from past positive and/or negative experiences, we cannot rule out that the order in which expectations were acquired, as well as their level of congruency, may have biased PA effects at neural level specifically in the CondExp group.

Additionally, whereas we formulated our hypothesis based on findings that conditioned and unconditioned expectations may recruit different neural networks to trigger PA (Carlino et al., 2015; Colloca et al., 2009), our study differs from this previous literature on several aspects. First, these studies focused on ERP components voltage amplitude of one electrode (Cz) that may reflect changes in ERP topography or changes in the global power of the ERP field. Since global field power modulations do not imply a modification in the configuration of the underlying neural generators (Murray et al., 2008; Tzovara et al., 2012), such metrics could not help testing our hypothesis and was thus ignored in the present study. In contrast, we focused on an index of topographic modulation insensitive to purely quantitative changes in field strength but able to detect modification of brain network configurations (Brunet et al., 2011). Second, the small sample sizes in previous studies (12–17 participants/group in Colloca et al., 2009; Carlino et al., 2015) may have resulted in overinflated effect size estimates and higher false positives/negatives rate (Button et al., 2013; Lakens, 2013; Schäfer & Schwarz, 2019). Since we estimated a sample size enabling to reach a 90% power to detect a medium effect size with a 5% α level, our results can be confidently interpreted as indicating that the effects of prior conditioning on the brain networks underlying placebo analgesia in the context of expectations is either

nonexistent or small. Of note, other neuroimaging techniques such as source estimations (Burle et al., 2015) or fMRI may have revealed brain network effects of prior conditioning that we could not detect with analyses of the field potential topography. Finally, the Colloca et al. (2009) and Carlino et al. (2015) experiments focused on laser-evoked potentials (LEPs), whereas we relied on contact heat evoked potentials (CHEPs). LEPs have been shown to be of shorter latency and of larger amplitude than CHEPs (De Schoenmacker et al., 2021). Together with the fact that each ERP only comprised on average 23.7 ± .8 trials, the use of CHEPs may have led to a signal-to-noise ratio too small to detect small topographic modulations. Further experiments relying on CHEPs may consider increasing the number of trials to compensate for smaller signal-to-noise ratio and reduced evoked amplitudes level.

5 | EXPLORATORY

We conducted exploratory ERP topography analyses over the whole ERP time-period to determine whether we may have failed to detect the true effect because of too large or inappropriate periods of interest. We observed two periods of significant topographic differences between groups, namely 386–398 and 825–852 ms post-stimulus onset. While the first period of significance falls right into the N2 component time-window described in the literature (Garcia-Larrea et al., 2003; Kakigi et al., 2004), it occurred slightly earlier than the POI we found (i.e., 408–500 ms; see Section 3.5). Regarding the second significant period, it is most likely related to the late segment of the late positive potential (LPP) component that Wang et al. (2020) hypothesized to index processes such as evaluation, memory and affect regulation (Zheng et al., 2019). Yet, based on the results of the global duration statistics, such short-lasting significant time-period (respectively 12 and 27 ms) should rather be considered as false positives than as potential indicators of true effects.

6 | CONCLUSIONS AND FUTURE DIRECTIONS

Our results do not confirm the hypothesis that different types of expectations depend on distinct PA-related brain networks. Future studies may control the order of acquisition and congruency of different types of expectations. Additionally, they may benefit from investigating the role that emotional arousal and associated brain areas play in mediating PA.

In sum, expectations formed through verbal suggestions or conditioning likely produce PA via corresponding brain network.

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CONFLICT OF INTEREST

All authors have declared no conflict of interest.

AUTHORS CONTRIBUTION

Wicht, Corentin Aurèle: Conceptualization, Methodology, Software, Formal Analysis, Investigation, Data Curation, Writing-Original Draft, Visualization, Funding Acquisition. **Mouthon Michael:** Data Collection, Methodology, Writing-Review & Editing. **Joelle Nsimire Chabwine**: Conceptualization, Methodology, Writing-Review & Editing. **Gaab, Jens**: Conceptualization, Methodology, Writing-Review & Editing. **Spierer, Lucas**: Conceptualization, Methodology, Resources, Writing-Review & Editing, Supervision, Project Administration, Funding Acquisition.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available In Zenodo at https://doi.org/10.5281/zenodo.6043795.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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Clinical Trial Unit (University of Bern, CH)
Clinical Data Manager (20-80%)

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Fribourg Canton Hospital, CH (HFR)
Research assistant in the Stroke Unit (10-20%)

11/2017 - 09/2018
University of Lausanne, CH & Swiss Federal Institute of Technology (EPFL), Lausanne, CH (Prof. Christine Mohr)
Graduate assistant at the Psychology Institute (90%) & teaching assistant for the seminar « Experimental Cognitive Psychology »

04/2017 - 05/2017
University of Fribourg, CH (PD Dr. Eric Schmidlin)
Teaching assistant for the seminar « Travaux pratiques de physiologie »

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Research assistant at the Neurology Unit (80%)

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Master in Cognitive Neurosciences (*insigni cum laude*)
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SCIENTIFIC PUBLICATIONS

- Predictors for returning to paid employment after transient ischemic attack and minor ischemic stroke, *in prep*.
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- Beta Electroencephalographic Oscillation Is a Potential GABAergic Biomarker of Chronic Peripheral Neuropathic Pain (2021), *Frontiers in Neuroscience*.
- Acute alcohol intoxication and expectations reshape the spatiotemporal functional architecture of executive control (2020), *Neuroimage*.
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Declaration of honor

I herewith confirm that I have written the present PhD thesis myself and that the thesis contains personal research carried out without illicit help. All references have been clearly stated.