Dynamics of attention and arousal in healthy and migraine populations

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Dynamiques de l'attention et de l'éveil chez les populations saine et migraineuse

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Résumé

L'attention est la fonction cérébrale qui nous permet de sélectionner et traiter préférentiellement les informations pertinentes de notre environnement. Elle repose sur un équilibre entre des processus volontaires et involontaires et est conditionnée par le niveau général d'éveil. De fait, des sons saillants dans notre environnement peuvent à la fois nous gêner dans une tâche en capturant notre attention ou nous rendre plus performants en déclenchant une augmentation transitoire d'éveil. Les processus attentionnels sont perturbés dans de nombreuses maladies neurologiques et psychiatriques. La migraine est une maladie neurologique qui, au delà des maux de tête sévères et réguliers, est caractérisée par une hypersensibilité sensorielle qui est maximale pendant les crises mais persiste de manière atténuée le reste du temps. Des résultats récents suggèrent que le traitement attentionnel des informations sensorielles est dysfonctionnel dans la migraine: un filtre attentionnel défaillant pourrait participer aux symptômes sensoriels observés dans la migraine. Le but de cette thèse a été rendu possible en partie grâce à des enregistrements MEG et EEG pendant une tâche d'attention compétitive permettant une évaluation conjointe de l'attention volontaire, de l'attention involontaire et de l'augmentation phasique de l'éveil. En premier lieu, nous avons cherché à isoler un marqueur électrophysiologique de l'augmentation phasique de l'éveil provoquée par l'irruption de sons saillants chez des participants sains. L'*early-P3*, un potentiel évoqué classiquement associé à la capture de l'attention, s'est révélé un bon candidat en tant que marqueur de l'éveil phasique. Dans un second temps, nous avons démontré que la migraine était associée à une altération du traitement attentionnel des sons, notamment au niveau de l'attention involontaire et des processus volontaires d'inhibition. Ces résultats ont été corroborés par une étude via questionnaires qui a révélé que les migraineux se plaignent de difficultés attentionnelles dans la vie quotidienne et que ces difficultés corrèlent avec la gêne sensorielle qu'ils ressentent. Dans un troisième temps, nous avons tenté de détecter des anomalies de la structure cérébrale dans la migraine grâce à des données d'IRM anatomique et d'imagerie du tenseur de diffusion, que nous avons confrontés aux résultats préalables de la littérature. Ni l'analyse de nos données anatomiques, ni la méta-analyse de la littérature n'a confirmé d'atteintes anatomiques dans la migraine. Ces travaux de thèse ouvrent de nouvelles pistes dans la compréhension des symptômes sensoriels dans la migraine et en parallèle offrent un nouvel outil pour étudier l'éveil phasique.

Mots-clés Attention volontaire, Attention involontaire, Migraine, Alerte phasique, Electroencéphalographie, Magnétoencéphalographie, Imagerie par résonance magnétique, Imagerie du tenseur de diffusion

Abstract

Attention is the cognitive ability which allows us to select and preferentially process relevant information in our environment. It relies on a balance between top-down and bottom-up processes and is heavily influenced by the ongoing arousal levels. Thereby, salient sounds in our environment can both hinder our performance during a task by capturing our attention or on the contrary boost our performance by triggering a transient increase in arousal. Attentional mechanisms are disturbed in numerous neurological and psychiatric disorder. Migraine is a neurological disorder which is not limited to recurrent and severe headaches: it is also characterized by sensory hypersensitivity which climaxes during migraine attack but also persists at a lower level in the pain-free period. Recent studies suggest that the attentional process of sensory inputs is dysfunctional in migraine: a deficient attentional filter may participate to sensory symptoms associated with the disorder. The aim of this work was made possible in part thanks to MEG and EEG recordings during a competitive attention task designed to evaluate conjointly voluntary attention, involuntary attention and phasic arousal. First, we attempted to isolate an electrophysiological marker of phasic increases in arousal triggered by the onset of salient sounds among healthy participants. The *early-P3*, an event-related response classically associated to attention capture, turned out to be a good candidate as a marker of phasic arousal. Then, we demonstrated that migraineurs presented a disrupted attentional processing of sounds, namely at the level of bottom-up attention and top-down inhibitory processes. These results were corroborated by a questionnaire study which revealed that migraineurs complain about attention difficulties in the everyday life and that these difficulties correlate with the sensory disturbances they experience. Finally, we aimed to detect anomalies of brain structure in migraine by analyzing newly acquired anatomical MRI and diffusion tensor imaging data, which we confronted to previous results of the literature. Neither the analysis of our anatomical data, nor the meta-analysis of the literature provided convincing evidence of an abnormal brain structure in migraine. This work provides new insights in the understanding of sensory symptoms in migraine and in parallel, offers a new tool to investigate phasic arousal.

Keywords Top-down attention, Bottom-up attention, Migraine, Phasic arousal, Electroencephalography, Magnetoencephalography, Anatomical magnetic resonance imaging, Diffusion tensor imaging

Résumé substantiel

La migraine est une maladie neurologique particulièrement prévalente dans la population adulte. Si la migraine est communément perçue comme limitée aux seuls maux de tête réguliers, elle est aussi associée à des troubles sensoriels caractéristiques. Pendant les crises de migraine se développe une hypersensibilité multimodale si bien que la lumière, le bruit, les odeurs et le toucher sont perçus comme extrêmement intenses et amplifient les maux de tête. Cette hypersensibilité s'atténue une fois la crise passée mais persiste à un niveau moins élevé. Des travaux récents suggèrent que la migraine serait associée à des perturbations du traitement attentionnel des stimuli de l'environnement. Il est possible que ces dysfonctionnements attentionnels participent aux symptômes sensoriels de la migraine. Cependant leur caractérisation dans la littérature est encore incomplète et le lien entre attention et hypersensibilité dans la migraine reste purement hypothétique.

L'environnement dans lequel nous vivons est saturé de sources d'informations mais nos ressources cérébrales sont limitées et incapables de toutes les traiter de manière efficace. L'attention est le processus cognitif qui nous permet de sélectionner les informations pertinentes de notre environnement afin de favoriser leur traitement. L'orientation de l'attention est guidée à la fois par des processus volontaires et involontaires. L'attention volontaire (ou endogène) est dirigée de manière contrôlée vers un but identifié et agit en facilitant le traitement des sources de stimuli pertinents tout en inhibant les autres sources de stimuli. L'attention involontaire (ou exogène) est un processus plus automatique et réflexe qui rend possible la capture de l'attention par un évènement extérieur afin d'évaluer s'il nécessite une réponse comportementale. L'équilibre entre les processus attentionnels volontaire et involontaire est crucial afin d'être efficace dans nos tâches du quotidien tout en restant réactif à notre environnement mais sans être perpétuellement distrait. Cependant, cet équilibre et l'efficacité de nos processus attentionnels en général est intrinsèquement lié à notre état d'éveil (aussi désigné sous le nom d'alerte). Si les processus attentionnels ont pour rôle l'allocation adéquate des ressources cognitives durant une tâche, le niveau d'alerte conditionne la quantité totale de ressources disponibles. Ce niveau d'alerte peut être modulé de manière tonique de part notre engagement dans une tâche mais aussi de manière phasique et transitoire, déclenché par des évènements saillants dans notre environnement. L'interaction entre attention et alerte est complexe comme l'illustrent les effets contradictoires des sons distracteurs dans les tâches attentionnelles. Selon la tâche utilisée, ils peuvent résulter en une détérioration des performances via la capture de l'attention du participant ou en une amélioration des performances via potentiellement une augmentation phasique du niveau d'alerte.

Le travail de thèse suivant a pour objectif de répondre aux questions suivantes qui formeront les trois axes de ce manuscrit. (1) Peut-on isoler un marqueur électrophysiologique de l'augmentation phasique d'alerte suivant un son saillant? (2) Est-ce que la migraine est associée à des difficultés attentionnelles? Si oui, quels mécanismes attentionnels seraient perturbés? (3) Est-ce que la migraine est associée a des anomalies anatomiques cérébrales? Si oui, est-ce que ces anomalies peuvent être liées aux symptômes sensoriels et à des possibles difficultés attentionnelles?

Afin de répondre à ces questions, des données EEG et MEG ont été acquises pendant que des participants sains et migraineux réalisaient la Tâche d'Attention Compétitive. Ce paradigme a été développé afin de produire des mesures comportementales et électrophysiologiques de l'attention volontaire, de l'attention involontaire et de l'alerte phasique et d'évaluer comment ces processus interagissent entre eux. Dans un premier temps, nous avons pu démontrer que l'early-P3, un potentiel évoqué produit par les sons distracteurs et que la littérature associait jusque là à l'attention involontaire, était un bon candidat comme marqueur de l'alerte phasique. Dans un second temps, nous avons démontré que, malgré des performances comportementales similaires dans nos deux groupes, des marqueurs électrophysiologiques (tant au niveau des potentiels évoqués que des activités oscillatoires) de l'attention volontaire et involontaire étaient perturbés chez nos participants migraineux, suggérant un défaut d'inhibition des informations non-pertinentes dans la migraine. Une étude via questionnaires a confirmé que les migraineux se plaignent de difficultés attentionnelles accrues comparés au reste de la population et que ces difficultés corrèlent avec la gêne sensorielle qu'ils subissent en dehors des crises. Dans un dernier temps, nous avons analysé des données d'IRM anatomique et d'imagerie du tenseur de diffusion (DTI) acquises en parallèle des données EEG et MEG. Aucune différence notable au niveau des volumes de matière grise, des volumes de matière blanche et de l'intégrité des faisceaux de matière blanche n'a pu être détecté. Cela a été confirmé par une revue systématique de la littérature à propos de l'anatomie cérébrale dans la migraine et une méta-analyse des résultats. Si une portion significative d'études rapportent des altérations de la structure cérébrale dans la migraine, les résultats ne convergent pas de manière convaincante ce qui suggère que l'anatomie du cerveau migraineux est inchangée.

Ce travail de thèse offre une meilleure compréhension du traitement attentionnel des informations sensorielles dans la migraine et ouvre un nouveau point de vue sur les symptômes sensoriels associés. Ce travail a aussi permis d'identifier un marqueur de l'alerte phasique chez les adultes sains, un résultat qui pourra devenir un outil aidant à une meilleure compréhension du rôle de l'alerte phasique dans les troubles neurologiques, neuro-développementaux et psychiatriques.

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List of acronyms

ADHD Attention-Deficit with Hyperactivity Disorder

BA Brodmann Area

CAT Competitive Attention Test

CGRP Calcitonin Gene Related Peptide

CNV Contingent Negative Variation

CON Cingulo-opercular network

CSD Cortical Spreading Depression

DAN Dorsal Attention Network

DTI Diffusion Tensor Imaging

EEG Electroencephalography

ERF Event-related fields

ERP Event-related potentials

ICHD International Classification of Headache Disorders

IDAP Intensity-dependence of auditory potentials

LC-NE Locus cœruleus – Norepinephrine

MEG Magnetoencephalography

(f)MRI (functional) Magnetic Resonance Imaging

Nd Negative difference

OR Orienting Response

PET Positron Emission Tomography

RON Reorienting Negativity

RT Reaction time

SBM Surface-based morphometry

STN Spinal trigeminal nuclei

TBSS Tract-Based Spatial Statistics

(r)TPJ (right) Temporo-parietal junction

VAN Ventral Attention Network

VBM Voxel-based morphometry

Part I

Theoretical framework

Figure 1: *"Travail interrompu", oil painting by William-Aldolphe Bouguereau (French, 1825-1905). A young woman from Ancient Greece is distracted from her tedious task of winding balls of wool. Her mind is wandering as Cupid anoints her with perfume and inoculates ideas of love.*

1 Auditory attention in humans

Cocktail parties were apparently very prevalent in the life of early researchers investigating attention, to the point that the "cocktail party effect" was one of the most discussed phenomenon in auditory attention research for decades (Pollack and Pickett 1957). Let's choose a more contemporary example of the role of attention in the everyday life. Imagine you are at a table in a bar with friends. You are surrounded by multiple sources of sounds: your friends are talking, other groups of people are talking in neighboring tables, loud music is played on the speakers, the fan is thrumming behind you, random noises happen from time to time: doors closing, glasses tinkling, people cheering, klaxons in the street nearby... It is impossible to make sense of all these sounds at the same time, you cannot understand what your friends are saying while also understanding the conversation at the neighbor table and deciphering the lyrics of the pop song played at the same moment. You can only focus on the source you deem relevant and all other events will be ignored, or at least not perceived with the same clarity. Cognitive resources are not boundless and it is not possible to fully process every simultaneous sources in our environment. Attention can be defined the cognitive process of selectively attend to relevant aspects of the environment. Attention is classically divided in several, sometimes overlapping, sub-processes. You can simply direct your attention to your friends' voices in order to have a clear understanding of the conversation: this is *attention orienting*. Voices from the neighboring table may be so overbearing that you need to tune them out and give priority to your friends' voices: this is *selective attention*. You may want to read a message on your phone while still following the conversation, attending to two sensory sources simultaneously: this is *divided attention*. The conversation may last a long time but you still want to keep listening: attending to one source over an extended period of time is *sustained attention*. Finally, attention can be oriented in two diametric fashions. You may decide to consciously orient your attention to yours friends' voice: voluntary, goal-directed attention is usually referred as *top-down attention*. However, a friend at the other side of the room may shout your name and even if you were not attending to their voice or this side of the room, it can still capture your attention as it may be an important situation: involuntary, stimulus-driven attention is usually referred as *bottom-up attention.*

In the rest of the chapter, I will first describe the basics of auditory perception. Then, I will discuss how attention can be oriented, which are the neural correlates of attention orienting and which electrophysiological markers are useful for the investigation of attention orienting.

1.1 Introduction to auditory perception

Perception is the act of representing and understanding our environment and auditory perception (or hearing) is the specific ability to perceive sounds. Auditory perception is not limited to the passive reception of auditory signals, it involves the organization, identification and interpretation of the sensory inputs. In this section, I will briefly discuss the basic mechanisms underlying auditory perception.

1.1.1 What is a sound?

Hearing is one of the five traditional senses and is defined as the perception of sounds, oscillatory pressure waves propagating through the ambient air. Humans are able to perceive sounds in the 20-20,000 Hz frequency range and they can identify and interpret them based on their acoustic properties, i.e. the temporal and spectral characteristics of the sound wave (Zwicker and Fastl 2013). The field of psycho-acoustics is dedicated to the understanding of the relationship between the physical aspects of a sound and how it is perceived by the listener. Commonly discussed properties of sounds include (American National Standard 2013):

- *Pitch:* Pitch is the "auditory attribute of sound according to which sounds can be ordered on a scale from low to high". It is closely and intrinsically associated with the frequency content of the sound: high-pitched sounds correspond to high frequencies, low-pitched sounds correspond to low frequencies. It is measured in Hertz (Hz).

- *Duration:* Duration is the "attribute of sound according to which sounds can be considered long or short". The perceived duration of a sound is usually proportional to the actual duration of the sound wave (Efron 1970).

- *Loudness:* Loudness is "the attribute of auditory sensation in terms of which sounds can be ordered on a scale extending from quiet to loud". It is linked to the sound pressure level and is measured in decibels (dB).

- *Timbre:* Timbre is the "attribute of auditory sensation which enables a listener to judge that two nonidentical sounds, similarly presented and having the same loudness and pitch, are dissimilar". It enables the listener to differentiate sources of sound production (a violin versus a piano for example) and gives the "color" to a sound. Attributes of timbre are quite elusive but include amplitude and frequency modulations or the spectral envelope.

- *Spatial localization:* It is the perceived origin of a sound in direction and distance.

1.1.2 Architecture of the auditory system

This paragraph is based on the Handbook of Clinical Neurology (Pickles 2015). Here I will provide a succinct and simplified description the anatomy of the auditory pathways (Figure 2).

- The transduction of acoustic waves into a neuronal signal takes place in the cochlea. Inside the cochlea, the basilar membrane contains the organ of Corti in which are present the sensory hair cells. Based on their location on the basilar membrane, sensory hair cells respond to a specific sound frequency (tonopic organization). Their role is to transduce the mechanical wave into electrical currents by extracting the sound energy and its frequency signature. The neuronal output is then transferred to the auditory nerve.

- The information is then relayed to the central nervous system through multiple parallel pathways. The auditory nerve fibers project onto the ipsilateral cochlear nucleus in the brainstem. The ventral part of the cochlear nucleus projects onto the ipsi- and controlateral superior olivary complex. In this structure, the spatial location of the sound is evaluated through the relative difference in intensity and latency from the inputs of each ear. The dorsal part of the cochlear nucleus and the superior olivary complex project onto the inferior leminiscus and then to the colliculus.

- From the colliculus, three ascending pathways lead to the cortex through thalamic nuclei. A tonotopic ascending pathway reaches the primary auditory cortex. A polysensory pathway, which combines auditory information to somesthetic information, and a diffuse non-tonotopic pathway both reach associative auditory cortical areas.

- The auditory cortex comprised a primary auditory cortex and associative areas. The primary auditory cortex (A1), located in the Heschl's gyrus and corresponding to the Brodmann's area 41, has a tonotopic structure in which neighboring neurons respond to neighboring frequency. The primary auditory cortex preferentially responds to pure sounds and is responsible for basic and advanced spatio-frequential analysis of auditory inputs. Associative auditory regions are located in and beyond the Heschl's gyrus, in the planum temporale, planum polare and the superior temporal gyrus and correspond to the Brodmann area 42 and 22 (partially). They are closely connected to the primary auditory cortex and respond preferentially to complex sounds.

- Corticofugal feedback efferent systems at all levels of the auditory pathway (associative areas, primary auditory cortex, thalamus, brainstem nuclei and even at the level of the

cochlea) have been described and participate to the modulation of auditory perception, intervening notably in attention processing, noise reduction, improvement of sound discrimination, etc.

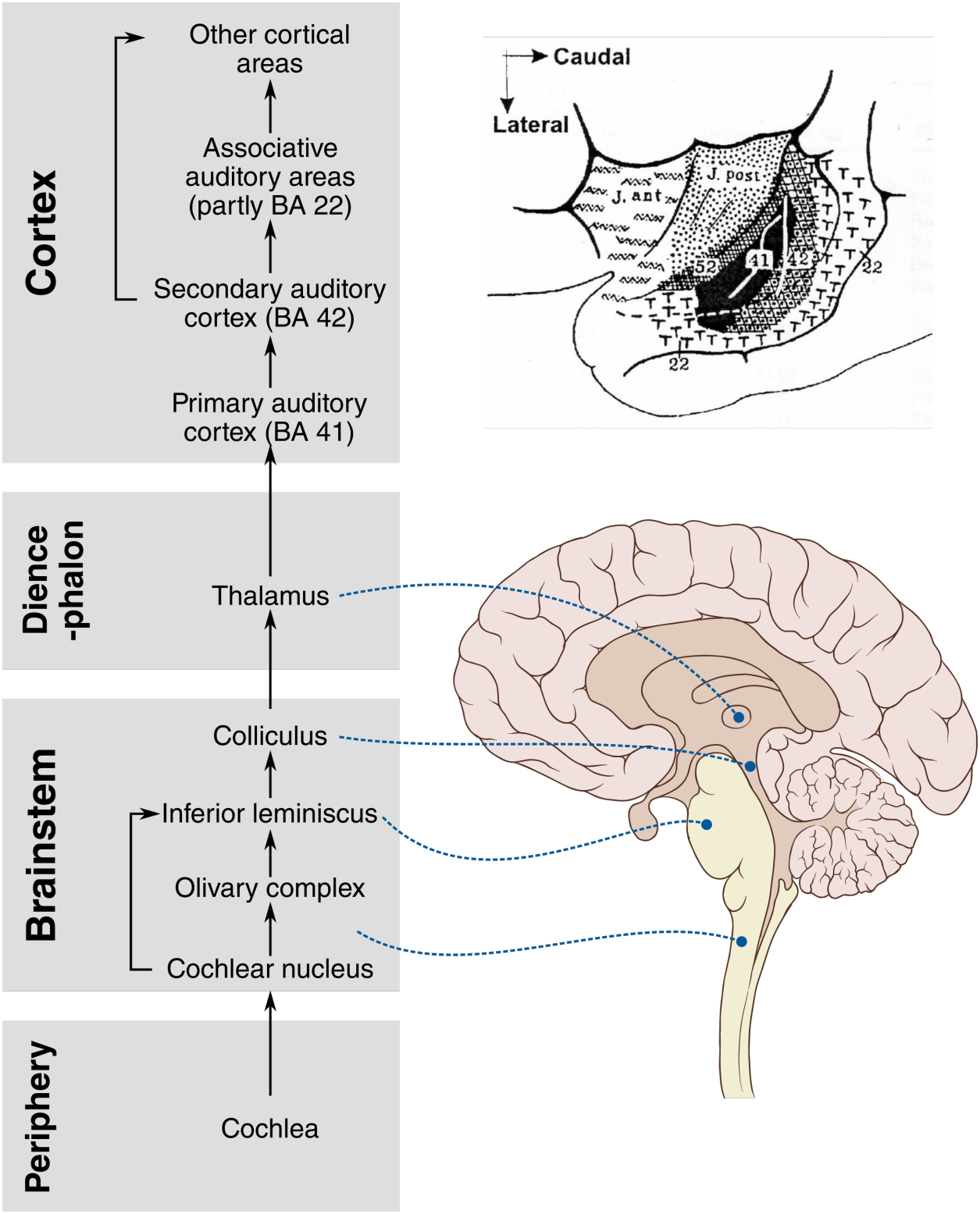


Figure 2: *Anatomy of the auditory pathways. BA: Brodmann area*

1.2 Neuropsychological models of attention

> Une seule pensée nous occupe, nous ne pouvons penser à deux choses à la fois. – Blaise Pascal, Pensées (1670)

1.2.1 Selective attention

Selective attention can be defined as giving priority to one stimulus over another. Research about selective auditory attention became a central topic in cognitive psychology in 1950's (Driver 2001). Early works aimed to solve the "cocktail party" problem: how are we able in a environment full of noise to listen only to the relevant stream of sounds? Classical experiments to investigate selective attention generally consisted in dichotic listening paradigms, during which the participant was presented with two simultaneous auditory streams in each ear. Broadbent's response to the "cocktail party" problem was probably the most influential work in the field of selective attention (Broadbent 1958). He equated the brain to a computer with limited computing resources, unable to process all inputs available at the same time. In his "early-selection" model, attention acted as a filter or a bottleneck: first, low-level "physical" properties of all inputs were extracted, then only relevant inputs will enter further processing while irrelevant inputs were filtered out. According to this theory, selective attention is only efficient when the attended and unattended inputs present clear acoustic differences and prevent the listener from reporting nothing more than the physical properties of the unattended sounds, as they would not undergo advanced processing. Later on, this theory was updated or disputed by numerous authors. "Late-selection" models postulated that the "bottleneck" happened in late stages of processing: all inputs including unattended ones are unconsciously processed to the stage of identification or semantics (Deutsch and Deutsch 1963; Duncan 1980), and irrelevant stimuli would be filtered out based on the physical and semantic resemblance with the target in mind. Treisman (1964) proposed a compromise model which postulated that unattended inputs are attenuated rather than blocked by the attention filter, allowing relevant but unattended information to enter further processing. In the following decades, numerous authors have tried to refine the early-selection, late-selection and "compromise" models of attention, without reaching a full consensus (Pashler 1998).

1.2.2 Orienting attention: the duality of the attentional function

Attention orienting is the process of simply directing one's attention towards a source of stimulation. Early research on attention orienting was primarily done in the visual modality, with paradigms using visual cues to trigger attention shifts, the most notable of all being

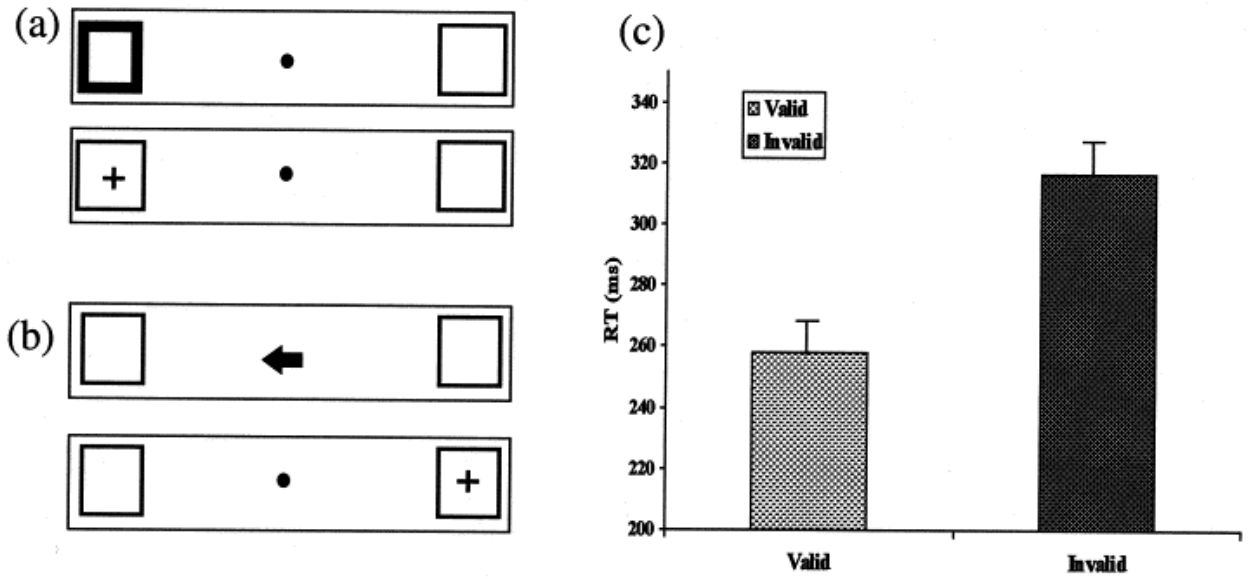


Figure 3: *Posner task. Participants are asked to fixate on the central point and to detect very transient peripheral targets. Before the target onset, attention is oriented using (a) exogenous cues or (b) endogenous cues. (c) Cues can either correctly predict the location of the upcoming target (*valid *trials) or incorrectly (*invalid *trials). Participants are behaviorally disadvantaged when presented with invalid cues compared to valid cues. Adapted from Coull (1998).*

the Posner task (Figure 3). Participants are usually faster, more accurate and more likely to detect a visual target if a prior visual cue accurately predicts the location of the upcoming target, even when head and eye movements are restricted by forcing the participant to fixate the center of the screen (Posner 1980; Most and Simons 2001). This illustrates the ability to shift one's attention towards a portion of the visual field, subsequently boosting performances. An important distinction between two types of attention orienting arise from these studies, depending on the chosen type of cueing. "Endogenous" cues happen at the center of the screen where the locus of attention is already located and consist in an arrow pointing at the location of the upcoming target; "exogenous" cues happen at the location of the upcoming target, at the periphery of the locus of attention. With endogenous cues the participant has to interpret the symbol to know where to direct attention, exogenous cues do not require such cognitive effort. Exogenous cues lead to lower reaction time in *valid* trials compared to endogenous cues, but higher reaction times in *invalid* trials; they are also difficult to suppress (Jonides 1981). This lead to conceptualize two distinct forms of attention orienting: top-down voluntary orienting which involves a cognitive effort to shift the locus of attention, and bottom-up orienting which involves reflexive and automatic responses to unattended stimuli.

Top-down attention Top-down attention is a voluntary, goal-driven process to enhance performance in which a location, a feature or an object is selected internally and focused upon. As stated above, it was mainly investigated using Posner and Posner-like paradigms in which a central cue either correctly indicates the location of the upcoming target (valid or informative trials) or provides no (uninformative trials) or incorrect information (invalid trials) on target location. By comparing performance between valid or informative trials and invalid or uninformative trials, it is possible to investigate the deployment of top-down attention. Compared to invalid cues, valid cues lead to shorter reaction times when participants have to detect or discriminate visual targets (Hayward and Ristic 2013; Posner 1980; Posner and Petersen 1990). Auditory top-down attention have been less investigated using this framework, however similar results have been obtained using auditory targets or auditory cues (Bidet-Caulet et al. 2015; Golob, Pratt, and Starr 2002).

Neural mechanisms of top-down attention Neuroimaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and intracranial EEG are useful to reveal the brain networks and structures involved in top-down attention. Top-down attention orienting can be investigated by observing activity patterns following cue presentation. fMRI studies using Posner-like paradigms have shown that top-down anticipation of an upcoming target is associated with a modality-specific pre-activation of the relevant sensory cortices. Visual targets call for a pre-activation of the visual cortical areas (e.g. Desimone and Duncan 1995; Kastner et al. 1999; Liu et al. 2016), auditory targets for a pre-activation of the primary and secondary auditory cortices (e.g. Bueti and Macaluso 2010; Jäncke, Mirzazade, and Joni Shah 1999; Smith et al. 2009; Voisin et al. 2006; Wu et al. 2007) and tactile targets for a pre-activation of the somato-sensory cortex (e.g. Langner et al. 2011; Macaluso et al. 2003). Top-down attentional modulations can happen at earlier processing stages for they have been detected in the thalamus in visual attention tasks (Schroeder 1995) and in the brainstem (Lukas 1980) and the cochlea (Giard et al. 1994) in auditory attention tasks.

These studies have mainly focused on top-down orienting in the absence of irrelevant stimuli competing for attentional resources and during the anticipatory period. Auditory top-down selective attention, in the sense of prioritizing one aspect of the environment over the rest, have been investigated using dichotic listening paradigm. The participant is subjected to two distinct auditory streams presented in each ear and is asked to attend to the relevant stream while ignoring the other one. Attending to the left or to the right during a dichotic listening have been associated with an increased activity in bilateral auditory areas (Jäncke et al. 2003; O'Leary et al. 1996; Zatorre, Mondor, and Evans 1999) and/or an asymetric activity

pattern that gives predominance to the areas contralateral to the attended ear (Alho et al. 1999; O'Leary et al. 1996). In bimodal tasks during which the participant is confronted to simultaneous but asynchronous streams of auditory and visual objects, activation in sensory cortical areas relevant to the modality of the attended stream is increased, while activation in sensory cortical areas relevant to the modality of the unattended stream is reduced (Ghatan et al. 1998; Johnson and Zatorre 2006; Kastner and Ungerleider 2000; Laurienti et al. 2002; Salmi et al. 2007; Salo et al. 2013). Data from intracranial EEG recordings during dichotic listening have shown that responses to the attended stream were facilitated in the primary and secondary auditory cortices, while responses to the unattended stream were attenuated (Bidet-Caulet et al. 2007).

All these results support the existence of two sub-systems of top-down attention: facilitation of relevant information and inhibition of irrelevant information (Bidet-Caulet, Mikyska, and Knight 2010; Chait et al. 2010; Gazzaley et al. 2005). Top-down facilitatory mechanisms are deployed during target expectancy which involves attention orienting and are necessary to optimal task performance (ElShafei et al. 2018). The combination of top-down facilitatory and inhibitory mechanisms are necessary for selective attention as illustrated by dichotic listening and bimodal tasks.

Cortical networks of top-down attention In their influential review, Corbetta and Shulman (2002) has identified a network of cortical areas implicated in the control of top-down, goal-directed attention based on previous fMRI and PET studies using visual Posner's tasks. When attending to a spatial location in anticipation of an upcoming target, there is a consistent activation pattern in the cortex: the dorsal attention network (DAN) (Figure 4). Visual cues trigger a transient activation of visual areas which is the followed by a bilateral activation of the intraparietal sulcus, the superior parietal lobule and the frontal eyes field during the expectation period. The same pattern is observable in the auditory modality during tasks involving auditory spatial attention (Kong et al. 2014; Lee et al. 2013; Mayer et al. 2006; Shomstein and Yantis 2004; Smith et al. 2009; Wu et al. 2007) but appears to extend to the ventro- and dorso-lateral prefrontal cortex (Salmi et al. 2009; Voisin et al. 2006) and the inferior frontal gyrus (Kong et al. 2014).

Bottom-up attention As I developed previously, voluntary top-down deployment of attention over a certain amount of time is crucial in order to execute a task in an adequate manner. Top-down selective attention acts by suppressing irrelevant events and prioritizing the processing of relevant objects. However, there is an ecological imperative to still remain aware of one's surrounding: it would be dangerous to ignore any dangerous events happen-

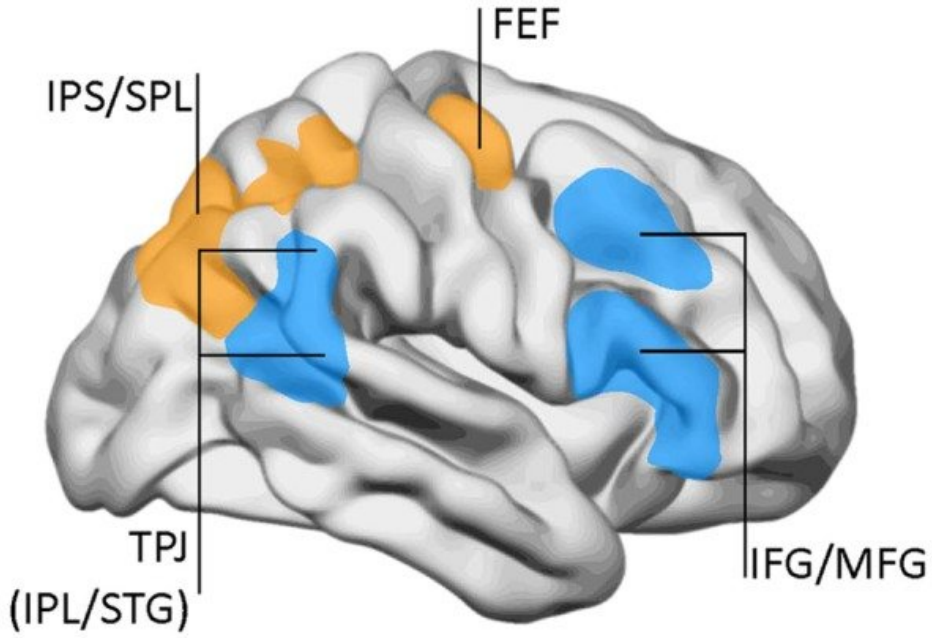


Figure 4: *The dorsal attentional network (DAN) and the ventral attention network (VAN). DAN (yellow/orange): FEF, frontal eye fields; IPS, inferior parietal sulcus; SPL, superior parietal lobe. VAN (blue): IFG, inferior frontal gyrus; IPL, inferior parietal lobe (posterior aspect); MFG, middle frontal gyrus; TPJ, temporo-parietal junction; STG, superior temporal gyrus. Adapted from Corbetta and Shulman (2002).*

ing in the background because all the cognitive resources are allocated towards the relevant goal. Our attention can be diverted from its primary goal by an unexpected event by interrupting the task at hand and reallocating resources towards this event. This phenomenon is commonly referred as *attention capture* and is the product of bottom-up attention (Most and Simons 2001). Contrary to top-down attention, bottom-up is externally driven, less voluntary, and more automatic.

Attentional capture can be triggered by task-irrelevant salient stimuli and is particularly prominent in the auditory modality as our ears cannot be easily shut down to avoid registering sound, unlike the eyes in relation to light. Salience can be defined as the phenomenon by which an object stands out from a scene. Salience is not dictated by behavioral goals: a fire alarm will attract our attention regardless of whether we wish to ignore it or not. What makes a sound (or a stimulus in general) salient and therefore attention-grabbing is a complex combination of features but which can be boiled down to two main categories (Hughes 2014). A sound may be salient because of its particular content which provides it behavioral relevance, independently of the context. This can be related to (1) its acoustic properties such as loudness, pitch, spectral shape (Huang and Elhilali 2017) or roughness (Arnal et al. 2019), (2) its emotional content as sounds with high negative or positive emotional valence

are more attention-grabbing (Hartikainen, Ogawa, and Knight 2012; Pool et al. 2016), or (3) its personal significance to the listener such as hearing one's own name or one's own ringtone (Holeckova et al. 2006; Roye, Jacobsen, and Schröger 2007). On the other hand, the salience may emerge from context-dependent properties of the sound. If "A" is a high-pitched sound and "B" a low-pitched sound, the presentation of "B" after a succession of "A" (AAAAAABAA) will capture the attention because it violates the expectation for another "A". This salience is only context-dependent and does not rely on the intrinsic properties of the B sound as a A sound would also trigger attention capture if it was incorporated in a succession of "B" (BBBBBBBABB) (Hughes 2014; Escera et al. 1998; Parmentier et al. 2008). Context-dependent salience is not limited to simply "deviance", it can be linked to the concept of novelty. According to Schomaker and Meeter (2015), novelty encompasses *deviance* (infrequent category that is dissimilar to other stimuli), *stimulus novelty* (unfamiliarity, something never experienced before and not stored in long-term memory), *contextual novelty* (differs from other stimuli offered in context, but has been seen before and stored in long-term memory) and *surprise* (unexpectedness, violates expectancy and/or explicit predictions).

Bottom-up attention in the auditory modality has been mainly investigated using a modified version of the oddball paradigm which I will refer to as "distraction-oddball" paradigm (for a more complete description of this paradigm, see 94). In summary, the participant is asked to respond as quickly as possible to visual or auditory targets, which are preceded by a task-irrelevant sound. In most trials, this task-irrelevant sound is a regular (*standard*) but in some trials, it is replaced by rare, oddball sound (*deviant*), breaking the repetitive sequence of *standard* sounds. In *deviant* trials, participants are usually slower to respond than in *standard* trials and this difference in reaction times is assumed to reflect attention capture (Escera et al. 1998; Parmentier and Andrés 2010; Schröger and Wolff 1998a).

Cortical networks of bottom-up attention A ventro-parietal network of cortical regions is considered to be the substrate of bottom-up attention, the *ventral attention network* (VAN). It comprises the right temporo-parietal junction (rTPJ) and the middle and inferior frontal gyri (Figure 4) and responds to behaviorally relevant objects outside the focus of attention (Corbetta, Patel, and Shulman 2008). It has been identified in parallel of the *dorsal attention network* using fMRI and PET. In the visual modality, its elicitation is observable during Posner tasks by constrasting brain activity in invalid trials during which the target pops up at an unexpected location to the activity during valid trials in which the target arrives at the expected location (reviewed in Corbetta and Shulman 2002; Corbetta, Patel, and Shulman 2008). The VAN is also activated during oddball paradigms by *deviant*

stimuli and the activation pattern is remarkably similar in the auditory and visual modalities (reviewed in Kim 2014). It has been proposed that the rTPJ, a major node of the VAN would act as a "circuit-breaker", interrupting top-down control of attention and enabling an attention shift (Chang et al. 2013).

Interaction between top-down and bottom-up attention Top-down and bottom-up attention have been usually investigated separately and it is still unclear if the two modes of attention interact, notably if top-down attention processes can modulate the bottom-up mechanisms of attention capture by unexpected stimuli. Miller et al. (2011) investigated this interaction using auditory distractors during a video game. They showed that that an increased engagement of top-down attention, by increasing the video game difficulty, leads to attenuated brain responses to the distractors. Providing a warning that a deviant sound will occur leads to decreased attention capture (Hughes et al. 2013; Sussman, Winkler, and Schröger 2003) and to recover more quickly from distraction (Shelton et al. 2009), illustrating the impact of top-down expectations on distraction. On the contrary, Pinto et al. (2013) argue that top-down and bottom-up attention are independent cognitive systems. They based this assertion on the absence of significant correlation between performance during a task evaluating top-down attention and during a task evaluating bottom-up attention.

As we have seen previously, cortical networks underpinning top-down and bottom-up attention are often presented as anatomically segregated. However, some overlap exist between them (Alho et al. 2014; Corbetta, Patel, and Shulman 2008; Katsuki and Constantinidis 2014; Salmi et al. 2009) suggesting that top-down and bottom-up attention could interact. A good candidate for maintaining the dynamic balance between the two modes of attention would be the lateral prefrontal cortex (Asplund et al. 2010). This brain structure has been implicated in top-down control of attention (Kastner and Ungerleider 2000; Lewis, Beauchamp, and DeYoe 2000; Voisin et al. 2006; Zatorre, Mondor, and Evans 1999), in both facilitatory (Barceló, Suwazono, and Knight 2000) and inhibitory mechanisms (Caclin and Fonlupt 2006). The lateral prefrontal cortex has also been associated to bottom-up attention capture (Han and Marois 2014; Watkins et al. 2007) and the inhibition of responses to unexpected stimuli (Suzuki and Gottlieb 2013).

1.3 Attention and M/EEG

Electroencephalography (EEG) is a neuro-imaging technique based on recording the spontaneous electrical currents produced by brain activity through electrodes placed on the scalp.

EEG offers a millisecond-range temporal resolution, which is far superior to the resolution of fMRI or PET. Therefore, EEG is a particularly powerful technique to investigate sensory processing and attention mechanisms as it allows the observation of very transient phenomena. However, EEG lacks in spatial resolution and despite modern analysis techniques, the accuracy of the reconstruction of sources of EEG signals is still in the range of several centimeters (Ferree, Clay, and Tucker 2001). Magnetoencephalography (MEG), which records magnetic currents instead of electric currents, alleviates some of the drawbacks of EEG. MEG and EEG offer the same fine-grained temporal resolution (Hari, Levänen, and Raij 2000). However, contrary to electrical currents, magnetic currents go through the meninges and the skull mostly unaffected due to the fact that the magnetic conductivity of organic tissue is much higher than the electric conductivity. Therefore, the signal-to-noise ratio is far superior and allows a better spatial resolution (Hämäläinen et al. 1993) and a finer detection of high-frequency, low-amplitude signals. Finally, the sensitivity of EEG and MEG depends on the orientation of the source and as a consequence, on the geometry of the cortical surface: EEG is more sensitive to radial and deep sources while MEG is more sensitive to tangential sources (Ahlfors et al. 2010). Applications of EEG and MEG usually center around two main cerebral phenomena: event-related responses – fluctuations of brain activity time-locked to the presentation of a stimulus –, and neural oscillations – repetitive patterns of neural activity.

1.3.1 Event-related potentials

Event-related potentials (ERPs) are variations in electrical voltage, a succession of positive and negative deflections elicited and time-locked to the presentation of a particular stimulus. Components of the ERP waveform can be differentiated based on their latency, their sign (positive or negative) and their scalp topography: each of these components is considered to be the manifestation of a specific cerebral process. ERPs have been widely used in attention research as they allow the observation of the rapid sequence of events leading the full attention processing of sensory information (Luck, Woodman, and Vogel 2000; Luck and Kappenman 2012). Some ERPs components can be explicitly elicited by attention orienting, while top-down attention acts by modulating the amplitude and latency of ERP components. In this section, I will present how attention is reflected in ERPs and I will mainly focus on the auditory modality. From now on, I will consider the expressions “evoked potentials” and “event-related potentials” interchangeably, even if sometimes a distinction is made in the literature. Magnetic equivalents of evoked potentials are referred as “evoked fields” and are considered to reflect roughly the same underlying brain activity. However as EEG and MEG have different sensitivities depending on the orientation of the cortical source of the signal,

the relative contribution of some sources may differ between evoked potentials and fields.

Auditory evoked potentials Following the onset of an auditory stimulus, three main episodes of evoked potentials are elicited (Näätänen 1990). Early-latency evoked potentials happen during the 10 to 12 milliseconds following the onset of the stimulus and originate from the brainstem. They correspond to the income of auditory information from the auditory nerve to the auditory cortex (as displayed in Figure 2). Middle-latency evoked potentials originate from cortical auditory areas (Heschl gyrus, planum temporale, superior temporal gyrus) and happen as soon as 9 ms to around 50 ms, suggesting that the auditory information is transmitted from the periphery to the cortex in less than 10 ms (Liégeois-Chauvel et al. 1994; Yvert et al. 2005). Late-latency evoked potentials happen from 50 ms to 500 ms (and more) and reflect the activity of cortical networks involved in sensory and cognitive processing of auditory stimuli. I will only discuss late-latency evoked potentials in the rest of the section, as they are by far the most researched class of ERPs as they present a larger amplitude.

Auditory stimuli necessarily elicit a sequence of obligatory responses: a first positive deflection, the P50 (or P1) around 50 ms, followed by a large N1-P2 complex. They reflect the minimal sensory processing of incoming sounds and are elicited even if the attention is not oriented towards the stimulus. The P50 emerges from the primary auditory cortices according to intracranial recordings (Korzyukov et al. 2007; Pantev et al. 1995; Yvert et al. 2002). Combined MEG and EEG recordings have confirmed that the P50 component can be adequately modeled with two dipoles in the bilateral superior temporal gyri but also that this component was associated with activation of areas beyond the primary auditory cortices, namely adjacent auditory association areas and the frontal lobe (Edgar et al. 2003; Huotilainen et al. 1998; Korzyukov et al. 2007; Nakagawa et al. 2014; Weisser et al. 2001).

The N1 is the most studied obligatory auditory evoked potential. It has been described extensively in the seminal review by Näätänen and Picton (1987) who claimed that the N1 wave comprises three sub-components:

- The component 1 (or N1b) peaks negatively around 100 ms and presents a fronto-central scalp topography, associated with a positivity around the mastoids. It is mainly generated in auditory areas. This is the component that is usually referred to as just "N1" in the literature.

- The component 2 is generated in the superior temporal gyrus and is observable on temporal electrodes. It is a biphasic component with a negative peak around 100 ms followed by a positive peak around 150 ms.

- The component 3 is a central sub-component peaking later than the component 1, appears to comprise sources located in the frontal cortex and is only elicited during low frequency presentation stimuli. It has also be referred as *the orienting component of the N1* and might be related to the reorienting of attention after an infrequent stimulus (Alcaini et al. 1994b).

Other classification schemes of the sub-components of the N1 have been used, leading to a complex jungle of nomenclature (McCallum and Curry 1980; Woods 1995). If it is consensually assumed that the N1 reflects pre-attentive sensory processing of auditory inputs, it is still elusive which specific cerebral mechanisms are associated with this component. The N1 elicitation only follows an abrupt acoustic event, such as the attack or the end of a sound or a change in pitch which has led to propose that it reflects acoustic feature and change detection. N1 generators can be found in the superior temporal gyrus, in a more posterior location that the P50 generators, and they present a tonopic organization (Pantev et al. 1995; Verkindt et al. 1995). Using MEG signals, a similar wave can be observed at roughly the same latency than the electrical N1. Simultaneous EEG and MEG measurements have established that this wave, the N1m, is the counterpart of the electrical N1 in the sense that they share the same generators and latency (Huotilainen et al. 1998; Virtanen et al. 1998). MEG also appears to be more sensitive to N1 generators due to the folding geometry of the Heschl gyrus.

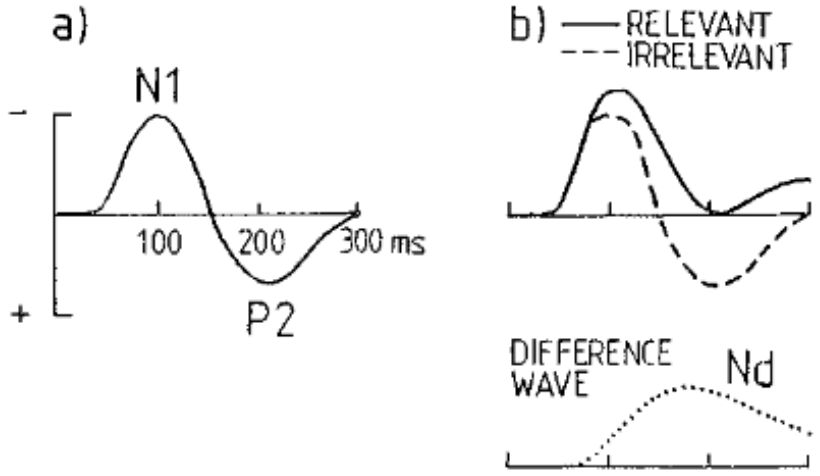
The P2 response peaks around 180 ms after sound onset and displays a fronto-central scalp topography (Crowley and Colrain 2004). Documentation on the P2 wave, notably about its functional significance or its neural substrates, is far less extensive than for other ERPs mentioned previously. The P2 would emerge from auditory associative areas including the planum temporale and the Brodmann area 22 (Godey et al. 2001; Yvert et al. 2005). It has been proposed that the N1 and the P2 were indistinct parts of a same components, the vertex potential (Davis and Zerlin 1966). However, functional, developmental, and experimental dissociations of the auditory N1 and P2 responses suggest that the two components represent at least partially independent processes (Crowley and Colrain 2004). Interestingly, temporo-parietal lesions abolish the N1 while the P2 remains functionally intact (Knight et al. 1980). The P2 appears to reflect further stimulus evaluation, including stimulus classification or the early process of attentional allocation (Arnott et al. 2011; García-Larrea, Lukaszewicz, and Mauguiére 1992). In the visual modality, the P2 is particularly sensitive to the emotional content of the stimulus as its amplitude is increased for disgusting and fearful stimuli compared to neutral ones (Carretié et al. 2004; Carretié et al. 2011; Kanske, Plitschka, and Kotz 2011).

An important feature of obligatory auditory evoked potentials is the amplitude reduction

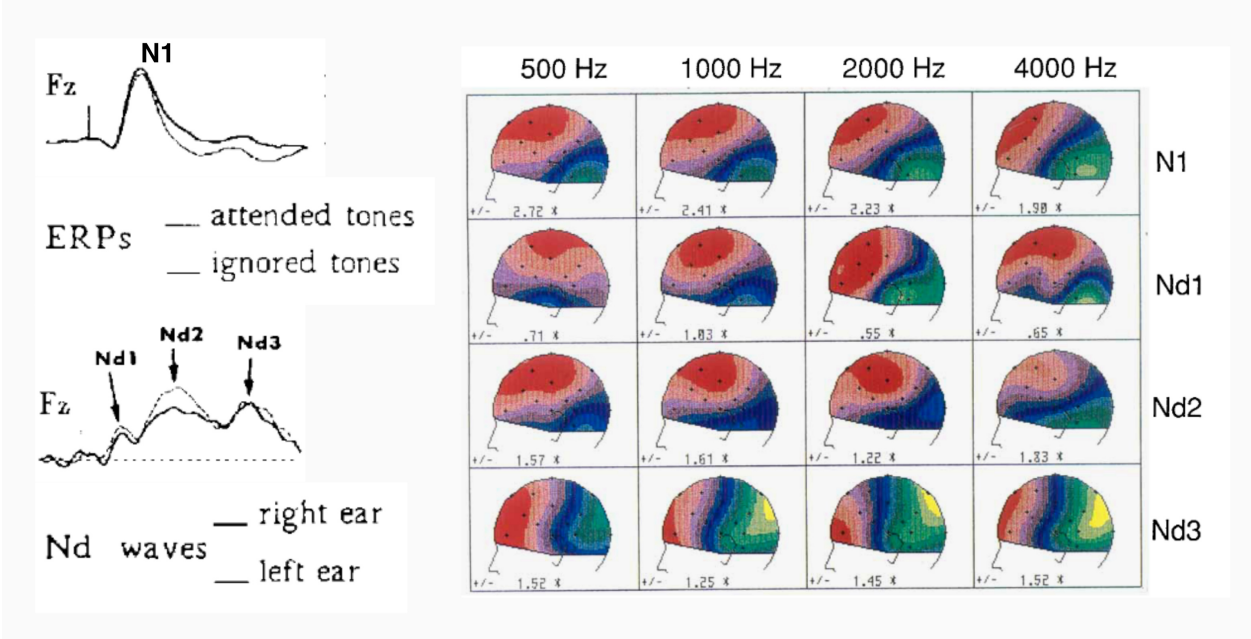
in a sequence of repeated stimulation, a process usually referred as *habituation*. In paired-click paradigms during which two clicks are presented within 500 ms of each other, the amplitude of the P_{50} elicited by the second click is found decreased (Knott, Millar, and Fisher 2009; Smith, Boutors, and Schwarzopf 1994; Zouridakis and Boutros 1992). This effect is attributed to *sensory gating*, an automatic neural process of filtering redundant, irrelevant information blocking further processing and preventing an overload of irrelevant information. There is also a overwhelming literature indicating N1 amplitude decrements during train of auditory stimuli. In the literature, a distinction is usually made between short-term habituation, an exponential reduction of the amplitude which reaches asymptote by the third or fourth repetition of a sound (Barry et al. 1992; Fruhstorfer, Soveri, and Järvilehto 1970; Ritter, Vaughan, and Costa 1968; Woods and Elmasian 1986), and long-term habituation, which can be observed over the course of a block or an experiment. Long-term habituation fits the classical definition of habituation, i.e. an adaptation to loss of novelty (Sokolov 1963), while short-term habituation would be more a reflection of the refractory period effect (Budd et al. 1998; Ritter, Vaughan, and Costa 1968). Impaired habituation have been associated with dysfunctional sensory processing in neurological disorders. Decreased sensory impairments reflected by an abnormal P_{50} behavior is a hallmark of schizophrenia (Potter et al. 2006) while habituation deficits are strongly associated with migraine (Coppola, Pierelli, and Schoenen 2009), as I will discuss later.

ERPs and top-down attention The effects of top-down attention on ERPs can be observed in two different situations: (1) top-down anticipatory mechanisms are reflected in ERPs during the period leading to an expected upcoming target, (2) top-down selective attention can facilitate the processing of attended stimuli and lead to enhanced obligatory ERPs. (3) top-down expectations can influence the cognitive processing of incoming stimuli as reflected by late ERPs.

In a simple detection task in which the participant is asked to respond as fast as possible to a sound (imperative stimulus), presenting a warning stimulus prior to the occurrence of the imperative stimulus will result in better performance (Sanders and Wertheim 1973). This is due to anticipatory behavior, which encompasses motor preparation, top-down attention and arousal processes: participants are not only preparing to respond, they are waiting for the imperative stimulus to happen. This is reflected electrophysiologically by a specific ERP, the contingent negative variation (CNV). The CNV is a negative slow wave that follows the sequence of obligatory ERPs elicited by the warning stimulus and whose amplitude increases with time (Brunia and van Boxtel 2001). The CNV can be separated in two components: (1) the early CNV, maximal at frontal electrodes and around 500 to 800 ms after the warning



(a) *A schematic illustration of the impact of top-down attention on obligatory auditory evoked potentials. When a participant attends to one ear or pays attention to sounds with a specific pitch, the N1-P2 complex in response to relevant sounds is shifted negatively. The difference wave obtained by subtracting the ERP to relevant sounds to the ERP to irrelevant sounds is called the negative difference (Nd) or Processing Negativity (PN). Adapted from Näätänen (1990).*



(b) *The negative difference. (Top left) ERPs elicited by attended and unattended sounds. (Bottom left) The attentional Nd waves, obtained by subtracting the ERPs to the tones when ignored from those to the same tones when attended. Three successive negative deflections can be observed. (Right) Scalp topographies of the N1 and the sub-components of the Nd, depending on the pitch of the attended tone. Please note that the Nd1 present tonotopic changes similar to those of the N1 wave, but not the Nd2 and Nd3. Contrary to the Nd1 and Nd2, the Nd3 topography strongly differs from that of the N1 and is maximal over prefrontal electrodes. Adapted from Alcaini et al. (1994a).*

Figure 5: *Top-down selective attention effects on ERPs.*

stimulus onset, is more associated with the orienting response, (2) the late CNV, with a more posterior topography and building up before the onset of the upcoming imperative stimulus, is considered to be an index of motor preparation (Gaillard 1977; Loveless and Sanford 1974). A large amplitude of the CNV, especially of its late component, is associated with faster responses, across participants or across trials of a same participant (Brunia and Vingerhoets 1980; Harkins et al. 1976; Hillyard 1969), suggesting a causal relationship between the CNV and behavioral performance. MEG and EEG studies have confirmed that the CNV (and its magnetic counterpart, the contingent magnetic variation – CMV) has generators in motor areas, but it is also associated with activations in fronto-parietal regions and in the sensory cortices relevant to the modality of the imperative stimulus (Gómez, Marco, and Grau 2003; Gómez et al. 2004; Gómez, Flores, and Ledesma 2007; Mento 2017). Top-down attention orienting can modulate the amplitude of the CNV: Bidet-Caulet et al. (2015) have shown using a Posner-like paradigm (described extensively page 100) that informative cues, which allow the deployment of top-down attention orienting processes, lead to an enhanced CNV compared to uninformative cues.

Top-down selective attention is also reflected in the obligatory ERPs amplitude. In selective dichotic paradigms, it has been noted that the amplitude of the N1 elicited by attended tones is larger than for the ignored tones (Alcaini et al. 1994a; Giard et al. 2000; Hillyard et al. 1973; Näätänen 1982; Näätänen 1990) (Figure 29). The difference ERP obtained by subtracting the response to attended stimuli to the response to ignored stimuli has been referred as negative difference (Nd) or processing negativity (PN) and is considered to reflect the active selection of relevant information. Top-down attention effects are observable at different steps of sensory processing. As demonstrated in Alcaini et al. (1994a), the Nd begins as soon as 50 ms and lasts until at least 500 ms after the sound onset (Figure 5b). The first peak (Nd1) shares the tonotopical organization of the N1, suggesting that top-down attention is first effective at the level of the primary auditory cortex. The second peak (Nd2) do not appear to be tonopically organized but still maintain temporal generators, illustrating top-down attention effects in auditory associative areas. The Nd has been associated with the *gain theory of attention* (or sensory amplification theory).[1] It states that selective attention acts through gating/inhibiting the processing of unattended stimuli while responses to attended stimuli are amplified in the relevant sensory cortices, in line with early-filer and attenuation models of attention (Giard et al. 2000; Humphreys et al. 1998). More recent data have demonstrated that distinct top-down inhibitory and facilitatory mechanisms are reflected in the Nd (Bidet-Caulet, Mikyska, and Knight 2010), illustrating that top-down

[1]The last peak (Nd3) happens past the window of obligatory ERPs and presents a frontal distribution, reflecting the role of the frontal cortex in top-down attention.

attention is not limited to the facilitated processing of relevant information but also includes an active rejection of irrelevant information.

I will discuss it in more detail in the next section (p.31) but target stimuli usually elicit late ERPs components, namely the P3b, beyond the obligatory responses. The P3b whose precise functional role is unclear appears to reflect cognitive evaluation of the stimulus and the orientation of attention towards it (Polich 2007). In an opposite trend than for obligatory ERPs, top-down attention mechanisms generally attenuate the late cognitive responses. In Posner and Posner-like paradigm, valid or informative cues lead to a decreased P3b and this effect is even stronger when the proportion of valid or informative trials is high (Arjona, Escudero, and Gómez 2016; Bidet-Caulet et al. 2015; Golob, Pratt, and Starr 2002; Gómez et al. 2008). It is generally interpreted as that stimuli from unexpected locations violate the prediction informed by the cue and therefore necessitate more cognitive evaluation. Therefore, top-down expectations can be reflected in reduced cognitive ERPs.

ERPs and bottom-up attention As I have discussed above, frequent and unremarkable sounds elicit a short sequence of obligatory ERPs. Auditory infrequent or remarkable stimuli trigger later ERPs which reflect further cognitive evaluation of the stimulus, most notably a late positive wave around 300 ms post-stimulus, the P300 response. The P300 has mainly been explored using the oddball paradigm, an experimental design in which infrequent *deviant* sounds interrupt a regular sequence of repetitive sounds (*standard* sounds). Oddball paradigms sometimes include *target* sounds which require a behavioral response or *novel* sounds, rare task-irrelevant unexpected sounds. Non-standard sounds elicit a P300, which has been considered to reflect the involvement of attention in the processing of the stimulus. Despite the simplicity of the paradigms used to elicit the P300, the precise brain mechanisms reflected by this component are not well-established. P300 responses are usually conceptualized within the framework of the *orienting response* as described by Sokolov (1963; 1990), defined as the organism's immediate response to a change in its environment, including the automatic attention orienting towards significant, meaningful events. According to the context-updating theory, the P300 indexes the updating of the mental representation induced by incoming stimuli (Donchin and Coles 1988). In an oddball sequence, the repetition of standard creates an internal model of the stimulus context. If a new standard sound is presented, the current "schema" is maintained and only obligatory ERPs are elicited. However, when a non-standard stimulus is presented, a mismatch is detected by comparing this "oddball" stimulus to the representation stored in working memory. Then, if this mismatch is considered behaviorally relevant, attentional mechanisms can be engaged in the updating of the expectancies, eliciting a P300.

However, the P300 is not single monolithic entity and encompasses various responses depending on the stimulus category and the task demands. Three distinct P300 components can be separated based on their latency, scalp topography and conditions of elicitation (Barry, Steiner, and De Blasio 2016). Nomenclature of P300 components has been historically very inconsistent: in the absence of a consensus, I will use the nomenclature I believe is the clearest (inspired by Barry, Steiner, and De Blasio 2016).

The P3b (also referred as "P3", "target-P3" or confusingly "P300"). The P300 was discovered fifty years ago and the first component to be described was the P3b (historically called P300) (Sutton et al. 1965). The P3b is elicited by target stimuli for which the participant is required to respond mentally or physically (Polich and Criado 2006; Polich 2007). This has been investigated using the single-stimulus paradigm during which target are presented in the absence of other stimuli, or using oddball paradigms during which target stimuli are interspersed in a regular sequence of standard stimuli. The P3b is maximal over parietal electrodes and has a peak latency around 300 ms. The scalp topography of the P3b reflects the preeminence of parietal generators, however source reconstruction studies have shown that it is associated with widespread activation all over the cortex, in frontal, temporal, motor and (relevant) sensory cortices (Bachiller et al. 2015; Bocquillon et al. 2011; Bocquillon et al. 2012; Halgren et al. 2011; Mento 2017; Volpe et al. 2007; Wronka, Kaiser, and Coenen 2012).

The P3a. It was first described by Squires, Squires, and Hillyard (1975) who observed that during an oddball paradigm, deviant sounds can elicit a fronto-central P300 whether the participant was paying attention or not to the auditory stream (counting tones or ignoring them). They coined this component the P3a. The P3a is a response elicited by unattended deviant sounds which differs from the P3b component by its earlier latency (220–280 ms) and its fronto-central scalp topography. P3a has been considered to reflect automatic attention capture as deviant sounds are followed by slower responses in active oddball paradigms (Berti and Schröger 2003; Escera et al. 1998; Escera et al. 2000; Escera et al. 2003; SanMiguel, Corral, and Escera 2008; Schröger and Wolff 1998b) and has been used as an index of distraction in clinical studies (e.g. Correa-Jaraba, Lindín, and Díaz 2018; Ferri et al. 2003; Gumenyuk et al. 2005; Kaipio et al. 2000; Keage et al. 2006; Rüsseler et al. 2002; van Mourik et al. 2007). P3a cortical generators can be found in the frontal, cingulate and auditory cortices (Bachiller et al. 2015; Molloy et al. 2015; Takahashi et al. 2013; Volpe et al. 2007; Wronka, Kaiser, and Coenen 2012).

The novelty-P3 (or nP3). The novelty-P3 was first described by Courchesne, Hillyard, and Galambos (1975). The authors inserted *novel* sounds (unexpected rare environmental sounds) as a third stimulus category in the traditional oddball paradigm and found

that they elicited a component that they coined the *novelty-P3*. The novelty-P3 peaks later than the P3a and the P3b (360–450 ms) and presents a fronto-parietal distribution (Barry, Steiner, and De Blasio 2016; Barry et al. 2020; Friedman, Cycowicz, and Gaeta 2001). A major characteristic of the novelty-P3 is to show quick habituation, as illustrated by the exponential decrement of its amplitude over trials. The functional significance of the novelty-P3 is still debated but it has been proposed to reflect novelty processing (Friedman, Cycowicz, and Gaeta 2001) and to represent the actual index of the orienting response (Barry et al. 2013; Barry, Steiner, and De Blasio 2016; Barry et al. 2020). Novelty-P3 generators would be located in the dorsal parts of the frontal and parietal lobes and in the anterior cingulate cortex (Barry et al. 2020).

In an influential study, Simons et al. (2001) re-examined data from the Courchesne and Squires studies using factor analyses and concluded that the novelty-P3 and the P3a were indistinguishable and that the two labels could be used interchangeably. This result has been widely accepted in the literature (Polich 2007) but it has not prevented both nomenclatures to persist in subsequent articles (Escera and Corral 2007; SanMiguel et al. 2010). However, this interpretation has been challenged by more recent studies which have demonstrated that novel sounds actually elicit a fronto-parietal P300 following the P3a, a component which matches the description of the novelty-P3 by Courchesne and collaborators (Barry, Steiner, and De Blasio 2016; Barry et al. 2020). To add to the confusion, in certain adaptations of the oddball paradigm (see Figure 21a), a biphasic P3a/novelty-P3 has been observed in response to novel sounds challenging the idea that the P3a is a unitary construct. This biphasic P3a comprises a fronto-central early component (named early-P3a, peaking around 240 ms) followed by a fronto-parietal component (named late-P3a, peaking around 320 ms) (Escera et al. 1998; Rinne et al. 2006; Yago et al. 2003). These two components can be modulated independently in basic (Holeckova et al. 2006; Roye, Jacobsen, and Schröger 2007) and clinical studies (Cortiñas et al. 2008; Gumenyuk et al. 2005). However, based on latency, topography and conditions of elicitation, it has been proposed that the early-P3a reflects the genuine P3a and that the late-P3a reflects the genuine novelty-P3 (Barry, Steiner, and De Blasio 2016). Finally, some stimuli can elicit both P3a and P3b responses: this is the case in oddball paradigms instructing to consider novel sounds as targets (e.g. Debener et al. 2005).

However, bottom-up distraction is not limited to the process of attention orienting supposedly reflected by the P300. Distraction triggered by unexpected events is generally described with a three-stages sequential model, with each stage reflected by specific ERPs (Escera and Corral 2007; Horváth, Winkler, and Bendixen 2008).

- The first processing stage features automatic filtering of irrelevant information which

do not access advanced sensory processing. This process is underpinned by two distinct mechanisms:

  - A simple change detection mechanism reflected by the N1 wave. The N1 reacts to sudden onset in the environment and the N1 response to unexpected sounds is deemed to index a transient detector mechanism (Berti 2013; Näätänen and Picton 1987). Infrequent sounds have also been associated with the elicitation of a specific subcomponent of the N1, referred as the orienting component of the N1 (Alcaini et al. 1994b) or the component III of the N1 (Näätänen and Picton 1987).
  - A deviance detection mechanism indexed by the mismatch negativity (MMN). The MMN reflects the brain's automatic response to any change in auditory stimulation, and usually elicited by deviant sounds in oddball paradigms (Näätänen et al. 2007). The MMN is maximal at frontal electrodes and peaks after the N1 (100–200 ms). It is widely considered to reflect memory-based deviance detection as it is elicited by events that violates the expectations created by a regular repetition of identical sounds.

- The second processing stage features attention orienting towards the unexpected event. First-stage change detection mechanisms (N1/MMN) are hypothesized to trigger higher-level cognitive and attention mechanisms, allowing further evaluation of the event. The second stage would be reflected by the P300 responses (especially the P3a and the novelty-P3).

- In the third processing stage, if the unexpected stimulus does not warrant a change in task priorities, the participant focuses back to the task at hand. This stage is reflected by the Re-Orienting Negativity (RON), a late frontal ERP with a negative peak 400–600 after the onset of the unexpected event (Schröger and Wolff 1998a; Horváth, Winkler, and Bendixen 2008). Few studies have investigated the functional significance of the RON but it has been hypothesized to reflect the attention reorientation process which shifts the attention focus away from the unexpected event and back on the task-relevant events. The RON is often absent of studies investigating distraction due to the short interstimulus interval in most oddball studies (~300 ms) which does not allow the observation of late ERPs or due to a lack of interest to the re-orientation process. If the RON is elicited in active experimental designs in situations when a reorientation on the task at hand is required, a similar late negative ERP following the P300 response can be observed in passive settings (Morlet et al. 2017; Oades, Zerbin,

and Dittmann-Balcar 1995). This component have been coined the "N3" (Barry and Rushby 2006; Kotchoubey and Pavlov 2019) and has been hypothesized to be a signature of "passivity" and a necessary closure of the cognitive processes triggered during the P300 (Kotchoubey and Pavlov 2019).

This model of the chain of ERPs involved in the processing of unexpected stimuli is a useful framework to investigate distraction, but data show that it may not reflect the complexity of the cognitive mechanisms at plat. The N1/MMN, the P3a and the RON are not strongly coupled ERPs as the P3a can be elicited without concurrent N1-increase or MMN elicitation and without subsequent elicitation of the RON (Horváth, Winkler, and Bendixen 2008).

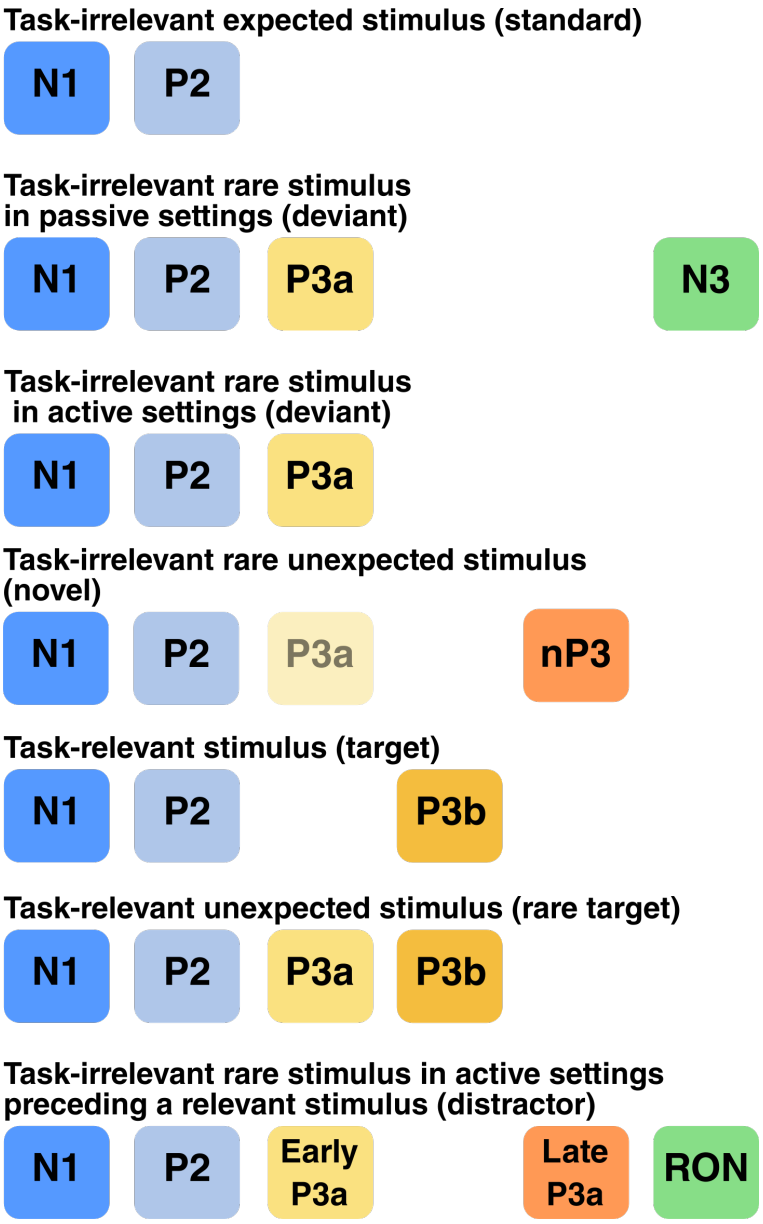


Figure 6: *Summary of the sequences of event-related potentials elicited by different auditory stimuli. Components in a same column present a similar latency and often a close scalp topography.*

1.3.2 Neural rhythms and attention mechanisms

Neural oscillations were first described as early as 1924 by Hans Berger who recorded large-amplitude rhythms induced by eye closure. They consist in sinusoidal signals generated by the brain and can be observed using EEG or MEG. They are characterized by main properties: frequency, power, and phase. Oscillations are clustered into frequency bands, including delta (1–4 Hz), theta (4–7 Hz), alpha (7–15 Hz), beta (15–30 Hz), gamma (>30 Hz). Power is the amount of energy in a frequency band and is mathematically associated with the amplitude of the sine wave. Phase is the position along the sine wave at any given time point. Neural oscillations would be the macroscopic manifestation of synchronized activity in a large neuronal ensemble; they result rhythmic patterns of action potentials produced by a given population of neurons. Neural oscillations play a key role in communication within and between neural ensembles and in cognitive functions, particularly attention (Buzsáki and Draguhn 2004).

Alpha oscillations Alpha-oscillations are usually observed among awake, eyes-shut and inactive participants and are maximal over occipital electrodes. Therefore, alpha oscillations were for a long time considered to reflect *cortical idling*, or in other words to be an electrophysiological correlate of the deactivated state of cortical areas (Pfurtscheller, Stancák, and Neuper 1996). Indeed, a suppression of alpha activity (sometimes referred to as *event-related alpha desynchronization*), has been historically observed when a participant is engaged in a cognitive or motor task (especially when difficult), suggesting that alpha rhythms are elicited when a cortical region is not involved in the task at hand (Pfurtscheller and Silva 1999). However, recent theories of alpha rhythms emphasize the active functional roles of alpha in information processing and attention.

According to *inhibition-timing hypothesis*, alpha oscillations are induced by inhibitory cells (GABAergic interneurons) and reflect dynamic changes of neuronal inhibition (Klimesch, Sauseng, and Hanslmayr 2007). The neuron firing rate would be sensitive to the phase of the alpha sinewave, alternating between periods of high and absent spiking activity. Low alpha amplitude would allow a tonic spiking activity – reflecting a general state of high excitability –, while increases in amplitude would promote a rhythmic spiking activity by only providing a small time-window for neuronal firing – reflecting a state of low excitability i.e. inhibition. Building on this theory, the *gating by inhibition hypothesis* states that alpha oscillations participate in shaping functional architecture of the different brain networks. According to this hypothesis, in a certain task, neural pathways could be either task-relevant or irrelevant: alpha power would increase in task-irrelevant brain areas, blocking information processing along task-irrelevant pathways, and subsequently gating the information flow to

the task-relevant pathway (Jensen and Mazaheri 2010).

This theoretical framework is useful to understand modulations of alpha activity during tasks involving top-down selective attention. In Posner-like tasks, the participant is attending to the cued hemifield in anticipation of a visual target: this is associated with alpha power decreases in contralateral visual areas responsible for processing the attended space and alpha power increases in ipsilateral visual areas responsible for processing the unattended space (Kelly et al. 2006; Marshall et al. 2015; Rihs, Michel, and Thut 2007; Rihs, Michel, and Thut 2009; Thut et al. 2006; Worden et al. 2000) (Figure 7). These observations are not specific to spatial attention: in a task during which participants were asked to attend to the color or the motion property of a visual stimulus, alpha increases were detected in color-processing areas when attending to motion and in motion-processing areas when attending to color (Snyder and Foxe 2010). Most of these studies have investigated the impact of anticipatory attention on alpha modulations in occipital areas, during visual tasks. The literature on alpha modulations in the auditory cortices has been historically scarce, in part due to the geometry of auditory areas which impedes their detection with EEG (Weisz et al. 2011). However, Müller and Weisz (2012) provided evidence of cortical generators of alpha activity in the auditory cortices and this study has been followed by several reports of auditory alpha modulations (Mazaheri et al. 2014; Weise et al. 2016; Weisz et al. 2014; Weisz and Obleser 2014). Importantly, alpha power appears to be a good predictor of behavioral performance. The increase in alpha power in irrelevant regions and/or the decrease in alpha power in relevant regions during the anticipation period before the target correlate with reaction time in various experimental designs (Bonnefond and Jensen 2012; Händel, Haarmeier, and Jensen 2011; Mazaheri et al. 2014; Payne, Guillory, and Sekuler 2013; Thut et al. 2006).

In the light of all these results, alpha synchronization and desynchronization in sensory cortices have been proposed to be the manifestation of top-down attentional facilitatory mechanisms. This is comforted by the recent evidence that the dorsal attention network would be coordinating alpha power modulation in sensory cortices. Interfering with the functioning of the nodes of the DAN using repetitive transcranial magnetic stimulation (rTMS) during a Posner task leads to worse performance and a disruption of anticipatory alpha desynchronization in the occipital cortex (Capotosto et al. 2009). A stronger synchrony (a measure of functional connectivity) in the alpha band between nodes of the DAN and the sensory cortices have been reported during visual and auditory spatial attention tasks (Doesburg, Bedo, and Ward 2016; Capotosto et al. 2009; Huang et al. 2014; Lobier, Palva, and Palva 2018; Müller and Weisz 2012; Weisz and Obleser 2014). However, the involvement of alpha rhythms in top-down inhibitory mechanisms is still controversial as the corpus of evidence linking alpha power increases to the active suppression of irrelevant stimuli is limited

(Foster and Awh 2019; Noonan et al. 2018).

As I have discussed above, alpha rhythms have been closely associated with top-down attention mechanisms and voluntary shifts of attention. However, a few studies seem to indicate that they may be involved in bottom-up attention orienting and distraction too. In two separate studies, a research group used an experimental design in which a non-predictive task-irrelevant auditory cue preceded a visual (Feng et al. 2017) or auditory (Störmer et al. 2015) target to discriminate. In "valid" trials (when the cue and the target were on the same side), participants presented better performance. The task-irrelevant cue triggered an alpha desynchronization in bilateral occipital cortices but which was more pronounced in the hemisphere contralateral to the sound's location: this alpha desynchronization in the contralateral occipital cortex was predictive of behavioral performances. During an active oddball paradigm with standard or novel sounds preceding visual targets, behavioral distraction in novel trials was associated to a pre-target alpha desynchronization in occipital cortices (Weise et al. 2016). This desynchronization was predictive of reaction time on a trial-by-trial basis.

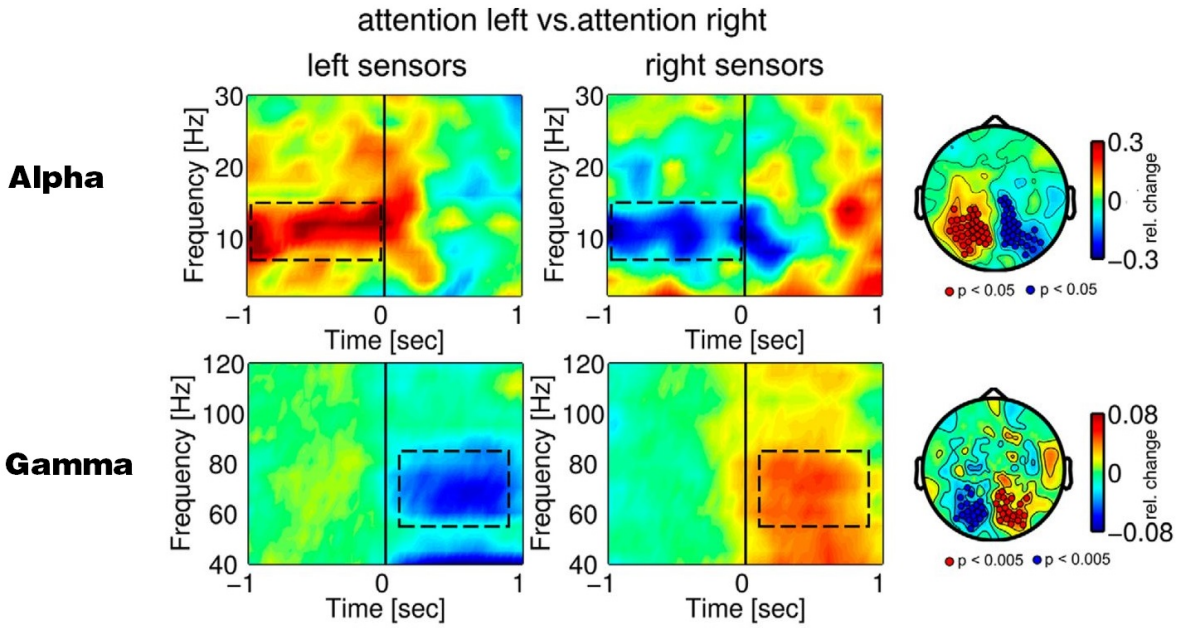


Figure 7: *Time-frequency representations of target-locked oscillatory power for left versus right cued trials during visual target expectancy. (top) Pre-target alpha power increased in sensors ipsilateral to the cue direction, whereas it decreased in contralateral sensors. (bottom) Post-target gamma power decreased relatively in sensors ipsilateral to the cue direction, whereas it increased in contralateral sensors. Adapted from Popov, Kastner, and Jensen (2017).*

Gamma rhythms If alpha rhythms have been observed and investigated since the 1920's, research on gamma rhythms is more recent and was not possible before the advent of digital EEG whose recording capacity (>200Hz) far surpassed that of its analogue counterpart (<25Hz). Gamma rhythms have been hypothesized to participate in *perceptual binding*. The conscious perception of an object as a coherent whole presume the ability to "bind" all the features associated with the object into a single phenomenal experience (Singer 2001). This gamma-binding hypothesis proposes that by synchronizing assemblies of neurons that process distinct features of an object, the "fractured" features of the object are linked into a unified, coherent percept (Tallon-Baudry and Bertrand 1999). However, it would be preposterous to assert a general theory of the functional role of gamma oscillations. Gamma rhythms are induced by sensory stimulation, they are associated with a wide range of cognitive processes and they have been detected all over the brain. Gamma activity could rather be conceptualized as a universal signal involved in all types of functional processes (Başar 2013).

Gamma rhythms have been associated with attention mechanisms. During attention tasks, gamma rhythms display the opposite behavior of alpha rhythms as gamma power is enhanced in task-relevant cortical areas (Figure 7). Attending to a location or to a feature is accompanied with increased gamma power in the visual area responsible for processing of this location or feature (human and monkey studies reviewed in Gregoriou, Paneri, and Sapountzis 2015). Electrocorticography data have shown enhanced gamma power in the auditory cortex when attending a sound or in the somatosensory cortex when attending tactile stimulation (Ray et al. 2008). During a dichotic listening experiment, attending to stimuli rather than ignoring them leads to increased gamma transient responses (Tiitinen et al. 1993); target and novels sounds produce gamma transient responses which originate from the same areas known to be generators of the P3b and the P3a (Lee et al. 2007). Voluntary attention orienting have been associated with gamma transient responses, originating from the attention networks (Ahveninen et al. 2013; Fan et al. 2007; Landau et al. 2007). Top-down attention would also be reflected by sustained (rather than transient) gamma responses in the dorsal attention network (Ossandón et al. 2012). Sustained gamma activities originating from visual areas have been found to be modulated by selective attention (Kahlbrock et al. 2012; Tallon-Baudry et al. 2005). Finally, similarly to alpha rhythms, gamma band activity correlates with behavioral performances (e.g. Ahveninen et al. 2013; Kaiser et al. 2006) and more specifically, gamma band activity in the lateral prefrontal cortex was shown to predict attentional performances (Rouhinen et al. 2013).

The alpha/gamma interplay in attention Cortical areas are organized with characteristic laminar patterns of feedforward and feedback projections. Intracranial recordings (often in the occipital cortex) in humans and non-human primates have consistently associated alpha and beta rhythms with feedback projections and gamma rhythms with feedforward projections (Buffalo et al. 2011; Lee, Whittington, and Kopell 2013; Mejias et al. 2016; Xing et al. 2012). The visual system is hierarchically organized with low-level areas representing simple features and higher areas representing the more complex aspects of the visual world. High-frequency oscillations appear to propagate in the feedback direction (from primary areas to associative areas) while slow oscillations are more associated with the feedback influence of high-level areas onto low-levels areas (Bastos et al. 2015; van Kerkoerle et al. 2014). These observations have led to a model of attention in which top-down processes are mediated through alpha rhythms while bottom-up processes are mediated though gamma rhythms (Fries 2015; Schroeder and Lakatos 2009).

1.4 The role of arousal in attention

It would be dishonest to discuss too much about attention without integrating the role of arousal. Arousal (sometimes referred as physiological activation) is classically defined as the psychological and physiological state of awoken, characterized by a condition of unspecific sensory alertness and readiness to respond. Behavioral performance and sensory perception do not solely depend on higher cognitive functions and the selective aspects of attention, it is conditioned by the arousal state of the participant. Attention and arousal are deeply enmeshed brain functions whose interactions are crucial to experience the world around us. Arousal is mediated by several neurotransmitter systems originating from the brainstem reticular formation but is more closely associated with the locus cœruleus and norepinephrine (LC-NE) system. Consequently, changes in arousal result in peripheral automatic responses, which are valued tools for the researcher to investigate arousal. In this section, I will describe the role of arousal in attention from physiological, psychological and neuroimaging standpoints.

1.4.1 Theories of arousal

Arousal and performance Reflections on the impact of physiological arousal on task efficiency have begun on the very beginning of the twentieth century. In experimental designs, arousal can be enhanced either “internally” by elevating task demands/difficulty which compels the participant to be more involved or “externally” using external stressors such as

white noise. Yerkes and Dodson (1908) trained mice to perform a discrimination task and modulated arousal using electric shocks and varying task difficulty. Based on the results, they derived a law stating that it exists an inverted-U relationship between arousal levels and task performance and that this relationship interacts with task difficulty (Figure 8). In other terms, they hypothesized that there is a moderate level of arousal optimal for task-efficiency, meaning that too little or too much arousal results in poor performance, and this optimal level depends on task difficulty. This model is in line with common-sense, empirical observations: a drowsy, sleep-deprived, fatigued person will often have trouble being efficient during a difficult task and so will an excessively anxious and stressed individual. Numerous following studies have reported a similar pattern: however the strength of the experimental evidence is dubious as most studies only used 3 levels of arousal and obtaining a U-relationship by chance is more likely than not. Yerkes and Dodson never discussed the underlying mechanisms and processes of this relationship and numerous psychologists have attempted to explained how arousal impacts performance. A comprehensive review of these theories is available in Eysenck (2012), I will present quickly the most prominent ones.

Easterbrooks's hypothesis states that the effects of arousal on performance are mediated by attention mechanisms. He posited that heightened arousal results in increased attentional selectivity, in other words that increased arousal narrows the range of cues that can be processed and used during a task (Easterbrook 1959). This model provides an explanation for the U-relationship: too little arousal leads to insufficient suppression of superfluous stimuli and not enough attention directed towards the task at hand; excessive levels of arousal, especially during difficult tasks, would disrupt performance by interfering with the encoding of any relevant input outside the very central focus of attention. Easterbrook's hypothesis has been hugely influential and is often used as the basis of subsequent theories of arousal.

Another seminal publication on arousal and performance was written by Kahneman (1973), who proposed the *Capacity model of attention*. Kahneman introduced to concept of effort into the equation which he defines as "the intensive aspect of attention". According to Kahneman, mental effort produces physiological arousal and can be measured (and therefore investigated) using peripheral responses such as pupil dilation, skin conductance or the heartbeat. During a task, the more effortful is the task, the more cognitive resources (referred as "capacity") are supplied to the task. However, as the total capacity is limited, high effort during difficult, demanding tasks would lead to a shortage of capacity available for performing secondary tasks or simply monitoring the environment (Figure 9). Also, if task difficulty plays a crucial role on determining the amount of effort engaged in a task, motivational factors are also likely to be involved. If Kahneman emphasized the concept of effort, he crafted a much larger framework in order to explain how attention and arousal

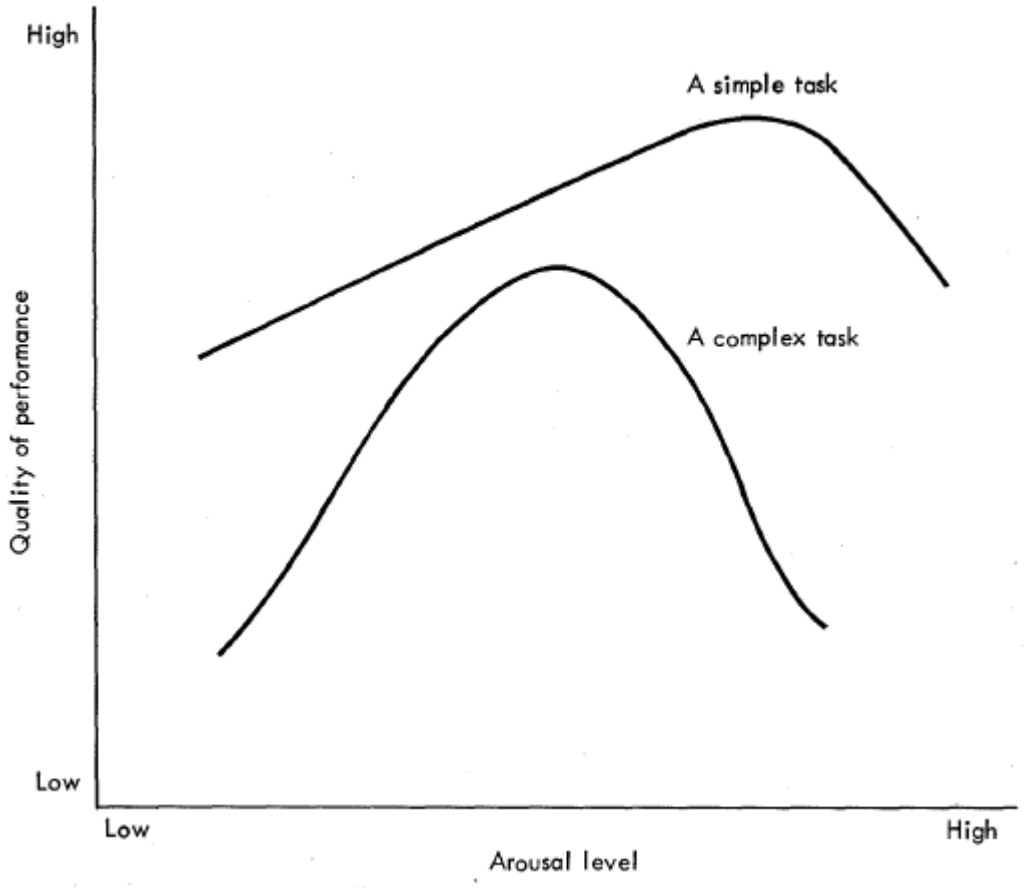


Figure 8: *The Yerkes-Dodson Law. Adapted from Kahneman (1973).*

interact. At the center of this framework are two core concepts: the *allocation policy* and the *evaluation of demands*. The allocation policy selects to which activities cognitive resources will be distributed and is controlled by voluntary processes (internal motivations) or involuntary processes (such as attention capture by novel stimuli). The evaluation of demands controls the amount of cognitive resources (i.e. the arousal level) to be supplied to meet current or anticipated demands (i.e. the activities or tasks that the allocation policy have chosen). Kahneman's theory implicitly distinguish two kinds of arousal: arousal produced by the individual actively involved in a task (i.e. effort) which is generally beneficial for performance and arousal produced by an external stressor which often result in a deterioration of performance because they interfere with the allocation policy (attention capture, attention narrowing...). If Kahneman's framework has been extremely influential in general, it has also experienced a "revival" in hearing impairment research as incorporated the *Capacity model of attention* to create the Framework for Understanding Effortful Listening (FUEL). If this model has been created for the hearing impairment research community, their work

to update Kahneman's theory is valuable even for basic auditory attention research (Figure 10).

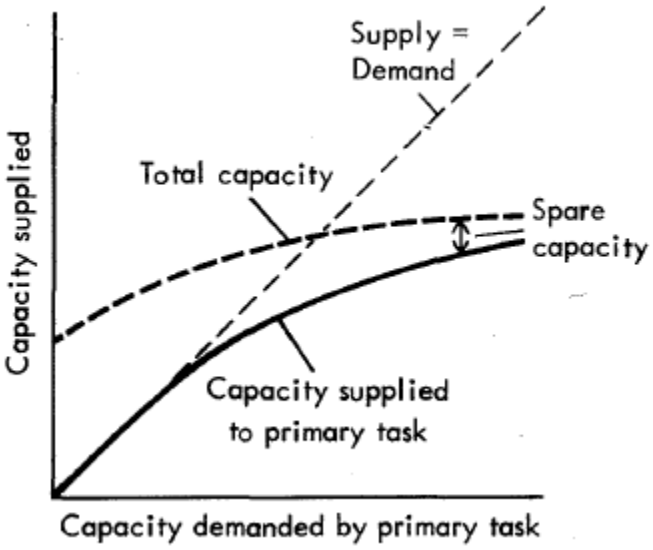


Figure 9: *Supply of capacity (i.e. cognitive resources) in response to the demands of the primary task. Adapted from Kahneman (1973).*

Thayer and Russell approached the concept a little bit differently and their hypotheses ended up to be in line with Kahneman's implicit postulate of two distinct arousal systems. Based on questionnaire data on which he performed a factor analysis, Thayer (1967) concluded that there were four activation factors: *General Activation* (lively, active, full of pep, energetic, peppy, vigorous, activated), *Deactivation-Sleep* (sleepy, tired, drowsy), *High Activation* (clutched up, jittery, stirred up, fearful, intense), and *General Deactivation* (at rest, still, leisurely, quiescent, quiet, calm, placid). Russell (1979) used Thayer's questionnaires and additional self-reported data for a factor analysis and discovered that one's internal emotional state could be described with a two-dimensional space with arousal level and pleasure-displeasure as orthogonal factors (Figure 11a). These works were precursors of the *Self-Assessment Manikin*, a widely-used psychometric to tool to classify a person's affective reaction to a stimulus according to three dimensions: pleasure, arousal and dominance (Bradley and Lang 1994) (Figure 11b).

Until now, I have discussed how arousal acts and fluctuates at the time-scale of an experimental task, or in other words, how the tonic level of arousal impacts the general performance of an individual. This echoes the psychological concepts of vigilance or sustained attention, which are the abilities to maintain the focus of attention for prolonged periods of time, from tens of seconds to several hours. However, arousal modulations can also be much

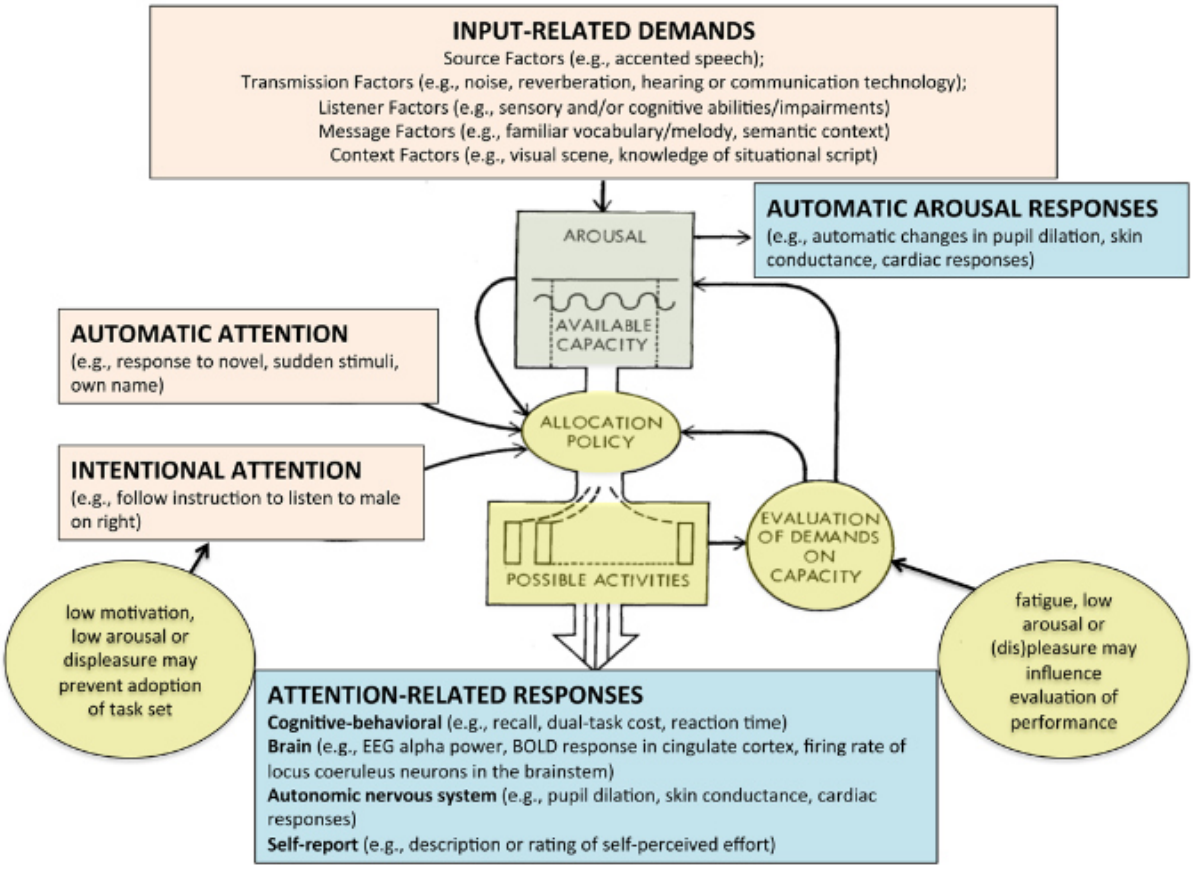


Figure 10: *The Framework for Understanding Effortful Listening (FUEL) by Pichora-Fuller et al. (2016) based on Kahneman (1973). The "inputs-related demands" might be specific to experimental designs in hearing impairment research using semantic stimuli but the rest of the framework is rather universal. This model in particular shows how top-down attention (here intentional attention), bottom-up attention (here automatic attention) and arousal are articulated .*

more transient and perceptible at the time-scale of the second or less.

Arousal and the orienting response

Description of the orienting response The orienting response (or orienting reflex, OR) was first mentioned by Pavlov (1927):

> "It is this reflex which brings about the immediate response in man and animals to the slightest changes in the world around them, so that they immediately orientate their appropriate receptor-organ in accordance with the perceptible quality in the agent bringing about the change, making full investigation of it."

Pavlov's studies were reevaluated in the 1960's and the OR brought to the awareness of psychophysiologists by the works of Sokolov (1963). The OR follows the presentation of a

novel stimulus and consists in wide-ranging complex of autonomic peripheral responses which occur within seconds after the stimulus onset (e.g. Uno and Grings 1965), including changes in electro-dermal (skin conductance), cardiac (heart rate deceleration), respiratory (pause in respiration) and pupil diameter (dilation) measures, and central nervous system responses such as alpha desynchronization (e.g. Barry and Beh 1972). Habituation with repetition is the most important characteristic of the OR. When a participant is presented a sequence of tones to attend, only the first two sounds elicit a skin conductance response (SCR) (Uno and Grings 1965). The OR is primarily elicited by novel, unexpected events that somewhat violate the expectations of the individual. However, the OR is not only dependent on the novelty of the stimulus, its intensity also contributes to its elicitation. It has been established without doubt that autonomic measures of the OR positively correlate with sound loudness (Barry and Furedy 1993; Jackson 1974; Turpin and Siddle 1979; Uno and Grings 1965). In summary, the OR results a phasic increase in arousal following novel or significant events in the environment, which leads to a transient state of sensory alertness state and readiness to respond.

It has been proposed that the OR represents a call for a reallocation of resources for further processing of the novel/significant stimulus (Kahneman 1973; Siddle and Spinks 1992). This is reflected by overt mechanisms, namely postural changes to orient towards the probable sources of stimulation (increased ocular motion or simply turning one's head toward an unexpected noise). Bottom-up attention orienting is merely a component of the OR and cannot be comprehend fully without considering all the physiological aspects of the OR.

Effects of phasic arousal Understanding the duality of the mechanisms elicited by novel sounds, i.e. bottom-up attention orienting and the orienting response, can shed light on the paradoxical effects of task-irrelevant salient sounds on behavior. Previously, I have associated unexpected salient sounds with distraction, attention capture and deterioration of performances. This pattern of results is very prevalent in experimental designs investigating attention, however this is far from being the only effect of novel sounds. There is a rich literature investigating the effects of *warning signals* or *accessory stimuli*. In those paradigms, task-irrelevant and (supposedly) totally uninformative sound may precede the onset of the target in some trials. Warning signals (sometimes referred as alerting cues) generally precede the target by several hundreds milliseconds, effectively warning the participant that a target will soon appear; accessory stimuli are played almost simultaneously with the target, with a delay inferior to 50 ms and sometimes nonexistent. Both warning signals and accessory signals have been associated with a reduction of reaction time (Hackley and Valle-Inclán

1998; Hackley and Valle-Inclán 1999; Hackley 2009; Posner, Nissen, and Klein 1976; Posner 2008; Ulrich 1996). It has been hypothesized that the faster responses are mediated by an automatic increase of phasic arousal elicited by the warning signal/accessory stimuli, facilitating target processing and leading to an increase of general readiness to respond (Hackley 2009). This theory is corroborated by the fact that faster responses are associated with large pupil dilation responses (Tona et al. 2016; Petersen et al. 2017). The effect of phasic arousal is modality-aspecific: faster reaction time can be observed regardless of the sensory modality of the warning signal and of the target (Fernandez-Duque and Posner 1997; Posner, Nissen, and Klein 1976). The effect of phasic arousal is also proportional to the intensity of the warning signal (Petersen et al. 2017).

However, according to the Yerkes-Dodson law, increases in arousal can lead to better performance as long as the optimal level is not exceeded. Therefore, it is conceivable that a salient stimulus may have detrimental effects on performance in certain experimental designs by increasing phasic arousal past adequate levels. This has been investigated in Poth (2019) in which the author used both warning signals and accessory stimuli during target detection task. When used alone, warning signals and accessory stimuli led to decreased reaction time, as expected. However, when both were presented during a trial, the beneficial effects were negated and reaction time was increased. This is a convincing illustration of the complex effects of phasic arousal on performance.

1.4.2 Neural correlates of arousal

Neurotransmitter systems of arousal All major neurotransmitter systems have been implicated in the regulation of arousal processes, notably via the ascending reticular activating system (ARAS). The ARAS is a set of interconnected nuclei (dopaminergic, noradrenergic, serotonergic, histaminergic, cholinergic, and glutamatergic) located in the brainstem which send neuromodulatory projections to the entire cortex and particularly the prefrontal cortex. In his comprehensive review, Robbins (1997) examined the anatomy and the functional roles of each system and concluded:

> "Each of the neurotransmitter systems we have described has rather different, sometimes context dependent, functions in arousal-like processes. The [locus coerulus–norepinephrine system] seem to have a protective function of maintaining discriminability in stressful or arousing circumstances or maintaining 'alerting' to salient external stimuli; the mesolimbic and mesostriatal [dopaminergic] systems play a role in the activation of output, whether cognitive or motor in nature; the latter system appears to play a greater role in the endogenous activa-

> tion of behaviour; the cholinergic systems appear to enhance stimulus processing at the cortical level in several different forms of processing, including attentional selection, discrimination learning and spatial working memory; and the [serotoninergic] systems may serve to dampen the actions of each of the others, for example by promoting behavioural inhibition and cortical de-arousal."

However, it is now consensually accepted that the locus coerulus–norepinephrine system (LC-NE) has the most central implication in the control of arousal.

The Locus Cœruleus–Norepinephrine system The LC is a small nucleus located in the reticular formation in the brainstem. It projects onto all cortical regions, the thalamus, the amygdala and the hippocampus and is their sole source of noradrenergic neurotransmission (Figure 13). It has been known for a long time that the LC is involved in the sleep-wake cycle and the regulation of cortical arousal (Berridge 2008; Sara 2009). There is growing evidence that the LC-NE system mediate cognition and attention processes in the prefrontal cortex (Arnsten 1998; Sara and Bouret 2012). Administration of clonidine, an agonist of the noradrenergic receptors that decreases baseline NE activity, leads to impaired performance in selective attention and working-memory tasks (Mair et al. 2005; Ramos and Arnsten 2007); a lesion to the LC is generally associated with impaired cognitive performance (Aston-Jones and Cohen 2005).

Physiological recordings of LC neurons in macaques or rodents have identified two modes of activity: *tonic activity* – a baseline rate of spiking activity, and *phasic activity* – rapid increases in the firing rate. Phasic LC activity have common conditions of elicitation with the orienting response. Novel stimuli or task-relevant targets trigger bursts of action potentials in the LC (Aston-Jones et al. 1994; Aston-Jones and Cohen 2005; Rajkowski, Kubiak, and Aston-Jones 1994; Sara, Vankov, and Hervé 1994) and this response to novelty rapidly habituates with the repetition of the stimulus (Hervé-Minvielle and Sara 1995; Vankov, Hervé-Minvielle, and Sara 1995). Arousing stimuli are particularly efficient to drive a phasic response from the LC (Berridge and Waterhouse 2003). Phasic LC activity would produce a widespread but temporally specific release of NE which would facilitate sensory processing and promoting task-appropriate behavior. LC activation would also mediate the autonomic responses classically associated with the OR (pupil dilation, skin conductance response, etc.), through a pathway that is not yet elucidated (Costa and Rudebeck 2016). Periods of elevated tonic LC activity are concomitant to degraded performance and more distractibility: the animal displays less engagement in the task a greater tendency to respond to nontarget stimuli (Aston-Jones and Cohen 2005). High tonic activity also diminish the phasic response to target stimuli (Figure 12). This pattern is in line with the Yerkes-Dodson law as excessive

levels of arousal are expected to result in disappointing performance and poor cue utilization.

It has also been proposed that the LC-NE system is directly involved in attention orientation and reorientation. The NE release by the LC could be seen as an "interruptor signal" that would drive the ventral attention network to "reset" the dorsal attention network, enabling a attention shift (Corbetta, Patel, and Shulman 2008; Dayan and Yu 2006; Sara and Bouret 2012).

The P300 responses, markers of phasic arousal? In two exhaustive and influential reviews, Nieuwenhuis and collaborators have proposed that the P300 responses would be a reflection of the phasic arousal component of the orienting response and the electrophysiological correlate of the LC phasic response (Nieuwenhuis, Aston-Jones, and Cohen 2005; Nieuwenhuis, de Geus, and Aston-Jones 2011). The argumentation is based on several observations and results. The main arguments include that: (1) the P300 responses, the LC-NE phasic responses and the autonomic components of the orienting response all share the same antecedent conditions: they are triggered by novel, salient, unexpected stimuli, (2) they all habituate with repetition (for further discussion, see Barry, Steiner, and De Blasio 2016; Barry et al. 2020), (3) their amplitude increases with the intensity of the stimulus, (4) the occurrence of a P300, an autonomic response or a LC phasic response is associated with better task performance. Surgical lesions of the LC in macaques cause decreased P3a-like response to deviant stimuli (Pineda, Foote, and Neville 1989), P3a and P3b amplitude are sensitive to the administration of noradrenergic drugs (Brown et al. 2015; Missonnier et al. 1999). The latency of the LC phasic response is around 150 ms (Aston-Jones et al. 1994; Rajkowski, Kubiak, and Aston-Jones 1994) and the slow velocity of ascending NE fibers (around 150 ms post-discharge to detect cortical effects) (Berridge and Waterhouse 2003) would be consistent with the latencies of the P300 responses. The difference in latency between the fronto-central P3a and the parietal P3b could be the result of the anatomy of NE fibers, which first innervate frontal areas and then progressively continue to innervate more posterior parts of the cortex (Morrison, Molliver, and Grzanna 1979).

The main limit of this theory is that a lot of the experimental attempts to correlate the magnitude of P300 responses to autonomic responses following novel sounds have led to inconclusive and inconsistent results (Barry et al. 2013; Berti, Vossel, and Gamer 2017; Kamp and Donchin 2015; Lyytinen, Blomberg, and Näätänen 1992; Marinkovic, Halgren, and Maltzman 2001; Rushby and Barry 2009).

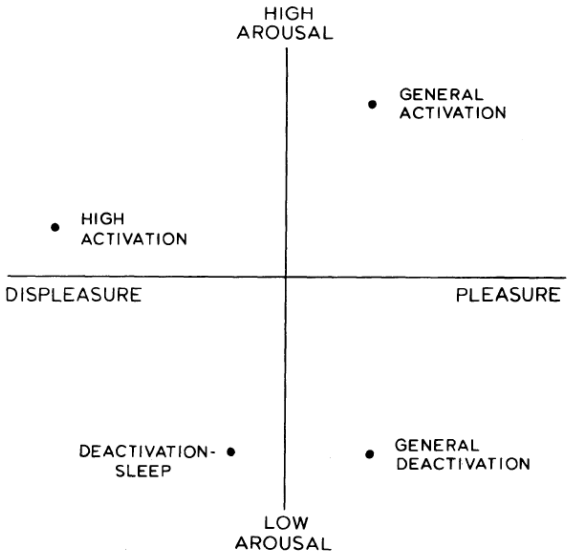
An arousal network There are now several converging fMRI studies suggesting the involvement of a cortical network in maintaining alertness (i.e. tonic arousal): the cingulo-

opercular/insular network (Figure 14). During tasks necessitating to maintain vigilance during long period, higher pre-stimulus activity in a cingulo-opercular network (which comprises the anterior cingulate cortex (ACC), the anterior insula, the frontal operculum and the thalamus) resulted in faster response speed. (Coste and Kleinschmidt 2016; Sturm and Willmes 2001; Sadaghiani and D'Esposito 2015; Sadaghiani and Kleinschmidt 2016). During a resting-state session, the CON activity positively correlated with the pupil diameter, confirming the association of this network with tonic arousal Kuchinsky, Pandža, and Haarmann (2016). The role of this network might be to exert a top-down control on LC activity. It has been established that the cingulate cortex (and the orbitofrontal cortex) send strong projections directly to LC (Aston-Jones and Cohen 2005; Rajkowski 2000).

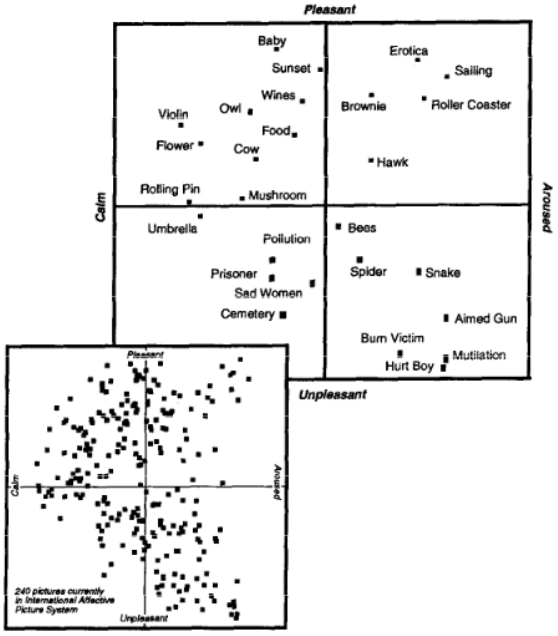
There is also a rich literature describing a *salience network*, a set of cortical areas whose activities during resting-state fMRI session correlate with the participants level of pre-scan anxiety (Seeley et al. 2007). The salience network has some major overlap with the cingulo-opercular network and it is still discussed whether the distinction between the two denominations is justified (Gratton, Sun, and Petersen 2018).

Arousal and oscillations Neural oscillations have been of crucial importance in sleep research as the stages of sleep can be distinguished in part based on the respective power of delta, theta and alpha waves. This framework has been extended to use oscillations as a tool to investigate changes in arousal in the awake participants. The ratio of theta to beta power in the EEG signal have been proposed to reflect tonic arousal (Clarke et al. 2019; Howells, Stein, and Russell 2010). It has been effectively used as a proxy for tonic arousal in ADHD research (Barry et al. 2004; Huang et al. 2015).

Attention and arousal are inseparable brain functions which should be investigated in tandem. Both attention and arousal can be triggered in a bottom-up fashion by salient events, both can be controlled in a top-down fashion by internal motives. If attention consists in allocating cognitive resources in the processing of selected sources of stimuli, arousal mediates the total amount of cognitive resources available. A balance between top-down attention, bottom-up attention and arousal is necessary to maintain task-efficiency while still being aware of one's environment. Distraction is a very transient and fleeting phenomenon: EEG and MEG are tools of choice to investigate attention and arousal as they provide information at a very fine-grained temporal resolution, allowing to access the different stages on sensory processing.



(a) *The location of Thayer's arousal factors on Russell's two-dimensional space to describe affects. Adapted from Russell (1979)*



(b) *Placement of several pictures in a two-dimensional affective space defined by the* Self-Assessment Manikin *pleasure and arousal ratings (upper plot), and 240 pictures from the International Affective Picture System plotted in the affective space (lower plot). Adapted from Bradley and Lang (1994).*

Figure 11: *The importance of arousal to measure emotion.*

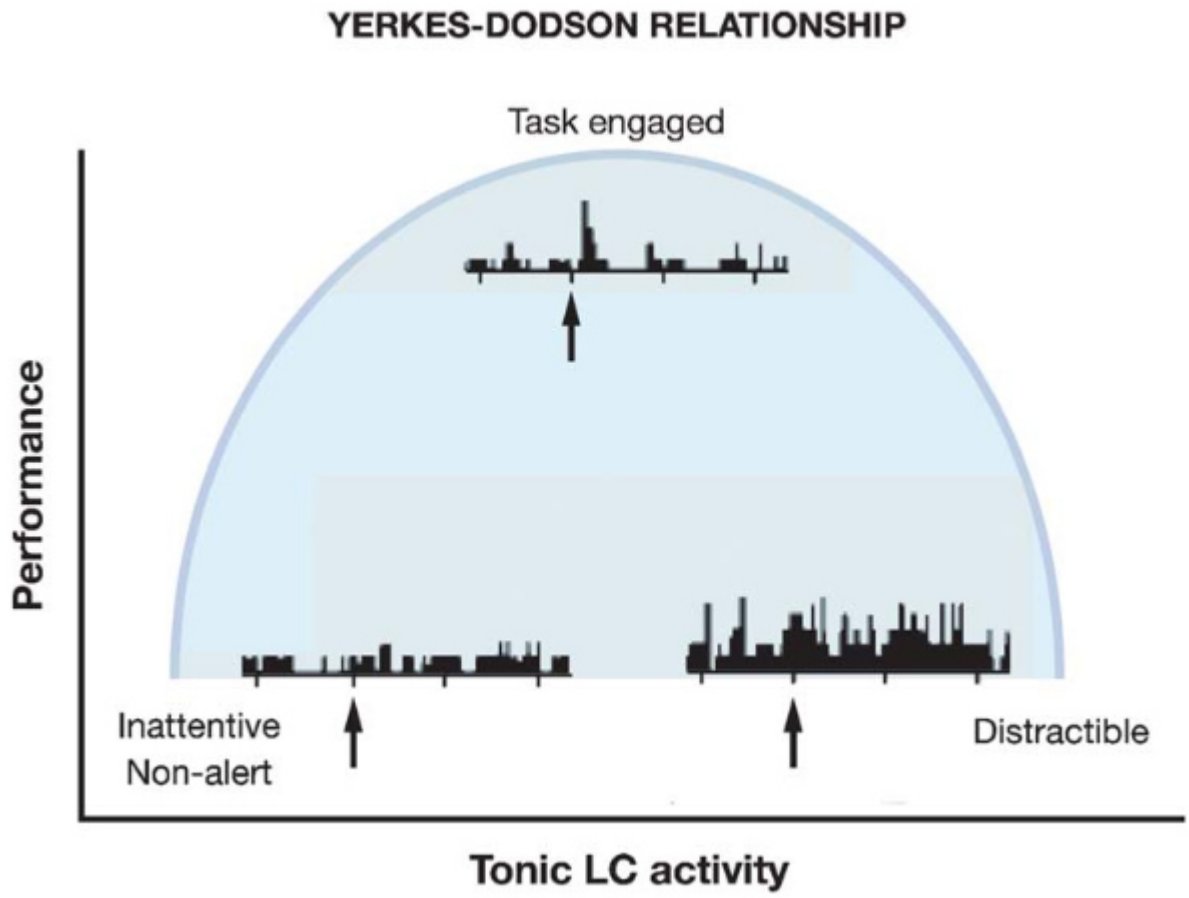


Figure 12: *Inverted-U relationship between LC activity and performance on tasks that require focused attention. Here is represented the spiking activity of the locus cœruleus before and after target presentation (indicated by the arrow): at moderate levels of tonic LC activity, the phasic peak of LC activity following the target is clearly visible, contrary to low and high levels of tonic LC activity. Adapted from Aston-Jones and Cohen (2005) based on intracerebral animal recordings.*

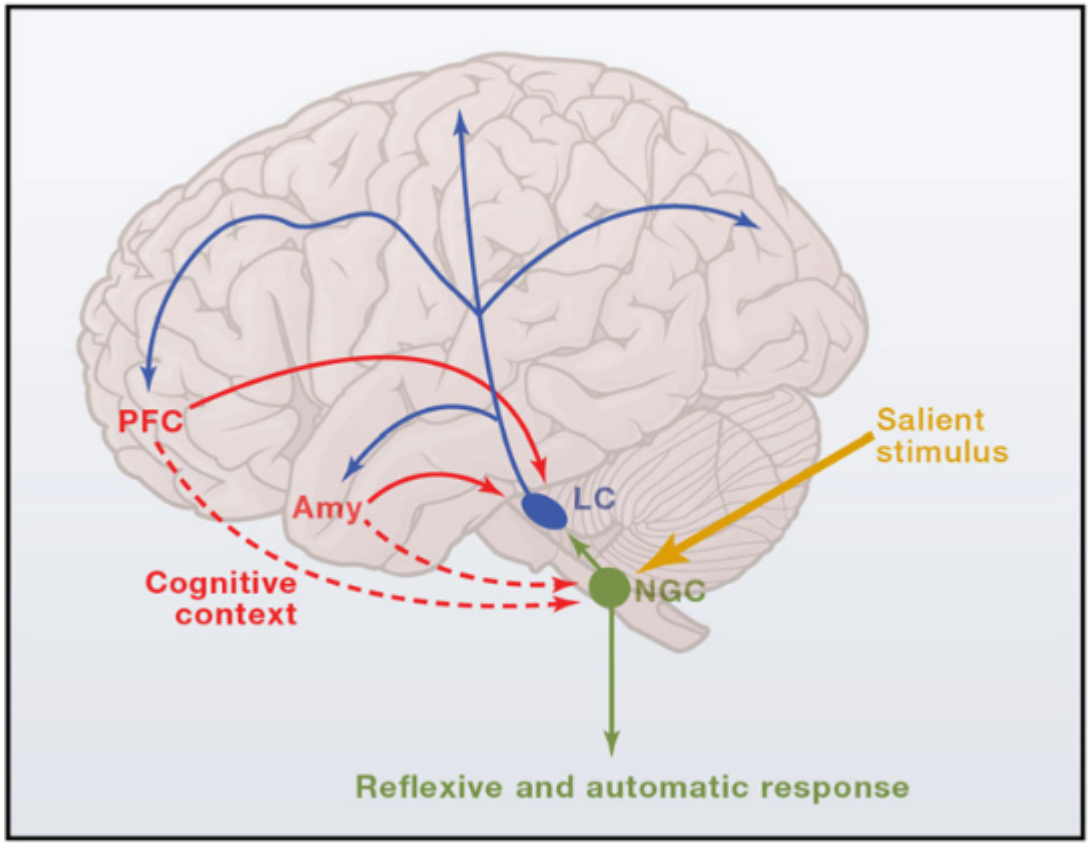


Figure 13: *Schematic overview of the proposed mechanisms underlying the LC activation and its function. Amy = amygdala; LC = locus cæruleus; NGC = nucleus gigantis cellularis; PFC = prefrontal cortex. Adapted from Sara and Bouret (2012).*

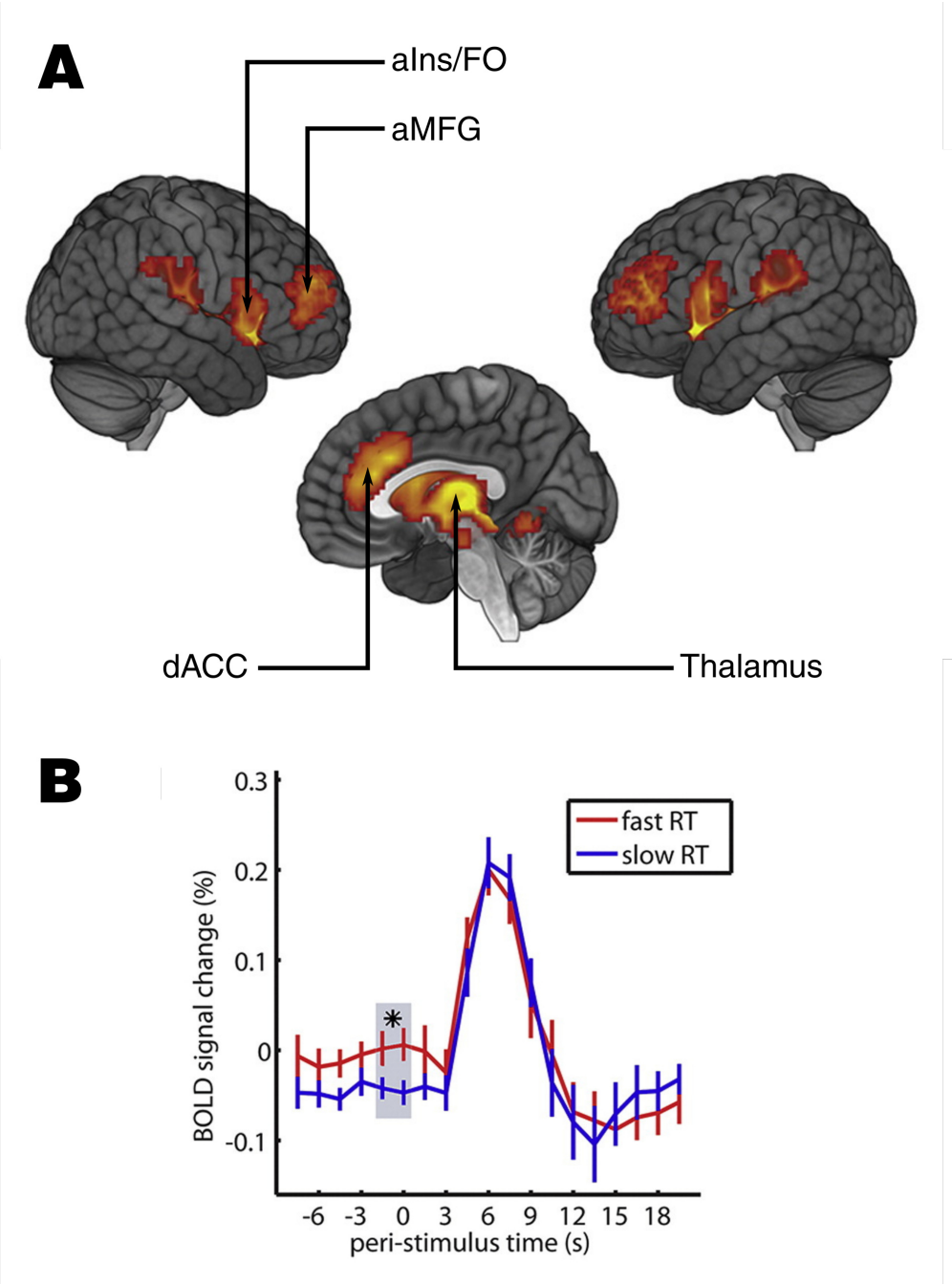


Figure 14: *(A) The activation of cingulo-opercular network during the pre-stimulus period. (B) Time-course of the BOLD signal change averaged over the entire cingulo-opercular network in fast and slow reaction time trials. aINS/FO = anterior insula/frontal operculum; aMFG = anterior middle frontal gyrus; dACC = dorsal anterior cingulate cortex. Adapted from Coste and Kleinschmidt (2016).*

2 Sensory processing disturbances in migraine

Numerous neurological conditions are associated with attention difficulties from neurodevelopmental disorders (e.g. autism spectrum disorders, attention-deficit and hyperactivity disorder), neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease), neurological disorders (e.g. epilepsy, brain trauma) or psychiatric disorders (e.g. alcoholism, depression, post-traumatic syndrome disorder). As I have discussed above, attention shapes our perception of our environment and a dysfunction of attentional mechanisms can lead to abnormal sensory processing.

In this thesis work, we will investigate the attention function in migraine, a very common neurological disorder, and how it may relate with the sensory hypersensitivity symptoms associated with the disease. In a first part, I will give a general presentation of migraine, from its symptoms to its underlying causes, to provide context. If you are not interested in the pathophysiology of migraine, you can skip this part and read directly from page 55. In a second part, I will focus on sensory processing disturbances, characterizing the pathological mechanisms involved and how attention fits into the pathophysiology of the disease.

2.1 Pathophysiology of migraine

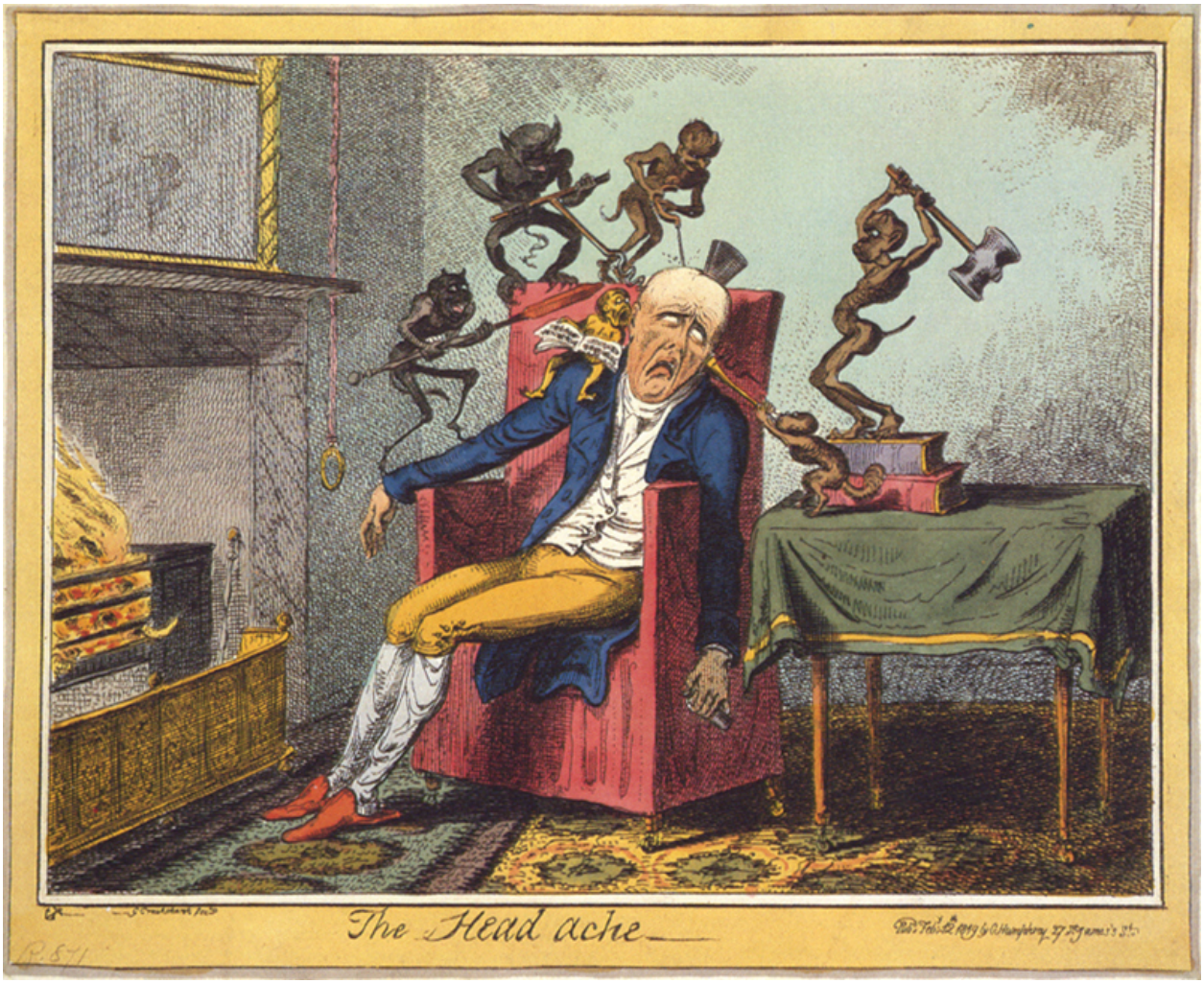


Figure 15: *"The Head Ache". Hand-colored etching by George Cruikshank (English, 1792–1878), possibly after Frederick Marryat (English, 1792-1848). Migraine headaches manifest through one-sided pulsatile and debilitating pain, which is exacerbated by bright light, noise, or touch. Migraine attacks can deeply affect daily life, leaving migraineurs unable to carry out even simple tasks.*

2.1.1 Brief history of migraine

[2]

Migraine is far from being a disease of modern times: descriptions of the disorder can be traced all the way down to the beginning of written history. Babylonian literature has evoked "head disease" that "flash[es] like lightning" nearly 4000 years ago (Rose 1995); the Ebers Papyrus written in ancient Egypt in 1550 BC mentions a courtesan of Pharoah's court afflicted with a "disease of one half of the head" (Ghalioungui 1987). However, it is unsure

[2]This section is loosely adapted from Katherine Foxhall's book, "Migraine: A History"

that these vague descriptions could be conclusively identified as migraine. The first clear description of migraine and its associated aura appears in Hippocrates' *Epidemics* in the 5th century BC, in which is mentioned a young man who suffered from:

> "[...] flashes like lightning in his eye, usually the right. And when he had suffered that a short time a terrible pain developed towards his right temple, then in the whole head, and then into the part of the neck where the head is attached behind the vertebra behind, and there was stretching and hardness around the teeth. He kept trying to open them, straining... vomits, whenever they occurred, averted the pains I have described, and made them more gentle. Phlebotomy helped." (Smith 1994)

Coherent concepts of migraine became apparent in the late Antiquity. Aretaeus of Cappadocia, a Greek physician from the 1st century AD, produced one of the first classification of headaches with *cephalagia* (acute headache, probably referring to tension headache), *cephalae* (chronic headache, probably referring to traumatic headaches) and *heterocrania,* whose symptoms match with those of migraine. He also wrote the first known description of the photophobia associated to migraine attacks:

> "the pain [...] remains in the half of the head. This is called heterocrania, an illness by no means mild, even though it appears to be slight [...] it sets in acutely, it occasions unseemly and dreadful symptoms [...] nausea; vomiting of bilious matter [...] there is much torpor, heaviness of the head, anxiety and weariness. For they flee the light; the darkness soothes their disease; nor can they bear readily to look upon or hear anything disagreeable; their sense of smell is vitiated." (Rose 1995)

Galen, a Greek physician from the 2nd century AD, described migraine as "a painful disorder affecting approximately one half of the head, either the right or left side, and which extends along the length of the longitudinal suture [...]" and then coined the term *hemicrania* from which the modern term of "migraine" is derived (hemi-crania: half of the head, as a reference of the unilateral pain during migraine attacks).

Migraine was taken seriously by European medicine in the Middle Ages as several medical texts can attest. Medieval practitioners were aware of the descriptions of migraine written by ancient physicians, and notably their humoral theory of migraine. Migraine was considered to be associated with yellow or red bile (choler) as it is explained in one of the most famous medieval encyclopediæ:

> "The head is grieved with an ache and an evil that physicians call Emigranea, as said Constantine. And he said, this ache and evil is most grievous: for who has that evil, feels in his head, as it were beating of hammers, and may not suffer noise, nor voice, nor light, nor shining. And this evil is of choleric smoke with hot wind and windiness and therefore he feels in his head putting & pricking, burning and ringing." De Proprietatibus Rerum ("On the Properties of Things") by Bartholomaeus Anglicus, 13th century

Remedies and therapies consisted in restoring balance in the humoral system. In Bald's *Leechbook*, an Anglo-Saxon extensive guide of standard practice for the medical practitioner, six herbal remedies for migraine are listed (e.g. "For ache of half the head. Take the red nettle of one stalk, bruise it, mingle with vinegar and the white of an egg, put all together, anoint therewith."). Bartholomeus Anglicus in *De Proprietatibus Rerum* and the *Wisdom of the Art of Medicine*, a 6th century medical text, recommended phlebotomy (bloodletting), purging and appropriate medications to treat the disease.

This humoral framework persisted into the early modern period, as can attest recipe books advising for herbs and various household ingredients (Foxhall 2019), and it was only during the end of the 19th century that migraine and its treatments were reconceptualized. Physicians challenged the concept of "bilious headache" and rather focused on the physiology of migraine. Two main theories confronted each other, supported by two influential figures of the time (Weatherall 2012). The *vascular theory* proposed by Peter Wallwork Latham is based on observation of experimental surgeries on migraine patients which showed that migraine attacks were associated with a vasodilatation of cranial vessels and on his exposure to studies on the sympathetic nervous system. Latham posited that violent emotions over-stimulate the sympathetic system leading to a constriction of cranial vessels before the migraine attacks, which would underly to aura phenomenon; then the attack would emerge from the sympathetic "depression" necessarily following the "excitation", leading to the dilatation of cranial vessels and the pain. The *nervous theory* proposed by Edward Liveing was inferred from the observation of numerous migraine cases in which he noted a comorbidity between epilepsy and migraine. He proposed that migraine attacks consisted in a cyclical discharge of accumulated tension in the nervous system. Liveing was convinced that "hemicrania, migraine, sick-headache, biliousness, blind-headache, suffusion dimidians, hemiopia, neuralgie ophthalmique and so forth" were all members of the same "pathological family". Liveing was an ardent detractor of a vasomotor mechanism of migraine attacks and observed the vascular disturbances described by Latham and other authors as mere epiphenomena. Despite lively debate, pathophysiology of migraine remained quite elusive and such theories were mostly speculative. In 1886, Gowers discussed the pathophysiology of migraine in its

Figure 16: *A doctor making a small bleeding to treat his patient's headaches, by Bartholomeus Maton, Dutch, 17th century.*

influential "Manual of Diseases of the Nervous System" and then in later clinical lectures (Gowers 1906) and discredited both of the theories, precipitating their decline. He pointed out that there was no conclusive evidence for the vasomotor changes at the center of the *vascular theory*, and he demonstrated that the link between migraine and epilepsy was tenuous and that they consisted in distinct clinical entities.

On the other hand, consensus was reached between physicians that migraine was an hereditary disease, as the prevalence in families could attest (Gowers 1886; Liveing 1873). Clinical experiments were conducted to find pharmacological treatments, including cannabis, caffeine and various pharmacological cocktails. The 1897 "Handbook of Materia Medica" recommended antipyrin, an antipyretic and analgesic, as "the most single valuable remedy for

headache, especially in migraine". However, migraine research could not shake out Victorian era's gender and class preconceptions, which heavily shaped physicians' view on the disease. Women were thought to be more prone to functional disorders of the nervous system including migraine, neurasthenia or epilepsy. In its influential *The Lancet* article in 1854 in which he proposed a classification of headaches, Patrick J. Murphy assured that "neuralgic headache" was "undoubtedly hysterical" in origin (Murphy 1854). Some considered migraine as a disease of modern life and specific higher classes. W. Bolton Tomson expressed that "from the standpoint of the evolutionist, instability of the highest nerve centres is due to their being the most recently evolved, and is therefore a necessary evil accompanying an intellectual advancement."; while Samuel Wilks wrote in a *The Lancet* article:

> "The migrainous patient frequently belongs to the most cultivated and intellectual class of society, and is of the temperament called neurasthenic, whilst the epileptic, in my experience, belongs to a lower grade, and is generally the stupid one of the family; [...] I will not go as far as to absolutely endorse an opinion expressed by more than one observant medical man, that migraine is never met with amongst the lower orders, although it is difficult to conceive how such services as those of policemen or engine-drivers could go on were it at all common amongst the working community." (Wilks 1888)

In the 20$^{\text{th}}$ century, theories on the pathophysiology of migraine multiplied but most of them did not lead to major advancements in the understanding of the disease or in potential therapies. Recent developments in medicine provided new frameworks in which migraine could be conceptualized. Migraine was proposed to result from the accumulation of body toxins, allergies and inflammatory reactions, disruption of the endocrine system... Psychology also took on the subject and attempted to describe a "migraine personality" – usually with driven, perfectionist and inflexible traits –, theories often also perpetuating classist and sexist views from the 19$^{\text{th}}$ century.

In the second half of the 20$^{\text{th}}$ century, two drugs revolutionized how migraine was treated, both agonists for 5-HT serotonin receptors: ergotamine – an ergot derivative known since the beginning of the century –, followed by the triptans, better tolerated by patients. Interestingly, they were developed for their vasoconstriction properties within the context of the vascular theory of migraine, a theory now disproven (Goadsby 2009). These discoveries re-legitimized the vascular theory of migraine, until the 1990's when it became clearer that the therapeutic effects of the molecules was mediated by their action on the brain neurotransmission, and not from the vasoconstriction effects on cranial vessels. Nevertheless, these drugs have changed the life of millions of migraineurs, by either preventative therapy aiming

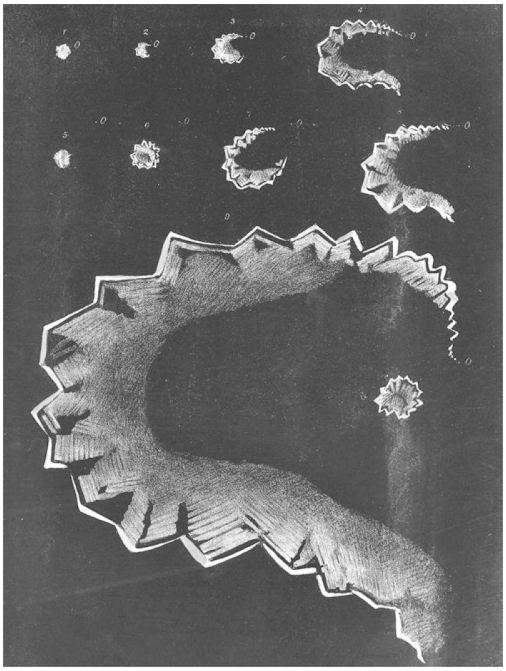
to lessen the frequency of the attacks or the treatment at the time of the attack in order to mitigate the symptoms (Goadsby, Lipton, and Ferrari 2002). The realization that the vascular theory was erroneous and that the mode of action of triptans involved effects on neurotransmission participated in part to the reclaiming of migraine by neurologists.

2.1.2 Signs and symptoms

> "I can feel the pounding in my temples, or in my eyes, depending on where the migraine is. If it's a migraine on one side, that eye gets very watery and my temple throbs, and the top of my skull feels like it's being pressed down on. I definitely have to avoid looking directly at light. Thankfully, I do not feel nauseous. With one particularly bad migraine, I could not get up from bed because every time I was upright, seated or standing, the pain [would be] in the left side of my head. I had to stay in bed lying on the side that did not hurt, while manually massaging my left temple until it had subsided slightly." *Eduardo, 32.*
>
> "I first start to feel tightness and pain in my neck, and I stretch it and roll it, trying to decide if [a migraine] is coming. Then I generally get sweaty and nauseous and anxious, a bit like I'm having a panic attack. Sometimes I get weird symptoms like a runny nose and sneezing. Then the pain starts, usually over one eye, and it feels like my head is going to explode. I have to avoid all light or it just feels like someone is stabbing me." *Elizabeth, 34.* (Andriakos 2019)

Definition Prevalence of migraine in the adult population is high, estimated between 10 and 20% (Henry et al. 2002; Lipton et al. 2007; Stewart, Shechter, and Rasmussen 1994), making migraine the most common neurological disorder in adults. Sex-ratio is strongly biased towards women, which are two to five times more likely to have migraine than men (Lipton et al. 2007; Russell et al. 1995). Almost 40% of women and 20% of men will contract migraine in their lifetime, usually before the age of 35 (Stewart et al. 2008).

The word "migraine" is a tricky word in colloquial language. In French and in English, it is often used as a through misuse of language as a general synonym for "headache", whereas migraine is a subclass of headaches and a legitimate neurological disorder. Since the antiquity, physicians have attempted to classify headaches based on associated symptoms and the localization of the pain. In 1981 was founded the International Headache Society which published in 1988 the first *International Classification of Headache Disorders (ICHD-1)*, a systematic classification of all headaches and explicit diagnostic criteria. This project has profoundly changed the way headaches are diagnosed and treated by medical professionals.



(a) *"Diagram of Transient Teichopsia," plate XXV, from Hubert Airy, "On a Distinct Form of Transient Hemiopsia," 1870.*

(b) *"Retour au château", by Giorgio de Chirico, 1969.*

Figure 17: Pictural depictions of the migraine aura. *Migraine aura precede migraine attacks in a subset of migraine patients and is often associated with visual symptoms. Scotoma alter a restricted part of the visual field: objects may be totally obscured or a flickering spot may appear close to the center of the visual field (scintillating scotoma).*

In 2018, the third (and current) edition (ICHD-3) was published in the journal Cephalalgia.

Migraine is a defined by the ICHD-3 as a disorder associated to the following symptoms (International Headache Society (IHS) 2013):

- Recurrent headache lasting between 4 and 72h when left untreated. These headaches must present at least two of the following symptoms:
  - *Unilateral location*: during a migraine headache, pain is usually localized on one side of the skull.
  - *Pulsating quality*: pain is often described as a "beating of hammers"; it is not continuous but throbbing.
  - *Moderate or severe pain intensity*: migraine headaches are usually painful enough to significantly impact daily tasks.
  - *Aggravation by routine physical activity* (e.g. walking or climbing stairs), sometimes referred as kinesiophobia.
- Headache is associated to at least one of the following symptoms:
  - Nausea and/or vomiting.
  - Photophobia and phonophobia (aversion to light and sound).
- The patient has suffered from at least 5 attacks fulfilling the symptoms above.

Differential diagnosis should aim to eliminate other types of headache, namely[3]:

- Other primary headaches (i.e. recurrent headache not caused by an underlying disease):
  - *Tension-type headache.* The most common type of headache affecting between 30% and 90% of the population (International Headache Society (IHS) 2013; Lyngberg et al. 2005; Rasmussen et al. 1991; Schwartz et al. 1998; Stovner et al. 2007), it is usually triggered by stress, anxiety, or unhealthy life habits.
  - Trigeminal autonomic cephalalgias, notably *cluster headache.* It is characterized by excruciating pain around one eye, associated to redness and tearing of the eye and to nasal congestion, happening during cluster periods lasting for weeks to months.
- Secondary headaches (i.e. the headache is to a presumed causative disorder)

[3]This is obviously not an exhaustive list

  - Headache attributed to head trauma, infection, vascular disorder, substance withdrawal etc.

- Neuropathies (i.e. a condition affecting nerves of the peripheral nervous system)
  - *Trigeminal neuralgia.* Characterized by episodes of severe, sudden pain in one side of the face that lasts for seconds to minutes, it is presumed to result from a demyelinisation of the trigeminal sensory fibers (Love and Coakham 2001).

Non-headache symptoms Migraine is frequently associated to non-painful symptoms that accompany the headache or appear before and/or after the headache. Apart from the aura phenomenon (described in the next paragraph), peri-ictal symptoms (during the premonitory and postdrome phase) have been less extensively researched than ictal symptoms (during the attack). Nevertheless, these manifestations are of great value as they give insight into migraine pathophysiology and they may participate to theraupetic approaches involving the prediction of migraine attack onsets.

Premonitory symptoms usually precede the onset of the migraine attack by a few hours, but can emerge up to 72 hours before the headache (Goadsby et al. 2017). There is a great diversity of premonitory symptoms, the most common being fatigue, difficulty concentrating, light sensitivity and a stiff neck. Less common symptoms include phenomena as curious as thirst, hunger, nausea, yawning, blurred vision, difficulty with thought and reading, frequent urination... Patients can accurately predict a migraine headache using premonitory symptoms in three quarters of the cases (Giffin et al. 2003).

Postdrome symptoms are largely similar in nature to premonitory symptoms (Blau 1991; Giffin et al. 2016; Kelman 2006). Postdrome symptoms can help the clinician to diagnose migraine (Blau 1991), especially in the context of migraine without aura (see below). The diversity of premonitory and postdrome symptoms is an indication that the whole brain is affected by migraine attacks.

Migraine triggers Migraineurs frequently report that certain environmental factors may trigger headache attacks. The analysis of migraine diaries from large samples of migraineurs have helped to identify the most frequent trigger factors. They include behavioral triggers (stress, skipping a meal, too much or too little sleep), hormonal triggers (menstruation among women), environmental triggers (weather, perfume or odor, bright light, loud noises, heat), psychotropic substances (alcohol consumption, smoking or caffeine withdrawal), dietary triggers (food, especially chocolate) and exercise (Andress-Rothrock, King, and Rothrock 2010; Kelman 2007; Martin and Behbehani 2001). Migraine attacks can also be triggered artifi-

cially using chemicals, notably nitroglycerin (Maniyar et al. 2014b) which has been used in clinical studies focusing on the headache phase. Identifying trigger factors has been proposed to be used as a prophylactic strategy to manage migraine headache as limiting the exposure to those factors may prevent the onset of an attack. However there is no conclusive evidence that this strategy is efficient in preventing attacks and it may be totally impractical as these factors are omnipresent in the everyday life (Martin 2010).

Subtypes of migraine and aura phase Several subtypes of migraine have been described in the literature and some have been included in the ICHD-3. One of the main dichotomy is the presence or the absence of a migraine aura. About a third of migraine patients experience migraine aura(Rasmussen and Olesen 1992), which are transient neurological symptoms that precede the onset of the migraine attacks and usually disappear once the pain is installed. Nowadays, migraine with aura (also referred to as *ophthalmic migraine*) and migraine without aura are usually considered to consist in two distinct clinical entities (Russell et al. 1996), as reflected in the ICHD-3 (International Headache Society (IHS) 2013). Most of migraine auras consist in visual disturbances (Russell and Olesen 1996), such as scotoma – a partial alteration of the visual field which results in a loss a visual acuity and the apparition of dark spots (see Figure 17b) –, scintillating scotoma – flickering lights or curious patterns such as zigzags (see Figure 17a) that appear in an area close to the center of the visual field –, or phosphenes – the impression of "seeing stars" i.e. bright spots in the visual field. Some patients also reported to experience palinopsia (images persist after their corresponding stimulus has left), micropsia (objects appear smaller than they are), or macropsia (objects appear larger than they are) associated with a migraine aura (Queiroz et al. 1997). Sometimes the visual aura is accompanied by a somato-sensory aura, often characterized by a tingling sensation in the hands, limbs and face. A minority of migraineurs with aura experience aphasia (speech impediment) in anticipation of the migraine attack. In *hemiplegic migraine*, the aura is accompanied by motor symptoms, namely stroke-like symptoms such as aphasia, ataxia, and weakness of half the body.

Another major dichotomy in the literature is the distinction between *episodic migraine* and *chronic migraine*. Chronic migraine is defined by the ICHD-3 as an attack frequency superior to 15 days per month in the absence of any preventative treatment. The prevalence of chronic migraine in the general adult population is estimated between 1.4 and 2.2% (Natoli et al. 2009), representing around 8% of migraine cases (Buse et al. 2012). In chronic migraine, attacks are so frequent that it is delicate to distinguish individual attacks from one another; patients are more often that not in moderate to severe pain and medication is unavoidable to maintain a tolerable quality of life. The constant use of triptans or ergotamine to prevent

and to manage the attacks can lead to *medication-overuse headache (MOH),* a secondary headache condition often observed in chronic migraine patients (Diener and Limmroth 2004).

Migraine presents a high comorbidity with vertigo, with 9-12% of migraineurs affected with vestibular symptoms (Lempert and Neuhauser 2009; Vuković et al. 2007), which has led physicians to coin the concept of *vestibular migraine* (International Headache Society (IHS) 2013). In vestibular migraine, vestibular symptoms such as vertigo and dizziness can happen in anticipation of the onset of migraine attacks or temporally unrelated to the attacks.

The societal burden of migraine For obvious reasons, migraine is associated to a decreased quality of life, especially in more chronic forms of the disease (Guitera et al. 2002). Migraine is linked to lower levels of household income, higher levels of depression and anxiety, and a high comorbodity with cardio-vascular diseases and respiratory disorders (Buse et al. 2010). The World Health Organization considers migraine on its own the sixth most disabling disorder in the world (in terms of years of healthy life lost to disability), headache disorders taken collectively were third highest (World Health Organization 2016). The Global Burden of Disease (GBD) study estimated in 2016 that in the age group 15–49 years, migraine alone would be the top cause of disability in the world (Steiner et al. 2018; Vos et al. 2017).

Migraine could be considered an epidemic in the broad sense of the word but it seems rather neglected from a public-health perspective. The Eurolight project was a large-scaled, questionnaire-based study conducted in 2016 among ten European countries aiming to evaluate the impact of headache disorders on public health (Andrée et al. 2011). Subsequent analyses have shown that migraine is underdiagnosed and undertreated: a minority of migraineurs have seen a general practitioner or a specialist, and an even smaller minority of migraineurs for whom a medication would be required have actually been prescribed acute or preventative medication (Katsarava et al. 2018). Among migraineurs requiring medication, only half of them were prescribed some after a consultation (Katsarava et al. 2018). Still, it seems important to mention that half of migraineurs present mild and infrequent enough headaches that over-the-counter medications are sufficient to manage the symptoms (Steiner et al. 2011). In France, the GRIM2005 study estimated that 30% of migraineurs had never consulted for headache, 30% were in active consultation and 40% had previously consulted but lapsed (Lantéri-Minet et al. 2007); only 2.3% of the French population present an active prescription for triptans, an acute specific treatment for migraine headaches, while the prevalence of migraine exceeds 15% of the adult population (Henry et al. 2002) .

The Eurolight project estimated migraine to cost 1222€ per person per year in the European Union, representing a €50 billion (almost 0.3% of the PIB) annual financial burden (Linde et al. 2012). Indirect costs – absenteeism and reduced productivity – account for 93%

of this total. Direct costs (7%, ~85€ per person per year) are related to healthcare intervention, including diagnostic interventions, prophylactic and acute medications, hospitalization and outpatient care. Another cross-sectional study estimated a much higher direct cost of migraine (closer to 500€ per person per year), a cost even larger for chronic migraine whose annual cost is around three times higher than that of episodic migraine (Bloudek et al. 2012).

2.1.3 Neurophysiological bases for migraine

Genetics of migraine Migraine present a strong genetic component. Twin studies have shown that migraine present an hereditability (genetic influence on phenotype) ranging from 34% to 57% (Mulder et al. 2003). First-degrees relatives of patients with migraine without aura have 1.9-fold increased risk of migraine without aura, while first-degrees relatives of patients with migraine with aura have 4-fold increased risk of migraine with aura (Russell, Iselius, and Olesen 1996).

Family hemiplegic migraine (FHM) is a rare subtype of migraine with aura characterized by dominant autosomal monogenic mutations. Three genes (all encoding ion transporters) may be impacted: CACNA1A (FHM1 subtype) which encodes a subunit for a neuronal calcium channels (Stam et al. 2008), ATP1A2 (FHM2 subtype) which encodes a Na^+/K^+ pump (Riant et al. 2005), and SCN1A which encodes a subunit of neuronal sodium channels (Dichgans et al. 2005). All these mutations may lead to increased neuronal excitability and the FHM1 mutation has been linked to increased susceptibility of Cortical Spreading Depression (CSD, described below) in animal models (van den Maagdenberg et al. 2004).

Even if familial types of migraine can be of interest for migraine pathophysiology, genome-wide association studies (GWAS) are more likely to paint a broader picture of the general genetic influence on migraine. GWAS compares the entire genome between two large groups of individuals with the hope to detect single-nucleotide polymorphisms (SNPs) associated with a particular disease. A recent meta-analysis (Gormley et al. 2016) comprising 60,000 migraineurs and 300,000 control participants have detected 38 loci associated with migraine, the most significant being: LRP1 – a lipoprotein involved in glutamatergic pain signaling, PRDM – involved in neuronal development, and TRPM8 – a ionic channel expressed on C- and Aδ-fibers (see next paragraph). Migraine appears to be a polygenic disease, with multiple predisposition factors.

Neural basis of headache pain and associated symptoms

Anatomy of trigeminovascular pathways The brain in itself in considered to be totally insensible to pain as it does not have nociceptors. The headache during migraine attacks

is thought to emerge from a peripheral source, namely sensory fibers innervating intra- and extracranial blood vessels (Olesen et al. 2009). Pial, arachnoid and dural arteries and veins present nociceptors and are innervated mainly by the ophtalmic division of the trigeminal nerve (Penfield and McNaughton 1940; Ray and Wolff 1940). This innervation of meninges and cranial blood vessels consist in non-myelinated (C-fibers) and thinly-myelinated (Aδ-fibers) axons whose cell somas can be found in the trigeminal ganglion; they convey the information to the spinal trigeminal nuclei (STN). The STN ascending projections transmit information to several brainstem nuclei, including the locus cœruleus and the periaqueductal gray, the hypothalamus and thalamic nuclei (Liu et al. 2009) (Figure 18). In turn, thalamic trigeminovascular neurons project to a wide range of cortical areas: the insula and motor, parietal association, somatosensory, auditory, visual and olfactory cortices (Noseda and Burstein 2013). Thalamus is also at the center of the pain matrix, a complex and fluid network of cortical and subcortical brain areas activated during nociceptive perception (Tracey 2005; Tracey 2008). The somatosensory cortices, the anterior cingulate cortex, the amygdala, the insula, the prefrontal cortex and the hippocampus are considered to be involved in pain processing, encompassing the sensory, cognitive, emotional, and memory dimensions of pain.

Theory of trigeminal sensitization Animal models of neurovascular headache were developed in the 1980's and have enabled to demonstrate that mechanical or electrical stimulation of the dura lead to response in nociceptive neurons in the thalamus, hypothalamus and the medulla (Davis and Dostrovsky 1986; Strassman et al. 1986). Using this animal model, it was observed that a irritation of the dura using inflammatory mediators can lead to a sensitization of peripheral neurons in the trigeminal ganglion: electrophysiological unitary recordings showed that these neurons became responsive to light mechanical stimulation of the dura which would trigger no response before sensitization (Strassman, Raymond, and Burstein 1996). This *peripheral sensitization* would account for the throbbing perception of migraine headache and its exacerbation by physical activity and head movements which increases the pulse pressure in the head. Subsequent studies also observed that after dura irritation, innocuous stimulation of the periorbital region of the face (also innervated by the ophtalmic branch of the trigeminal nerve) triggered massive neuron firing in the STN, whereas innocuous stimulation of other parts of the body triggered responses in trigeminovascular thalamic neurons, which was not the case before sensitization (Bernstein and Burstein 2012; Burstein et al. 2010). These instances of *central sensitization* would respectively account for (1) the cephalic cutaneous allodynia (pain following non-noxious stimulation) and muscle tenderness observed during migraine headache (Burstein et al. 2000), (2) the extra-

cephalic cutaneous allodynia also associated with the migraine headache.

The theory of "peripheral and central sensitization" is today the most accepted framework to explain migraine pathophysiology (Bernstein and Burstein 2012; Goadsby et al. 2017; Noseda and Burstein 2013). It postulates that a peripheral trigger, namely an inflammation of the dural meninges, leads to sensitization of first-order (trigeminal ganglion), second-order (trigeminal spinal nuclei) and third-order (thalamus) trigeminovascular neurons. It provides explanation for the source and the nature of migraine headaches but also to its complex associated symptomatology, including cephalic and extra-cephalic allodynia. As stated previously, the trigeminovascular ascendant pathways project in several brainstem and diencephalic structures. Disruption of hypothalamus functioning, a structure responsible for the regulation of numerous bodily functions, would account for the nausea, vomiting and hunger disturbances observed during the headache phase (and beyond). Disruption of thalamic functioning would account for sensory symptoms (developed below).

Cortical spreading depression If the theory of sensitization is clearly important to explain migraine pathophysiology, it does not provide a mechanism for the activation of meningeal receptors. Some researchers have proposed that *cortical spreading depression (CSD)* would be the physiological trigger of migraine headache (Charles and Baca 2013; Noseda and Burstein 2013). CSD is a phenomenon first described in the 1940's in animal models by Aristides Leão (Leao 1944) and has now been extensively studied in numerous animal models. In humans, it has been observed in patients with brain injury, including brain trauma, meningeal hemorrhage and stroke (Dreier et al. 2009; Hartings et al. 2011; Woitzik et al. 2013). It consists in a slow propagating wave of anormal brain activity that disturb neuronal, glial, and vascular functions. It involves a massive depolarization of neurons and glials cells, which release locally K^+ and H^+ ions, ATP, glutamate and various other metabolites in the extracellular milieu, leading to cellular swelling and drastic vascular changes (Charles and Baca 2013).

But what is the link with migraine? First, the CSD phenomenon is surprisingly similar to the aura that precede the migraine headache: the evolution of the scotoma patterns during the migraine aura maps the temporal and spatial progression of the wave across the occipital cortex (Lashley 1941). There is evidence from animal studies that CSD may activate meningeal nociceptors (Zhang et al. 2010) via the release of calcitonin gene-related peptide (CGRP) and nitric oxide by vascular cells (Noseda and Burstein 2013), as well as central neurons of STN (Zhang et al. 2011). Evidence also come from the genetic factors underlying migraine: patients with familial hemiplegic migraine, an hereditary form of migraine, may present a monogenic mutation, which has been associated with an increased susceptibility

of CSD in animal models (Leo et al. 2011; van den Maagdenberg et al. 2004).

However, this theory is still very controversial (Borgdorff 2018). First and foremost, the features of CSD have never been observed in human migraineurs. Scalp EEG recordings do not show particular changes during migraine aura (Lauritzen, Trojaborg, and Olesen 1981; Parain et al. 2007) and no electrocortical EEG recordings of migraine aura have been attempted as it is not routinely feasible in migraine patients (unlike patients with brain injury). Then, several physiological hallmarks of CSD (cell swelling, increased cerebral metabolism, etc.) have not been observed in human migraineurs (Borgdorff 2018). Also, it does not provide explanation for premonitory symptoms preceding the attack. And finally, if CSD seems to be a physiological correlate of migraine aura, migraine aura is present in only a minority of migraineurs. It is unlikely that different migraine subtypes do not share the same basic pathophysiology (Goadsby et al. 2017).

Migraine, a metabolic disorder This theory stems from the observation that many of migraine triggers – physical activity, skipping meals, dehydration, or lack of sleep – are linked to cerebral energy metabolism and the level of oxidative stress (Borkum 2016; Gross et al. 2019). Magnetic resonance spectroscopy (MRS) studies have shown between attacks, migraine is associated with abnormal mitochondrial oxidative phosphorylation and lower levels of ATP suggesting deficient energy production and increased energy consumption in the migraineur brain (Cevoli, Favoni, and Cortelli 2019; Ramadan et al. 1989; Reyngoudt et al. 2011). There are indirect evidence for disruption of glucose metabolism and mitochondrial function in migraine (Gross et al. 2019). GWAS demonstrated that migraine is associated with SNPs in loci in mitochondrial DNA and nuclear genes coding for mitochondrial proteins (Gormley et al. 2016) and some other studies suggest that the epigenetic regulation of mitochondrial DNA might be disrupted in migraine (Fila, Pawł owska, and Blasiak 2019; Roos-Araujo et al. 2014).

It has been postulated that the disruption of metabolic equilibrium would activate chemosensitive neurons in hypothalamic (an activation during the premonitory phase already observed in fMRI studies (Maniyar et al. 2014b; Schulte and May 2016) and brainstem systems which would in turn initiate the migraine attack. The attack itself would help to restore energy homeostasis in the brain, partly via the release of CGRP and pituitary adenylate cyclase-activating peptide (PACAP) (Gross et al. 2019). Metabolic abnormalities would also increase the susceptibility of CSD, causing the migraine aura in some patients (Kilic et al. 2018). However, the link between decreased cerebral energy and trigeminovascular activation remains to this day elusive.

2.1.4 Migraine treatments

The management of migraine relies on acute treatments to relieve the headache during the attack and preventative treatments (prophylaxis) to reduce the frequency and the intensity of the attacks (Antonaci et al. 2010; Goadsby, Lipton, and Ferrari 2002). Most developed countries provide national guidelines for medical practioners for treatment of migraine. In France, they are produced by the Société Française d'Études des Migraines et Céphalées (SFEMC) (Lanteri-Minet et al. 2014); recommandations are also issued by the task-force of the European Federation of Neurological Societies (EFNS) (Evers et al. 2009).

Acute treatment

Non-specific treatments Non-specific treatments are usually preferred when the pain is mild to moderate. They should be taken at the time of the attack to relieve symptoms of the attack. They usually consist in paracetamol and nonsteroidal anti-inflammatory drugs (ibuprofen, aspirin...), sometimes in association with an anti-emetic such as metoclopramide to relieve nausea and vomiting symptoms. Opioids are generally avoided as they may induce drug abuse and addictive behavior, and exacerbate digestive symptoms. Published studies estimate that around half of migraineurs can adequately self-manage their symptoms with over-the-counter medications, due to mild and infrequent headaches (Steiner et al. 2011).

Specific treatments Specific treatments are reserved for patients with recurrent, severe and/or long headache. They consist in two drug families: ergot derivatives and triptans, both agonists of serotonin receptors. Ergotamine has the advantage of its low cost and long experience of its use by medical practitioners. Triptans are usually preferred to ergotamines as they have less erratic pharmacokinetics, a more selective pharmacological effect, evidence-based prescription descriptions and they are generally safer as they are not associated with adverse vascular effects. However, triptans are more expensive and are contraindicated for patients with cardiovascular diseases. Triptans are now widely used (around 2% of the French population has a prescription for triptans (Braunstein et al. 2015)) and evidence show that their efficiency surpass those of non-specific treatments (Cameron et al. 2015). However, overuse of triptans is a concerning health issue. In France, 5.4% of regular users and 2.3% of the total number of users of triptan are over-users (Braunstein et al. 2015). Triptan overuse can lead to medication-overuse headache (MOH), a condition described in the ICHD-3, characterized by continuous daily headache and may be accompanied by more severe photo- and phonophobia (Créac'h et al. 2009).

It exists 14 classes of serotonin (5-hydroxytryptamine, 5-HT) receptors: triptans are selective agonists of the 5-$HT_{1B/1D}$ receptors (Humphrey et al. 1990). Triptans were initially developed for their vasoconstrictive properties on cranial blood vessels, at the time when the vascular theory of migraine was still popular. Indeed, 5-HT_{1B}receptors is preferentially expressed on cranial vessels compared to peripheral vessels (Razzaque et al. 2002) and triptans intake lead to vasoconstriction of cranial vessels (Humphrey et al. 1990). However, it is now accepted that the effects of triptans on the headache is independent of vascular changes, and is mediated exclusively by neural mechanisms (Hoskin, Kaube, and Goadsby 1996). Triptans decrease trigeminal activity by inhibiting the release of proinflammatory peptides (CGRP, PACAP) on peripheral trigeminal nerves endings and by inhibiting trigeminovascular neurons in various central targets (STN, periaqueductal gray, thalamus...) (Goadsby et al. 2017).

Prophylaxis

Current drugs Prophylactic drugs are recommended when headache frequency and severity are high, in an attempt to avoid overuse of acute treatments, notably triptans. Most prophylactic drugs are not specific to migraine and are old molecules with a long experience of use repurposed for migraine treatment. First-choice prophylactic drugs include beta-blockers (propanolol, metropolol), antiepileptic (valproic acid, topiramate), calcium channel blockers (flunarizine), and tricyclic antidepressants (amitriptyline). Each drug presents its own list of side-effects but common adverse effects across prophylactic drugs include tiredness, drowsiness or weight fluctuations (Goadsby, Lipton, and Ferrari 2002). Current prophylactics are far from being a panacea: they present a poor tolerability, numerous contraindications, serious side-effects and their efficacy is limited, especially for chronic forms of migraine (Silberstein 2015).

CGRP mechanism antagonists CGRP is a neuropeptide widely distributed in areas of the trigeminovascular pathways, particularly in central neurons of the STN, and in the peripheral trigeminal ganglion and its C- and Aδ-fibers projecting to meningeal vessels, while CGRP receptors were also identified in the aformentioned areas and in the vascular cells of meningeal vessels (Goadsby et al. 2017; Karsan and Goadsby 2015; Van rossum, Hanisch, and Quirion 1997). It has been observed that CGRP injections to migraine patients with aura trigger a migraine headache, but not in control participants (Hansen et al. 2010). Based on these observations, CGRP appears to be central in the mediation of pain in migraine, which makes it an interesting treatment target. Clinical trials are currently in place to test

drugs blocking CGRP mechanisms.

Gepants were developed as CGRP-receptors antagonists for the acute treatment of migraine. They do not present any vasoconstrictive properties, which limit possible side-effects and contraindications compared to triptans (Negro and Martelletti 2019). The first drug from this family (ubrogepant) was approved by the US Food and Drug Administration for treatment of acute migraine in late 2019 (Kreimer 2020). In parallel, CGRP antibodies (nezumab) and CGRP-receptors monoclonal antibodies have been designed as preventative treatment. In clinical trials, these molecules appear to be well-tolerated and to be clinically efficient in preventing migraine attacks (Reuter 2018). Erenumab appears to be the most promising drug, validated by several clinical trials (Lattanzi et al. 2019). However in France, the Haute Autorité de Santé (HAS), which assesses potential drugs before their introduction to the market and their reimbursement, issued a critical notice about erunemab which would present "insufficient clinical relevance" and only advised it for chronic migraine if other prophylactic drugs have failed (Haute Autorité de Santé 2019). Erunemab is to this day not available in France.

Non-drugs treatments Due to the side-effects and the low tolerance of pharmacological treatments, some non-pharmalogical strategies have begun to emerge. There are some evidence that behavioral therapies may be helpful to manage symptoms: they include relaxation techniques, meditation or cognitive behavioral therapy (Puledda and Shields 2018). There is also a rapidly-growing interest for invasive and non-invasive neuromodulation treatments. Based on the knowledge on migraine pathophysiology and the implication of several specific nerves, several systems propose to stimulate the nervous system centrally or at the periphery as an acute or preventative treatment (Puledda and Shields 2018). Non-invasive systems include stimulation of cranial nerves or of the vagus nerve, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in order to restore normal levels of cortical excitability. These systems are still at the stage on clinical trials and the evidence of their efficiency is still debatable, however some results are promising and these neuromodulation systems may be a recognized treatment strategy in the future.

2.2 Alterations of sensory processing in migraine

2.2.1 Sensory symptoms

Hypersensitivity

Ictally The most debilitating sensory symptoms in migraine are without doubt associated to the headache phase. The ICHD-3 described photophobia and phonophobia as core symptoms of migraine (International Headache Society (IHS) 2013). Photophobia ("fear of light") and phonophobia ("fear of sound") should not be taken literally, these symptoms bearing little resemblance with actual phobias. Indeed most migraineurs during an attack will prefer a dark silent room and will employ avoidance strategies to minimize visual and auditory stimulation; but photophobia and phonophobia go beyond a simple emotional, anxious component and encompass heterogeneous subjective experiences and physiological processes (Russo and Recober 2013). Photophobia can either refer to: (1) light-induced ocular pain (photo-oculodynia), (2) the exacerbation of the headache by bright lights (photocephalodynia) and (3) increased sensitivity to light and glare (Noseda, Copenhagen, and Burstein 2018). In an influential psychophysics study, Drummond showed that migraineurs report higher glare and light-induced pain during their headache than other headaches sufferers or healthy participants, for all levels of illumination (Drummond 1986), one of the first attempts to quantify migraine hypersensitivity. Migraineurs during attacks also present lower threshold for light-induced pain compared to healthy controls (Vanagaite et al. 1997). Similar observations were made in the auditory modality: migraineurs present lower aversion threshold for sounds during the attack (Vingen et al. 1998; Ashkenazi et al. 2009). These results confirm subjective reports by migraineurs: migraine headaches increase the sensitivity and decrease the tolerance for bright lights and loud noises, which can in turn worsen the pain. In addition, Noseda and collaborators (2017) have demonstrated that visual stimuli and especially blue wavelengths may trigger and/or worsen autonomic symptoms during a headache, including "chest tightness, throat tightness, shortness of breath, fast breathing, faster-than-usual heart rate, light-headedness, dizziness, nausea, vomiting, dry mouth, salivation, rhinorrhea, stuffy sinus, and/or lacrimation". This phenomenon participates to photophobia and the avoidance behavior present among migraineurs.

There has been a major focus on photophobia (and in a lesser extent phonophobia) in clinical research, but sensory disturbances extend besides the visual and auditory modalities. From one-third to half of migraineurs report ictal osmophobia, i.e. an unpleasant perception of normally neutral or pleasant smells during the attacks (Kelman 2004; Rocha-Filho et al. 2015; Zanchin et al. 2005; Zanchin et al. 2007). This symptom appears to be particularly specific to migraine compared to other headache disorders and it has been proposed that osmophobia becomes a diagnostic criterion along photo- and phonophobia in the ICHD (Chalmer, Hansen, and Olesen 2019; Rocha-Filho et al. 2015; Silva-Néto, Peres, and Valença 2014; Wang et al. 2012; Zanchin et al. 2005). Frequently reported inconvenient odors include food smells, perfume, paint, and cigarette smoke (Blau and Solomon 1985; Kelman 2004;

Zanchin et al. 2007) and would be associated to taste abnormalities (Kelman 2004).

From 40% to 80% of migraineurs experience cutaneous allodynia during their attacks, i.e. pain in response to non-noxious stimuli, with a higher prevalence in chronic migraine and migraine with aura (Bigal et al. 2008; Burstein et al. 2000; Lipton et al. 2008; Lovati et al. 2007; Mathew, Kailasam, and Seifert 2004). However, it would be less specific than osmophobia as it is also present in other headache disorders (Bigal et al. 2008). Most migraineurs suffering from allodynia report disturbance limited to the scalp on the side of the pain; symptoms usually consist in hypersensitivity, soreness and tenderness of the scalp (Mathew, Kailasam, and Seifert 2004). This sensitivity can be to thermal stimulation, making it difficult to take a shower or rest one's face on a pillow; static mechanical stimulation, as wearing tight clothes or jewelry can become intolerable; dynamic mechanical stimulation, such as combing one's hair or shaving (Lipton et al. 2008). A subset of those migraineurs also report extracephalic allodynia, with disturbances extending to the rest of the body, usually in the upper limbs (Lipton et al. 2008).

Interictally Research on sensory processing during the interictal phase is much scarcer. However, there are some evidence that sensory disturbances exist well beyond the headache phase, admittedly at a lower magnitude. In questionnaire studies, migraineurs self-report to be more intolerant than healthy controls to visual (Cucchiara et al. 2015; Mulleners et al. 2001), olfactory (**demarquayRatingOlfactoryJudgements2006a**) or tactile stimuli (Lovati et al. 2008). They are more likely to avoid sensory stimulation than healthy controls, even outside attacks (Genizi et al. 2020). These sensory complaints are even more pronounced in migraineurs with aura compared to migraineurs without aura (Granovsky et al. 2018; Pearl et al. 2020). Quantitative studies have shown that, even if the aversion thresholds for light and noise decrease during the headache phase, migraineurs still present lower thresholds interictally than healthy controls (Ashkenazi et al. 2009; Drummond 1986; Main, Dowson, and Gross 1997; Main, Vlachonikolis, and Dowson 2000; Vanagaite et al. 1997; Vingen et al. 1998). This is reflected through autonomic responses as migraineurs present increased interictal pupillary-light reflexes to visual stimulation (Cortez et al. 2017). They may also present lower pain thresholds to thermal and mechanical noxious stimulation, suggesting an extension of allodynia beyond the headache phase (Schwedt et al. 2011; Uglem et al. 2017; Weissman-Fogel et al. 2003). In the olfactory modality, migraineurs judge odors less pleasant than healthy controls, but do not perceive them as more intense (**demarquayRatingOlfactoryJudgements2006a**). It has been hypothesized that an altered hedonic judgement to environmental stimuli might participate to the interictal hyperresponsiveness in migraine (Demarquay and Mauguière 2016).

2.2.2 Mechanisms of migraine hypersensitivity

Physiological models of hypersensitivity Physiological models of photophobia have been constructed based on the research about the trigeminal pathways in migraine, the "sensitization" framework and the anatomy of the visual pathways. In a series of articles, Noseda and collaborators (2013; 2017; 2018) proposed a neural basis for light-induced symptoms during the migraine attacks (i.e. the increased light sensitivity, the exacerbation of headache by light, the light-induced ocular pain and the light-induced autonomic symptoms) and the cutaneous cephalic and extracephalic allodynia (already discussed p.68).

Some blind migraineurs can still display symptoms of photophobia, but only if their optic nerve is intact. Retinal projections to the central nervous system constitute distinct image-forming and non–image-forming pathways, the latter being crucial for regulation of biological functions such as the circadian rhythm (Noseda et al. 2010). Therefore, one can infer that a visual percept would not be necessary to elicit photophobia and the non-image-forming retinal pathway would still be implicated in its elicitation. (Noseda et al. 2010) demonstrated from animal experiments that trigemino-vascular thalamic neurons, who respond to dura stimulation, are also sensitive to light stimulation. These neurons, as I discussed earlier, project on sensory cortical areas, including the primary and secondary visual cortices. The convergence of retinal pathways and of the nociceptive trigeminovascular ascending pathways in the thalamus would provide an explanation for the exacerbation of pain by light and the exacerbation of light sensitivity by the migraine attack (p.80). In other terms, pain processing and visual processing would intermingle in the thalamus and subsequently modulate each other. Light-induced autonomic responses would rely on different neural pathways. Retinal ganglions cells also project on hypothalamic neurons, which regulate autonomic responses via peripheric ganglions (Noseda et al. 2017). This suggests that the hypothalamus would also be a hub in which converge trigemino-vascular and retinal pathways, enabling visual stimulation to affect autonomic functions.

The visual and tactile sensory modalities have attracted more interest than the others. Although there is less evidence to support this claim, it is probable that phonophobic symptoms are underlied by the similar neural basis. Some thalamic trigemino-vascular have been shown to project on auditory cortices, suggesting that the migraine attack might interfer with auditory processing via the trigemino-vascular pathway (Noseda et al. 2011).

Functional neuroimaging, sensory processing and migraine Functional MRI (fMRI) and Positron Emission Tomography (PET) have been used to investigate brain responsiveness to sensory stimuli and to possibly determine markers of hypersensitivity. Systematic reviews of functional neuroimaging studies in the visual modality have described that most

of them investigated brain responsiveness interictally, using different types of visual stimulation (flickers, gratings, patterns, continuous light...) (Demarquay and Mauguière 2016; Schwedt et al. 2015). Results converge in favour of a greater activation of primary and/or associative visual cortical areas, suggesting a basal hyperresponsiveness of visual areas associated with migraine. Over-activations sometimes extend beyond the occipital cortex to the parietal cortex and the middle and inferior frontal gyri, indicating that the cognitive processing of visual inputs may also be abnormal in migraine. In the olfactory modality, a fMRI study found that abnormalities of the brain response to odors was restricted to the headache phase (Stankewitz and May 2011) while a PET study found altered patterns of activation interictally (Demarquay et al. 2008). Few of those studies have attempted to link this hyperactivation of sensory cortices to clinical sensory complaints. In a visual study, migraineurs and healthy controls were asked to rate their degree of discomfort for four light intensities (Martín et al. 2011). Migraine patients reported higher visual discomfort than controls and the number of fMRI activated voxels in migraineurs was higher only for low and medium-low light luminance levels. Using $[^{15}O]H_2O$ PET, it has been shown that migraineurs afflicted with photophobia in the premonitory phase show an activation of the extra-striate visual cortex compared to migraineurs with no photophobia (Maniyar et al. 2014a). Functional studies have also provided some evidence in favor of the sensitization theory, which conjectures that the convergence of trigeminal and other sensory information may underlie migraine hypersensitivity. In a $[^{15}O]H_2O$ PET study during the pain-free period, pain stimulation of skin areas innervated by the trigeminal nerve have been found to potentiate the activation of visual cortical areas by light (Boulloche et al. 2010). The same authors focused on the headache period and found that the activation of visual cortical areas was decreased after headache relief by triptans, suggesting the the hyper-responsiveness of the visual cortex underlies ictal photophobia (Denuelle et al. 2011).

fMRI also provides measures of resting-state functional connectivity, allowing the investigation of functional networks in the brain, their potential alterations in neurological and psychiatric disorders and the detection of possible biomarkers. In migraine, resting-state has been extensively investigated by tens of studies, comparing ictal migraineurs or interictal migraineurs to healthy participants. Systematic reviews of functional connectivity studies in migraine have observed that according the literature, migraine would be associated to altered connectivity within numerous networks, including the pain matrix, major cortical resting-state networks (salience, fronto-parietal, default-mode...) or several brainstem-cortex pathways (Schwedt et al. 2015; Skorobogatykh et al. 2019). However, those results are highly heterogeneous, hardly reproducible and no specific pattern seems to emerge: there is today no convincing evidence of a connectivity biomarker associated to migraine (Skorobogatykh

et al. 2019).

In conclusion, functional imaging studies in migraine show that migraine is associated a hyper-responsiveness of cortical sensory areas both during the interictal and ictal state. However, evidence is lacking to demonstrate that this hyper-responsiveness is indeed the cause of sensory symptoms, and that it is not simply the product of sub-cortical dysfunctional mechanisms.

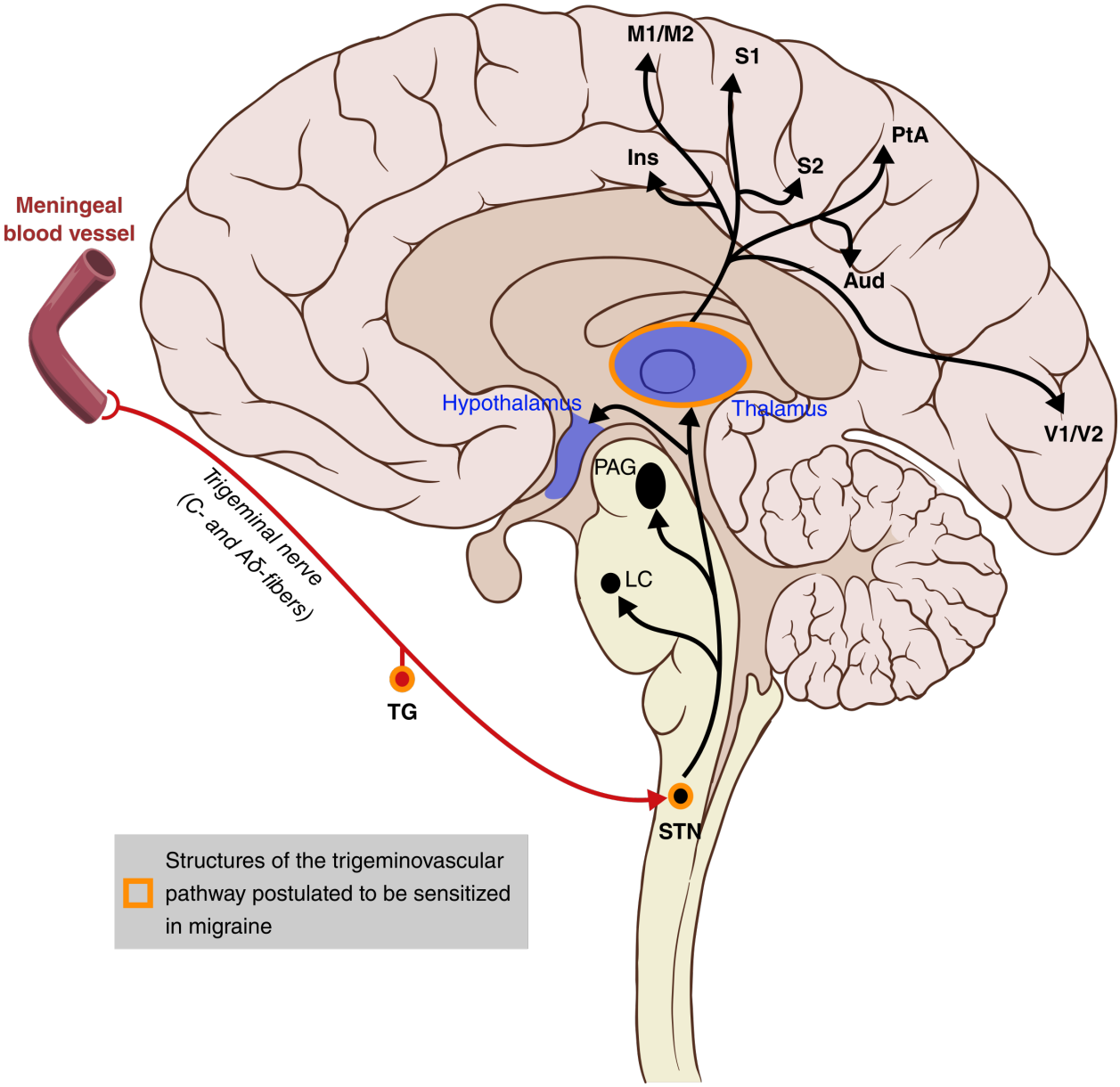


Figure 18: *Schematic representation of the trigeminovascular pain pathways involved in migraine pathophysiology. TG: trigeminal ganglion; STN: spinal trigeminal nuclei; LC: locus cæruleus; PAG: periaqueductal gray; M1/M2: primary and secondary motor cortices; S1/S2: primary and secondary somatosensory cortices; V1/V2: primary and secondary visual cortices; Ins: insula; PtA: parietal associative cortex; aud: Auditory cortex. Adapted from Goadsby et al. (2017) and Noseda and Burstein (2013).*

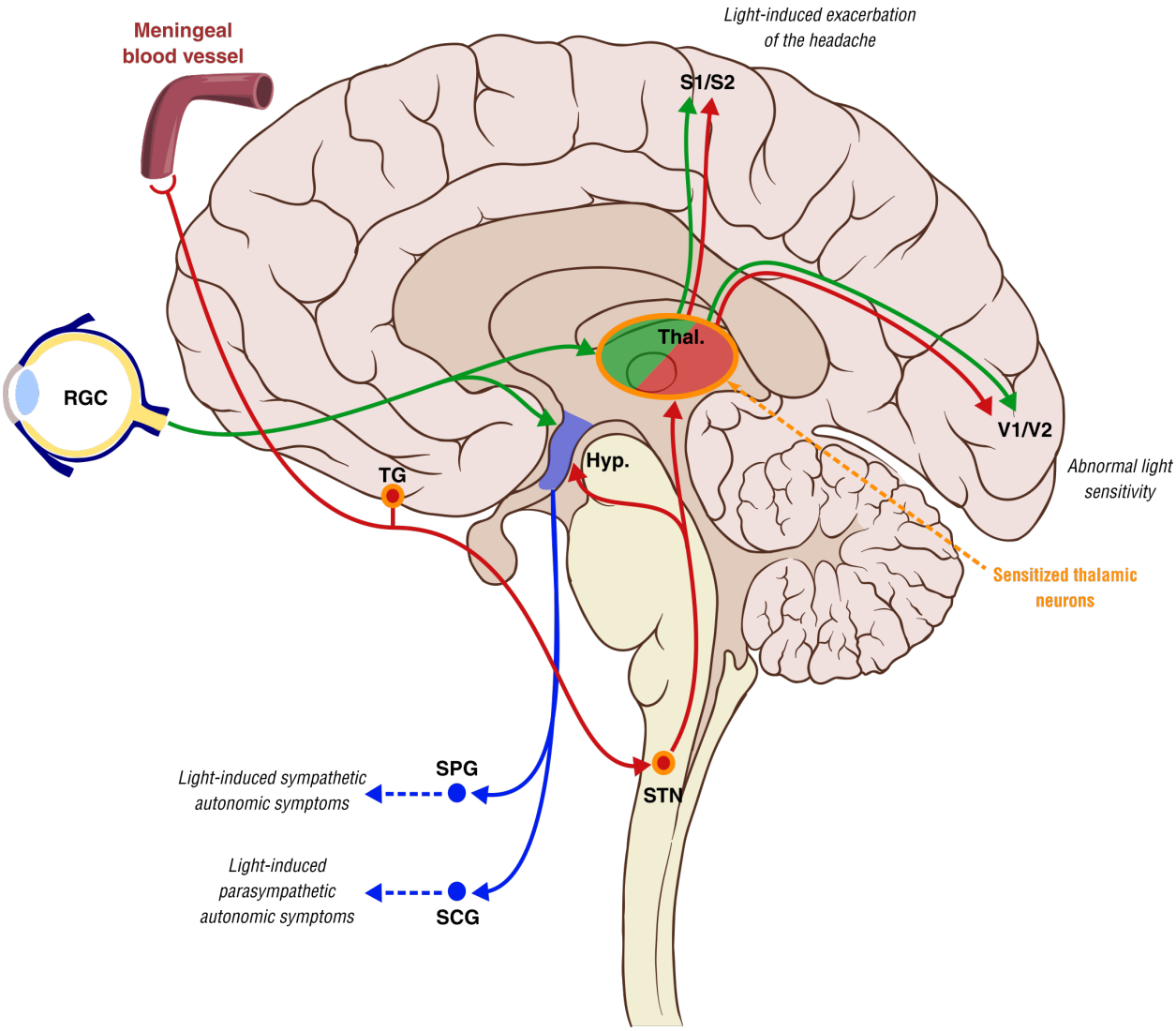


Figure 19: *Mechanisms of photophobia in migraine. RGC: retinal ganglion cells; TG: trigeminal ganglion; STN: spinal trigeminal nuclei; S1/S2: primary and secondary somatosensory cortices; V1/V2: primary and secondary visual cortices; Hyp: hypothalamus; Thal: Thalamus; SPG: sphenopalatine ganglion; SCG: superior cervical ganglion. In green, retino-thalamo-cortical pathways; in red, trigeminovascular pathways; in blue, hypothalamo-(para)sympathetic pathways. Adapted from Noseda et al. (2017) and Noseda, Copenhagen, and Burstein (2018).*

Electrophysiology, sensory processing and migraine EEG is a powerful technique to investigate hypersensitivity in migraine. Its superior temporal resolution provides a fine-grained insight on the different stages of sensory processing through the study of evoked potentials, while the study of oscillatory rhythms opens a window on cortical excitability and functional connectivity.

Clinical use of EEG in migraine Routine EEG is not particularly useful for the clinical assessment of migraine and is not recommended by official guidelines in most of cases Sandrini et al. (2004). Interictal EEG may be useful for a differential diagnosis with epilepsy as it distinguishes between the phenomenon of migraine aura and occipital epilepsia preceding seizure. EEG also appears to be unable to detect any signal abnormalities associated with the cortical spreading depression (CSD), the physiological mechanism thought to underlie the migraine aura: it is still unclear if it is an evidence of the absence of CSD associated to migraine in human individuals or if this negative result is due to the intrinsic properties of the EEG technique de Tommaso (2019).

Habituation deficits The most prominent EEG abnormality described in migraine is the lack of neurophysiological habituation during the interictal period (Coppola, Pierelli, and Schoenen 2009). In healthy individuals, repeated sensory stimulations usually result in amplitude decrement of event-related responses (ERPs). Habituation is an adaptive mechanism protecting the brain from over-stimulation consisting in declining responsiveness to repeated/sustained stimulations, which can be seen as a form of sensory filtering. (Rankin et al. 2009). The very first study to investigate habituation in migraine focused on the contingent negative variation (CNV), a slow negative wave considered to reflect both attentional anticipation and motor preparation to an imperative stimulus (Brunia and van Boxtel 2001). They observed a suppression of CNV habituation in the migraine group and proposed that this would be a biomarker of migraine (Schoenen et al. 1985). This result was replicated in subsequent studies, which also showed that it was the early phase of the CNV (initial CNV, iCNV) that was specifically affected and that this lack of habituation was amplified with disease duration (Kropp and Gerber 1995; Kropp, Siniatchkin, and Gerber 2000; Kropp et al. 2015; Schoenen and Timsit-Berthier 1993; Siniatchkin et al. 2000). P3-complex responses (P300, P3b, P3a) also show a deficit of habituation in migraine in most studies, irrespective of the sensory modality (auditory or visual) of the paradigm used for their elicitation (Evers et al. 1999; Evers et al. 1998; Siniatchkin, Kropp, and Gerber 2003; Wang, Schoenen, and Timsit-Berthier 1995; Wang and Schoenen 1998).

Regarding earlier “sensory” ERPs, Schoenen et al. (1995) investigated habituation in

migraine using a pattern reversal paradigm with a 3.1 Hz reversal rate. While controls participants presented decreasing amplitudes of N1-P1 and P1-N2 components with the repetition of stimulation runs, migraineurs presented stable or even increasing amplitudes of those components. This lack of habituation of visual ERPs was confirmed by subsequent studies (Afra et al. 1998; Bednář, Kubová, and Kremláček 2014; Bohotin et al. 2002; Ozkul and Bozlar 2002) and was accompanied by a tendency for a lower initial ERP amplitude in migraine. Habituation in the visual modality has also investigated using steady-state visual evoked potentials (SSVEP), electrical brain responses to repeated visual stimulation at specific frequencies. Results strongly suggest that the excitability of the occipital cortex is abnormal among migraineurs (de Tommaso et al. 2014; de Tommaso 2019). In the auditory modality, authors have preferred the study of intensity-dependence of auditory potentials (IDAP), paradigms observing responses to stimulation of increasing intensities. Enhanced IDAP are considered to be a proxy of a lack of short-term habituation and were reported among migraineurs in most studies (Ambrosini et al. 2003; Judit, Sándor, and Schoenen 2000; Wang, Timsit-Berthier, and Schoenen 1996). Among migraineurs, auditory ERPs also increased over successive blocks of trials over the course of an experimental session, contrary to the control group whose responses habituated over time: these results reveal a lack of long-term habituation which mirrors the results found in the visual modality (Coppola, Pierelli, and Schoenen 2009). Initial auditory ERPs (at the beginning of the blocks) were also found to be of lower amplitude in migraine, similar to what is observed in the visual modality. Deficits of short-term habituation of the auditory P50, which reflects the response of the primary auditory cortex, was also observed in migraine when using paradigms with pairs of auditory stimuli (Ambrosini et al. 2001; Siniatchkin, Kropp, and Gerber 2003). Lack of habituation have also been observed in the somato-sensory modality and notably for noxious stimuli (Coppola, Pierelli, and Schoenen 2009; de Tommaso et al. 2014) but no EEG study to this day has investigated habituation in the olfactory modality (Demarquay and Mauguière 2016).

Surprisingly, this lack of habituation was found to normalize in the days preceding the migraine attack and is totally absent during the attack. This has been observed for visual and auditory obligatory ERPs (Judit, Sándor, and Schoenen 2000), the visual P3 (Evers et al. 1999) and the CNV (Kropp and Gerber 1995). However, it is not the case for noxious stimulation which still fail to habituate during migraine attacks (de Tommaso et al. 2014). In light of all this literature, some authors claimed that the lack of habituation is a biomarker of the interictal state in migraine and a hallmark of the disease (Coppola, Pierelli, and Schoenen 2009). It affects both early sensory and late cognitive ERPs and both short- and long-term habituation appear to be dysfunctional.

The mechanisms underlying the habituation deficits are still poorly understood. One hypothesis would be that they stem from a increased excitation-inhibition balance in the cortex, which would be hyperexcitable in migraine (Aurora and Wilkinson 2007). However, it does not account for the fact that migraineurs present weaker ERPs amplitude to the initial stimuli of a block. Another (non-exclusive) hypothesis states that migraineurs present a lower basal level of cortical pre-activation. According to the "ceiling" theory, an individual's sensory cortices have variable baseline activation levels, but their maximum activation level (the ceiling) remains constant. During repetitive stimulation, the maximum activation level is reached rapidly, and subsequently the response amplitude decreases sharply (habituation) in individuals with normal baseline activation, while habituation is delayed or absent in individuals in whom baseline activation is low (de Tommaso et al. 2014). These theories have been investigated using (repetitive) transcranial magnetic stimulation (TMS/rTMS), a technique useful for the evaluation of cortical excitability. However, the results are often paradoxical and resist simple explanations: both theories are still passionately discussed in the literature (Demarquay et al. 2013; Stankewitz and May 2007; de Tommaso et al. 2014). The abnormal cortical excitability in migraine has been postulated to stem from a dysfunctional thalamo-cortical connectivity (de Tommaso et al. 2014), based on the observation that early somato-sensory and visual evoked high-frequency oscillations (HFO) are reduced in migraine (Coppola et al. 2005; Coppola et al. 2007; Sakuma et al. 2004). A non-exclusive explanation would also involve the serotoninergic neurotransmission. 5-hydroxytryptamine (5-HT) or serotonin is an inhibitory neurotransmitter in the brain, notably synthesized in neurons of the brainstem raphe nucleus which project throughout the brain and regulate numerous cerebral functions including sensory processing. Chronically low 5-HT availability in the brain has been considered to be at the basis of migraine and is modulated through the migraine cycle (Hamel 2007), as evidenced by PET studies (Demarquay et al. 2011a; Lothe et al. 2008). Interestingly, habituation in migraine correlates negatively with platelets serotonin levels (which may reflect the levels in the central nervous system), which drop during the migraine attacks concomitant to the normalization of habituation deficits (Evers et al. 1999). Serotonin reuptake inhibitors correct habituation deficits in migraine (Ozkul and Bozlar 2002).

However in the last decade, several researches have voiced their concern against the "dogma" of habituation deficits in migraine. It has undergone a replication crisis leading to a heated controversy (Ambrosini 2015; Ambrosini et al. 2016; Brighina, Cosentino, and Fierro 2016; Magis, Lisicki, and Coppola 2016; Sand 2014). No habituation deficits of visual ERPs were observed in several studies (Omland et al. 2013; Omland et al. 2016; Sand et al. 2008): authors proposed that the culprits of those "spurious" results may be due to

an insufficient blinding of the investigator and a poor selection of the participants (Sand 2014). Also, most positive studies showing a lack of habituation of visual ERPs came from the same group of collaborating authors. However, since then one other research group has detected a lack of habituation of visual ERPs using a blinded study (Bednář, Kubová, and Kremláček 2014). In the auditory modality, a recent study failed to observe any short- and long-term habituation in women with menstrual migraine, using a novel adaptation of the oddball paradigm (Demarquay et al. 2011b). Another limit of the habituation "framework" is that it does not really provide a mechanism for the photo- and phonophobia during the migraine attacks, as habituation deficits actually recede in anticipation of the headache. It may be tempting to link the lack of habituation to interictal sensory disturbances, especially in the visual modality: however to our knowledge, no study has attempted to research the potential relationship between habituation deficits and interictal hypersensitivity.

However, habituation deficits may integrate well with the "migraine as a metabolic disease" theory. Intense sensory stimuli, including odors, blue light and loud noises can increase oxidative stress (Gross et al. 2019): a lack of habituation in migraine would lead to less sensory gating and therefore more oxidative stress and energy depletion in the brain during the interictal period, potentially leading to a migraine attack to restore the homeostatic equilibrium.

Alteration of attentional processing of sensory stimuli A less-researched, alternative hypothesis could explain sensory disturbances associated with migraine: dysfunction attentional modulations would cause migraineurs to have an exacerbated and non-selective orienting to all stimulation in their environment, leading to sensory discomfort. Several studies have investigated "cognitive" ERPs, i.e. components supposed to reflect higher cognitive processing of sensory stimuli such as the P3 responses, or have used paradigms designed to investigate attentional mechanisms.

Two studies have used auditory passive oddball paradigms and one of them found a reduced P3a amplitude in migraine (Koo et al. 2013) while the other found no difference (Wang, Schoenen, and Timsit-Berthier 1995) . A study from our group used the classic habituation paradigm by presenting trains of standard and deviant auditory stimuli to participants. The analysis of the responses to the first stimuli of the trains showed a larger orienting component of N1 (see Alcaini et al. 1994b) but no difference regarding the sensory component of N1 among migraineurs(Demarquay et al. 2011b). The P3a was also reported to be larger in migraineurs and this increase was found to normalize during migraine attacks. In a following article, the authors carried out further analyses of the response to deviant sounds (Morlet et al. 2014). MMN was similarly elicited by deviant stimuli in both patients and

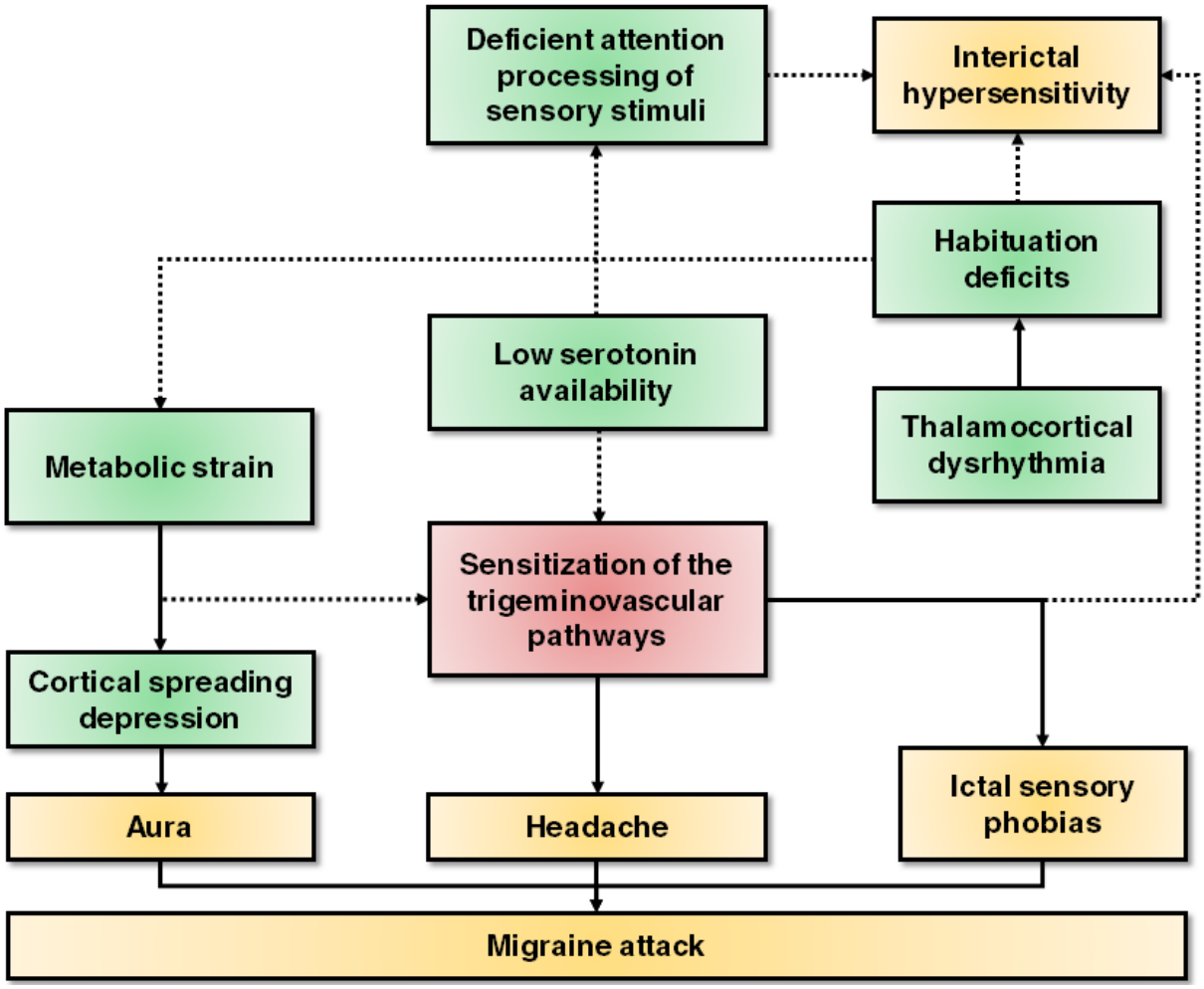


Figure 20: *Summary of current models of migraine pathogenesis and their relations with sensory symptoms. Dashed lines indicate hypothetical connections, for which there is currently little or no experimental evidence. Loosely adapted from de Tommaso et al. (2014).*

healthy controls but migraine patients showed an increased N1 orienting component to all incoming stimuli and a prolonged deviant-specific N2b response. These results suggest that preattentive processes of deviance detection are not altered in migraine, however attention orienting appears to be enhanced among migraineurs.

Beyond its lack of habituation, the early phase of the CNV (iCNV) has also been found to be increased in migraine (Böcker et al. 1990; Kropp and Gerber 1995; Kropp et al. 2015; Nordhout et al. 1986). This increase is even more exacerbated in patients with a long history of migraine (Kropp, Siniatchkin, and Gerber 2000; Kropp et al. 2015) and normalizes before attacks (Kropp and Gerber 1995). This result has been interpreted by authors as a hyperactivity of the noradrenergic system. From a cognitive point of view, it may be a sign that migraineurs have difficulties to engage top-down processes in preparation

for an imperative stimulus, or that they present abnormal arousal levels and difficulties in modulating them.

Using an original visual paradigm, Mickleborough, Truong, and Handy (2011) have suggested migraineurs have an altered top-down attentional control of the visual cortex, underlying a decreased ability to suppress responses to unattended events in the visual periphery. These attentional abnormalities were confirmed in a fMRI study from the same group which showed that migraine is associated with a deficient suppression of unattended events and suggested that migraineurs have a heightened orienting response to unexpected stimuli in peripheral locations, as evidenced by an increased activation of the right temporo-parietal junction (rTPJ) (Mickleborough et al. 2016).

Alteration of oscillatory activities Most EEG studies have preferred to investigate sensory processing through ERPs, rather than through oscillatory activities, probably because ERPs analyses have historically been more simple and streamlined. However, there is some literature on oscillatory rhythms in migraine but it is quite scattered and less comprehensive than the literature on evoked responses.

Several groups have explored basal oscillatory activities using resting-state EEG during the interictal period. One study reports that interictal migraineurs appear to present increased theta power in all cortical regions and increased delta activity at the side of the head becoming painful during the next headache attack (Bjø rk et al. 2009), another suggests that the cortical sources of alpha rhythms are abnormal (Clemens et al. 2008), while a third found higher occipital lower-band alpha power in migraine (O'Hare, Menchinelli, and Durrant 2018), somewhat contradicting an older study reporting lower alpha power in migraine (Neufeld, Treves, and Korczyn 1991). A resting-state MEG study focused on the ictal period and detected aberrant brain activity in the high frequency range (>55 Hz) (Liu et al. 2015). On the other hand, in healthy participants, photic stimulation via repetitive flashes causes a decreased alpha-band synchronization all over the brain, while migraineurs show an opposite pattern with a hypersynchronization of the alpha-band activity (Angelini et al. 2004; de Tommaso et al. 2005).

Present results do not provide a clear picture on how oscillatory rhythms may be affected in migraine and how it could related to migraine symptoms. Further research is needed to better understand how a potential "dysrhythmia" may account migraine pathophysiology.

2.3 Migraine and cognition

2.3.1 Cognitive disturbances in migraine

Although cognitive symptoms are not considered among the core symptomatology of migraine, many migraineurs often complain of intellectual impairment, especially during the attack and during the premonitory and postdrome phases (Giffin et al. 2003). Cognitive symptoms are actually considered by migraineurs as the second most intense and disabling aspect of the disease, obviously ranked below the pain but more disabling than sensory symptoms (Gil-Gouveia, Oliveira, and Martins 2016). These complaints usually include difficulty in thinking, concentrating and speaking. Cognitive impairment seems to increase with disease severity (Santangelo et al. 2016).

Numerous studies have investigated cognitive impairments in interictal migraine, often using standardized neuropsychological tests on clinic-based or population-based samples. The results can be quite inconsistent, with some studies finding mild cognitive impairment and other detecting no cognitive abnormalities. In the most up-to-date systematic meta-analysis of the subject, Vuralli, Ayata, and Bolay (2018) concluded that:

> Migraine had a moderate to marked effect on processing speed and visuomotor scanning speed, whereas basic attention and delayed verbal memory were mildly affected, and more complex psychomotor processing speed tasks were not significantly affected. Some studies observed mild to moderate impairments in non-verbal memory whereas others found no effect or better performance in migraineurs. Verbal skills (auditory comprehension, reading, aphasia screening, verbal reasoning, vocabulary, phoneme detection) were mildly impaired. In terms of executive function, migraine had a moderate to marked effect on sustained attention and working memory. There was slight dysfunction in the inhibition domain in migraine patients. In the domains of mental flexibility and set shifting, several studies reported that migraine patients exhibited a moderate or marked impairment. One study that included problem solving and decision making also found a marked impairment in these domains in migraine patients.

The discrepancies in the literature were partly explained by the chosen population samples: clinic-based samples tended to include individuals with more severe migraine symptoms, as they are more likely to consult a physician. Longitudinal studies sometimes detected some baseline cognitive dysfunction in migraine, however they have not provided any conclusive evidence of a cognitive decline associated with the migraine disease (Baars, van Boxtel, and Jolles 2010; Kalaydjian et al. 2007; Rist et al. 2012; Waldie et al. 2002). This strongly

suggests that potential cognitive alterations observed in migraine are not caused by cumulative attacks but that migraineurs share a risk factor for cognitive dysfunction. And despite the fact that research has detected some deteriorated cognitive performance in migraine, it is important to emphasize that between attacks cognitive functions are not impacted to a degree that daily activities are seriously affected.

Cognitive performance can be impacted by risk factors associated to migraine. Due to to repetitive headaches, migraineurs are more likely than the general population to develop anxiety, depression (Devlen 1994; Lantéri-Minet et al. 2005; Wacogne et al. 2003) and sleep disorders (Cevoli et al. 2012; Vgontzas, Cui, and Merikangas 2008) which are known to negatively influence cognitive performance (Eysenck et al. 2007; Gotlib and Joormann 2010; Killgore 2010); chronic forms of migraine are often associated to medication overuse (Diener and Limmroth 2004), which may have short- and long-term adverse effects on brain function, and to lower socio-economic status (Buse et al. 2010). Cognitive disturbances observed in migraine might be neither specific nor intrinsic to the disease, just a product of the decreased quality of life experienced by the patients. It would be interesting to compare migraine to other headache disorders: however, studies about cognition in these other disorders are scarcer and direct comparisons with migraine are lacking (Vuralli, Ayata, and Bolay 2018). In tension-type headache (TTH), a common headache disorder, a small-scale study suggests than decreased cognitive performance is present during the headache but normalizes after the headache has ended (Smith 2016). In cluster headache, cognitive processing is not impacted between attacks (Evers 2005).

2.3.2 Migraine and attention

As mentioned above, difficulties to concentrate is a common complaint of migraineurs in the premonitory, headache and postdrome phases (Giffin et al. 2003; Giffin et al. 2016). Several studies have evaluated attention functions in migraine, usually in the context of a non-specific battery of neuropsychological tests to perform a general evaluation of cognitive abilities. The results should be regarded with caution as these paradigms do not always target specifically attention functions: differences in performance compared to controls may stem from dysfunction in neighbor cognitive functions (executive functions, processing speed, etc.), rather from attention specifically. Classically used tests to investigate attention include the Trail Making Test, the Stroop Task, Symbol Search or the Continuous Attention Test (Vuralli, Ayata, and Bolay 2018). Neuropsychological tests confirmed that migraine attacks negatively impact attention (Farmer et al. 2000). Children with migraine present impairments of selective and divided attention during the interictal period (Costa-Silva et al. 2016; Moutran et al. 2011; Villa et al. 2009); adults with migraine are reported to have normal attention

functions in some studies (Burker, Hannay, and Halsey 1989; Conlon and Humphreys 2001), while other suggest attentional alterations (Han et al. 2018; Martins et al. 2012; Mulder et al. 1999; Pira et al. 2000; Zeitlin and Oddy 1984). Discrepancies in the literature may originate from differences in the study design, especially the chosen population, and in the evaluation methods (i.e. which test has been used). To my knowledge, only one research group have investigated attention in migraine using paradigms designed specifically to evaluate attention functions. In a series of articles (2011; 2011; 2016), Mickleborough and collaborators first found that migraineurs present increased bottom-up attention orienting to stimuli in the peripheral visual field. However during cueing tasks, migraineurs show similar or even enhanced top-down attentional effects compared to healthy controls. Through fMRI, they found that this exacerbated top-down attention orienting observed behaviorally was accompanied by an increased activation of the right temporo-parietal junction (rTPJ), a cortical area part of the ventral attention network and involved in attention switch (Corbetta, Patel, and Shulman 2008). The implication of the rTPJ in migraine was later confirmed by another group which found abnormal functional connectivity between the rTPJ and both temporal poles in a resting-state fMRI study (Lisicki et al. 2018).

Epidemiologic studies can also shed some light on the association between migraine and attention difficulties. The comorbidity between Attention Deficits with Hyperactivity Disorder (ADHD) and migraine have been highlighted by several converging studies (e.g. Fasmer et al. 2012; Paolino et al. 2015) and a systematic meta-analysis (Salem et al. 2017). This association is specific to migraine and does not exist for tension-type headache. In a massive questionnaire study, Carpenet et al. (2019) showed that the levels of self-perceived ADHD symptoms were selectively associated with migraine, especially hyperactivity symptoms.

The physiological mechanism underlying potential attentional alterations in migraine is still elusive. Villa et al. (2009) proposed that the disruption of the noradrenergic and dopaminergic systems may predispose to attention deficits in migraine, these neurotransmitters (and serotonin) having already been linked to ADHD etiology (Oades 2005). There is converging evidence in favor of a chronic dopamine hypofunction in migraine (Akerman and Goadsby 2007; Barbanti et al. 2013), notably since it has been established that the clinical susceptibility to migraine is associated with polymorphisms of the D2 and D4 dopamine receptors (Peroutka, Wilhoit, and Jones 1997). Similarly, migraine has been proposed to be a chronically sympathetic hypoactivity disorder (Peroutka 2004; Rubin et al. 1985; Shechter et al. 2002). However, as discussed previously, the neurotransmitter most consistently associated to migraine pathophysiology is with no doubt serotonin (Hamel 2007). These three neurotransmitters are involved in the regulation of attentional functions (Robbins 1997; Coull 1998): dopamine has a crucial influence on the frontal lobe and contributes to behavioral

adaptation and to anticipatory processes necessary for preparing voluntary action (Nieoullon 2002); norepinephrine and catecholamines in general regulates arousal whose adequate levels are needed for an efficient selective attention; serotonin may act as a counteract for the two neurotransmitters mentioned before by promoting behavioral inhibition and cortical de-arousal.

Attentional difficulties observed in the literature may stem from the increased anxiety levels in the migraine population. It has been established that anxiety has a major impact on attention and cognitive performance: high anxiety increases the susceptibility for distraction and multiplies its effects, has adverse effects on top-down orientation processes and exacerbates the responses to threat-related stimuli as anxious individuals develop an attention bias (Eysenck et al. 2007). Therefore, anxiety may be a confounding factor in studies investigating attention in migraine and can independently explain the group effects, even if some studies are aware of this issue and have controlled for bias in anxiety and depression in their study design. Both anxious and depressive symptoms are related to increased reactivity to negative stimuli, which surely accounts for the hyper-responsiveness of migraineurs to emotional stimuli, especially negative ones, in several fMRI and EEG studies (Andreatta et al. 2012; Buodo et al. 2011; Steppacher, Schindler, and Kissler 2015; Szabó et al. 2019; Wang et al. 2017).

As developed previously (p.84), EEG studies suggest that the attentional processing of sensory stimuli is disrupted in migraine. Further investigation of attention functions in migraine may shed light on migraine interictal hypersensivity: exacerbated, non-selective attention orienting to all stimuli may explain why migraineurs are so easily bothered and distracted by their environment. No study has attempted to link attention difficulties to hypersensitivity to this day. And even if an association was established, the causal relationship may not be that straight-forward. Attention deficits may impair the sensory filter that enables in everyday life to ignore irrelevant sources of stimuli, leading to a general state of hyper-responsiveness in migraine. In this framework, attention deficits are inherent to the migraine disease and are one of the causes participating to sensory hyper-responsiveness. However, the causal relationship may be opposite. Migraineurs have experienced numerous attacks during which sensory stimulation is extremely uncomfortable or even painful: the cumulative attacks may have created a negative association with all sensory stimuli (classical conditioning) which makes migraineurs perceived them as more stressful and salient even outside attacks, triggering an exacerbated orienting response.

2.3.3 Migraine and arousal

Is migraine associated with deficits in brain regulation of arousal? Dysfunctional regulation of arousal is an interesting matter, as it may account for the attention difficulties associated with the disease and increased responsiveness to environmental stimuli. Nevertheless, this question is not present as such in the literature. However, there is still indirect evidence of an association between migraine and arousal.

First, arousal levels appear to be impacted by the migraine cycle. The premonitory and post-drome phases are often associated to fatigue or on the contrary to excessive energy (Giffin et al. 2003; Giffin et al. 2016).

Then, as stated previously, migraine is a clear risk factor for anxiety and depression, which are more prevalent among migraineurs than in the general population. Anxiety is a biological warning system that prepares the body to react to potentially dangerous situations. It is associated with higher tonic arousal levels through the activation of sympathetic systems (Malmo 1957). Chronic anxiety may lead to state of hyper-arousal at rest, even outside of objectively stressful situations. In a recent study, the precise dimensions of the affective disorders symptoms (anxiety & depression) have been explored using questionnaires (Louter et al. 2015). If they confirmed that migraineurs are indeed more prone to affective disorders symptoms than the general population, migraine was more associated to "anxious arousal" than to "general distress" (lack of positive affect) and "anhedonic depression" (negative affect). This result confirms that hyper-arousal may be central in the migraine symptomatology.

There are also more physiological evidence of dysfunctional regulation of arousal in migraine. Reduced norepinephrine plasma levels and increased adrenergic receptor sensitivity suggest a weaker basal sympathetic activity (Peroutka 2004). However, migraineurs seem to retain the ability to increase plasma norepinephrine levels following physiological stressors. Migraineurs also present an abnormal functional connectivity and activation patterns of the locus coeruleus (LC) (Moulton et al. 2014), a brainstem nucleus responsible for most norepinephrine production in the brain and which has a key role in the regulation of tonic and phasic arousal (Sara and Bouret 2012). The LC is responsive to trigeminal stimulation and is thought to have a role in the pathophysiology of migraine attacks and the fatigue symptoms in the premonitory phase (Vila-Pueyo et al. 2019). Finally, as discussed previously, the increased CNV amplitude observed in migraine has been interpreted by some authors as a sign of a sympathetic hyper-activity during the task. Based on this literature, it is complicated to provide a comprehensive view on potential alterations of arousal regulation in migraine. Results seem to point towards lower interictal levels of tonic arousal in migraine, concomitant to exacerbated phasic arousal responses but this interpretation may not capture

the complexity of the situation.

Conclusions

Migraine is more than headaches. It is a complex neurological disorder characterized by cyclical physiological changes with the migraine attack as its climax, a neurological storm which affects the cortex, the brainstem and the peripheral nervous system engendering a wide diversity of symptoms. According to both old and new theories, the migraine attack seems to act as a "brain reset", sweeping away an accumulated tension in the brain that has built up during the interictal period. At its core, migraine is a also sensory disorder. Sensory hypersensitivity peaks during the headache and never really dissipates once the headache has passed. However, the sensory abnormalities are not limited to a hyper-responsiveness to external stimuli: sensory processing plays a key role in the pathogenesis of the disease. During the headache, sensory stimulation exacerbate the pain and the discomfort; during the interictal period, intense stimuli can trigger the onset of a migraine attack and cumulative stressful sensory inputs may even participate to the accumulation of oxidative stress in the brain. Despite centuries of research and despite the fact that migraine is the most prevalent and the most disabling neurological disorder, the underlying mechanisms of the disease still have not been elucidated and efficient treatments are still lacking.

The most puzzling paradox of migraine is that despite a clear role of genetic factors in the vulnerability to the disease, the prevalence of the disease is still really high. Vulnerability to recurrent debilitating headache surely should hinder survival and impair fitness, natural selection should have maintain this disorder at a very low prevalence. In a thought-provoking article, Elizabeth Loder (2002) has discussed if there is actually an evolutionary advantage to the vulnerability to migraine. Among other hypotheses, she proposes that migraine may have been a defense mechanism, encouraging the individual to withdraw from situations which trigger headaches. Avoiding noisy and visually confusing environments may have helped to avoid predators, the low threshold for nausea may be useful to regurgitate potentially toxic foods, avoiding hunger and sleep deprivation would also be beneficial... Migraine could also be a "disease of modern times", a trait that natural selection did not have time to eliminate. With the development of civilization, humans are in an increasingly rich environment to the point of sensory overload and in which trigger factors are more and more prevalent. Migraine has still a lot of secrets to unveil...

Part II

A common method: The Competitive Attention Test

In the following experimental works, we have used the Competitive Attention Test, an original task developed by Aurélie Bidet-Caulet to investigate the interaction between top-down and bottom-up. Here are a description of the reasons behind the conception of this task, of its procedure and of previous results obtained using this task.

1 Rationale

Imagine you are a student in a classroom. You are expected to listen to the teacher in order to write down the course. You are surrounded by irrelevant information: students are chatting behind you, the clock is ticking loudly, birds are flying by the window, there are plenty of posters on the walls; however you manage to focus on the teacher's speech and on the notes written on the blackboard. Although you are effectively concentrating on the lesson, you are probably not totally impervious to your environment. If a car is honking in a street nearby or if another drops a heavy book on the floor, it will surely interrupt your attention for a few moments before you are able to focus back on the teacher.

Distractibility is the tendency to have one's attention captured by unexpected events. Most adults present a "healthy" level of distractibility which enables them to be efficient in their daily tasks: it is considered to be achieved through an adequate balance between voluntary, top-down attention and involuntary, bottom-up attention. However, some populations present exacerbated distractibility, namely young children (Gumenyuk et al. 2001; Tipper et al. 1989; Wetzel and Schröger 2014), the elderly (Zanto and Gazzaley 2014) and possibly people with Attention Deficit and Hyperactivity Disorder (ADHD) (e.g. Gumenyuk et al. 2005; Slobodin, Cassuto, and Berger 2018), which hinders their ability to be efficient in situations requiring enduring focus such as attending a class or a lecture.

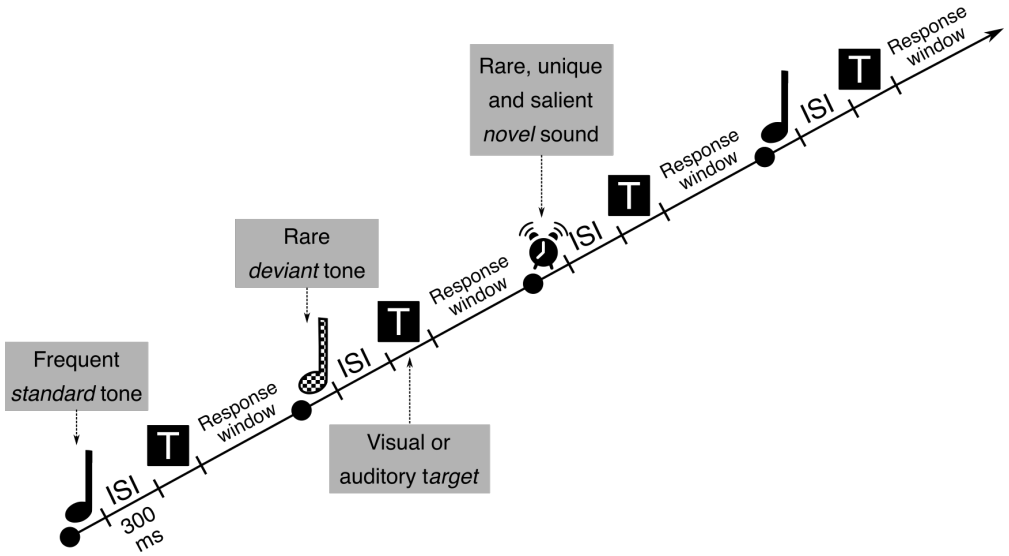
> "There are no windows and my gaze drifts toward the orange door of my classroom. My foot bounces up and down, and my attention pings around during the lecture. My professor is speaking just a few feet away, but he fades in and out of my focus.
>
> I drift between the PowerPoint on the screen in front of the classroom and the notes on my computer. I absently enter bullet points. Occasionally, a ripple of laughter flows through the classroom. My classmates' questions and stories, along with my professor's responses, swirl around me and fill the room.
>
> This isn't a boring class. This lecture on mental health and exercise definitely interests me. And my professor does his best to keep us engaged with amusing and interesting stories.

> Still, like a pinball, my focus bounces from one thing to another. The lecture is the last thing my brain wants to pay attention to, even though I want to pay attention and I'm trying hard to. But I'm caught up in the chaos of the sounds of my fellow students—zippers, coughs, pen, keyboard clicks. . . "
>
> What ADHD Feels Like to Me, MacKay (2016)

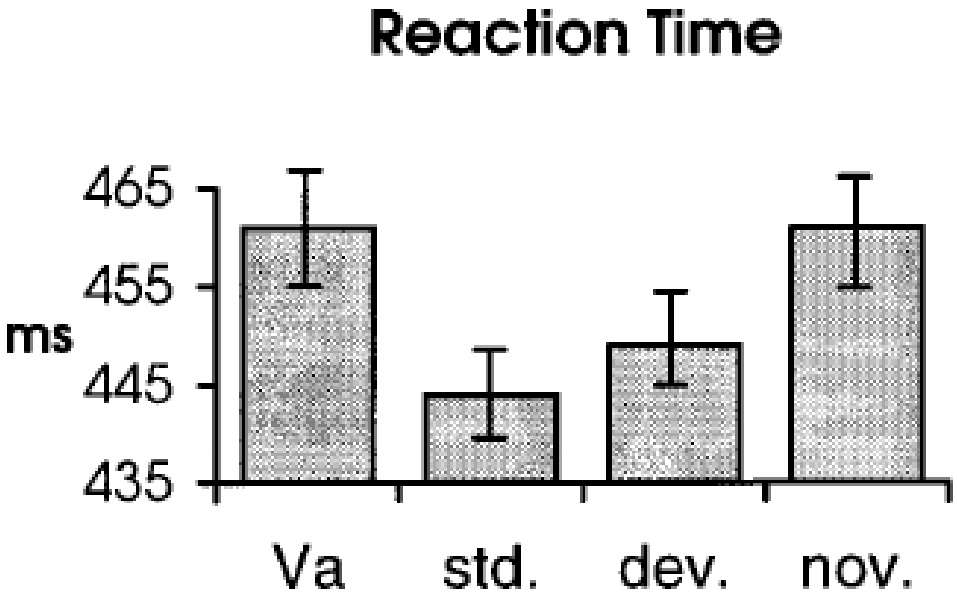
There exist several neuropsychological tests which evaluate attentional functions. The Continuous Performance Test (CPT, Klee and Garfinkel 1983) and the Test of Variables of Attention (T.O.V.A., Greenberg and Waldman 1993) roughly consist in boring tasks during which the participant is asked to respond to target stimuli while inhibiting responses to non-target stimuli; they are considered to evaluate *impulsivity, sustained* and *selective attention*. The Test of Everyday Attention (TEA, Robertson et al. 2001) aims to recreate everyday tasks using eight test subsets and is considered to evaluate *sustained, divided* and *selective attention*. The famous Stroop Task uses cognitive interference to evaluate *selective attention*.

However useful these tests may be for diagnosis in clinical settings, they are often not designed to specifically investigate distraction. They mainly focus on voluntary attention and do not attempt to measure involuntary orienting responses. To our knowledge, the only prominent neuropsychological test which evaluate distraction (as well as other dimensions of attention) is the German Test-battery of Attention Performance (KITAP, Sobeh and Spijkers 2012). Besides, these paradigms, as a result of their designs, are often unfit for functional neuroimaging studies and mostly rely on the visual modality.

In the auditory modality, distraction was mostly investigated using task inspired from the oddball paradigm, which I will refer to as the "distraction-oddball paradigm", for lack of an official name. First used in 1975 (Squires, Squires, and Hillyard 1975), the classic oddball paradigm consists in the presentations of sequences of frequent sounds among which are interspersed rare *deviant* and/or *target* sounds. It has been proven to be of immense value in the research about attention and information processing. It has also much contributed to research on evoked potentials with the characterization of the MMN and the P3a/P3b responses. The distraction-oddball paradigm updates this experimental design to evaluate specifically distraction (Escera et al. 1998; Schröger 1996). All trials comprise a target stimulus (either visual or auditory) to be discriminated, always preceded by a task-irrelevant *standard, deviant* or *novel* sound (see 21a). *Deviant* and *novel* sounds, compared to the *standard* sounds, lead to prolonged reaction times in response to the target stimulus (Andrés, Parmentier, and Escera 2006; Berti and Schröger 2003; Berti, Roeber, and Schröger 2004; Escera et al. 1998; Rinne et al. 2006; Schröger 1996; Wetzel et al. 2006). This difference in reaction time between *standard* trials and *deviant/novel* trials is consid-



(a) Typical task design of an active auditory oddball paradigm. *Task-irrelevant sounds are followed by a target stimulus to which the participant is asked to respond. In most trials, usually 80% or more, a* standard *sound is presented. In few trials, a* deviant *tone (i.e. a tone which differs slightly from the* standard *stimulus, usually in terms of pitch, duration or loudness) is presented. In some versions of the paradigm,* deviant *sounds are replaced with or exist along* novel *sounds, which correspond to ecological and salient sound (e.g. car horn, phone ring, etc.) which only played a few times during a whole session. The inter-stimulus interval (ISI) is usually short, around 300 ms. Adapted from Wetzel et al., 2012.*



(b) Behavioral results to an active audiovisual oddball paradigm. *Mean reaction time in the target-alone condition (Va) and in the conditions in which the target occurred after the standard tone (std.), the deviant tone (dev.), or the novel sound (nov.). The bars indicate the standard error of mean. Adapted from Escera et al. (1998).*

Figure 21: *The distraction-oddball paradigm*

ered to be a proxy of behavioral distraction. Numerous studies have used these paradigms to measure distractibility in healthy adults (Escera et al. 1998; Escera et al. 2003; Yago et al. 2003), in children (Gumenyuk et al. 2001; Wetzel and Schröger 2007), in the elderly (Getzmann, Gajewski, and Falkenstein 2013), in children with ADHD (Gumenyuk et al. 2005; van Mourik et al. 2007), in schizophrenia (Cortiñas et al. 2008) or in mild cognitive impairment (Correa-Jaraba, Lindín, and Díaz 2018).

The distraction-oddball paradigm has the advantage to present a very simple procedure and the task is easy enough to be performed by young children and clinical populations. However, there is a major concern that the measure of distraction provided by the active oddball paradigm might not reflect a pure attention capture phenomenon but rather a complex composite of different attention functions. First, in their influential article that has established the distraction-oddball paradigm as a tool for investigating distractibility, Escera et al. (1998) observed that participants responded more slowly in trials in which no sound preceded the target compared to trials in which a standard sound is played before (see Figure 21b), this effect dissipating in *novel* trials. This result invalidates the postulate that novel sounds only yield distraction. If all target stimuli are preceded by an oddball sound, the latter may then act as a warning signal (see p.46) or even as temporal cue since the inter-stimulus interval (ISI) between the oddball sound and the target is constant. Second, it is possible that the participant will actively suppress the flux of oddball sounds to maintain the focus on visual targets, attenuating the effects of distraction by novel sounds. This is supported by a study from SanMiguel, Corral, and Escera (2008) which showed that increasing the working memory load limits the distraction effects of novel sounds, suggesting that distraction is controlled under top-down mechanisms. Therefore, behavioral effects following *deviant* and *novel* sounds in the oddball paradigm cannot be solely attributed to bottom-up attention capture: they are likely to encompass also either arousal or top-down attentional processes. Finally, the "distraction-oddball" paradigm only focus on bottom-up attention capture and not the deployment of top-attention, which does not paint a full picture when investigating distractibility.

Therefore there is a need for a new paradigm to investigate distractibility in which:

1. Distractors are truly task-irrelevant: they cannot act as temporal cues. It would enable to produce a reliable measure of distraction.

2. Distraction and facilitation effects by salient, unexpected "distracting" sounds can be evaluated separately.

3. As distractibility relies on the balance between top-down and bottom-up attention,

joint but separate measure of both dimensions of attention is essential. It would enable to understand how they interact within a single task setup.

2 Procedure

The Competitive Attention Task (CAT) was developed by Aurélie Bidet-Caulet and was first described in 2015. The paradigm aims to produce reliable measures of both top-down and bottom-up attention, and to investigate how they interact. The original version was used in behavior-only and EEG experiments and a variant was preferred for MEG experiments.

2.1 First version (EEG, behavior)

2.1.1 Methods

The CAT is an adaptation of a Posner cueing task using visual cues and auditory targets (Figure 22). Participants were asked to detect a target sound and to respond as fast as possible, as soon as they heard it. Target sounds were monaural and were randomly presented either at the left or right side. They are played close to the hearing level of the participant so they would have to engage more attentional processes. A visual cue always appeared around 1150 ms before the target sound onset.

Top-down attention was evaluated through the modulation of the cue informational value. *Informative* cues (single arrow, 66.6% of the trials) allowed the participant to predict the side of the presentation of the target in order to respond faster; *uninformative* cues (double arrow, 33.3% of the trials) did not give information on the side of presentation of the target sound. *Informative* cues were always valid (unlike the actual Posner task); that is, the target was invariably presented on the side predicted by the cue. The assumption was that participants engage more top-down anticipatory processes in *informative* trials compared to *uninformative* trials, in which the participant is unable to attend to the side of presentation of the incoming target.

Bottom-up attention was evaluated through the effects of distracting sounds. In 25% of the trials, a salient task-irrelevant binaural sound (300 ms) was played at some point between the cue offset and the target onset. If the distracting sound onset was early (around 750 ms before the target onset), the trial was categorized as DIS1; if the distracting sound onset was as at an intermediate position, the trial was categorized as DIS2. If the distracting sound onset was late (around 350 ms before the target onset), the trial was categorized as DIS3. A catalog of 30 sounds was used in order to ensure that distractors retain their novelty throughout the experiment. In the 75% remaining trials, no distracting sound was played;

trials were categorized as NoDIS. As the distractor-target delay is not fixed, it is assumed that distractors cannot act as temporal cues. Moreover, the presence of a preceding cue and the absence of distractors in most trials mitigate a possible warning effect by distracting sounds.

Reaction times were recorded. Trials in which the participant does not respond after the target are considered as *miss*, trials in which the participant responds before the target onset are considered as *false alarm*. EEG signals were recorded using a 32-electrodes EEG headset and event-related potentials were computed.

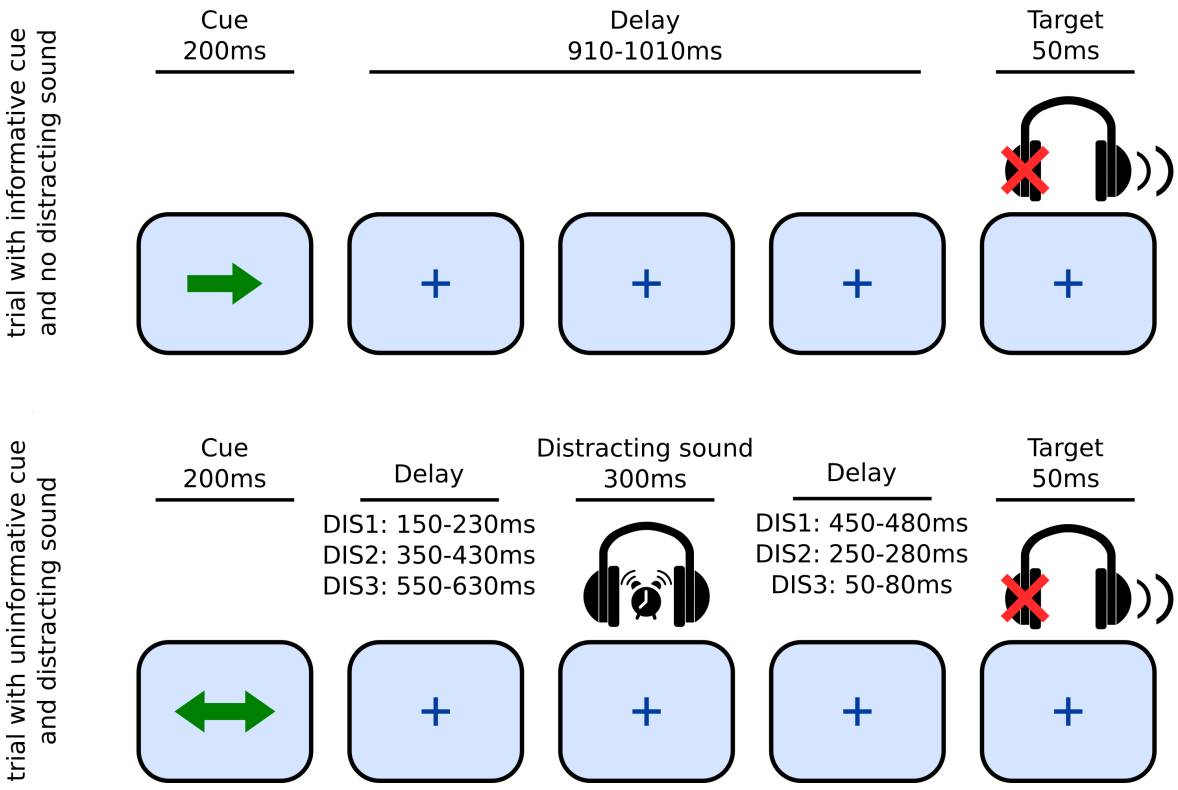


Figure 22: Original version for EEG. *First row: Example of a distractor-free trial (75% of the trials). A visual cue (200 ms) precedes the onset of a monaural target sound (50 ms) by a random delay (900–1010 ms). In 66.6% of the trials, a one-sided cue indicates in which ear (left or right) the target sound will be played (informative trial). In the other 33.4% of the trials, a two-sided visual cue does not provide any indication in which ear (left or right) the target sound will be played (trial not depicted in the figure). Second row: Example of a trial with a distractor (25% of the trials). All parameters are identical to trials with no distracting sound, except that a binaural distracting sound (300 ms duration), such as a phone ring, is played during the delay between cue and target. The distracting sound can equiprobably onset in three different time periods after the cue offset: in the 150–230 ms range, in the 350–430 ms range, or in the 550–630 ms range. Participants were instructed to respond to the target as fast as possible and to use the cues to their advantage.*

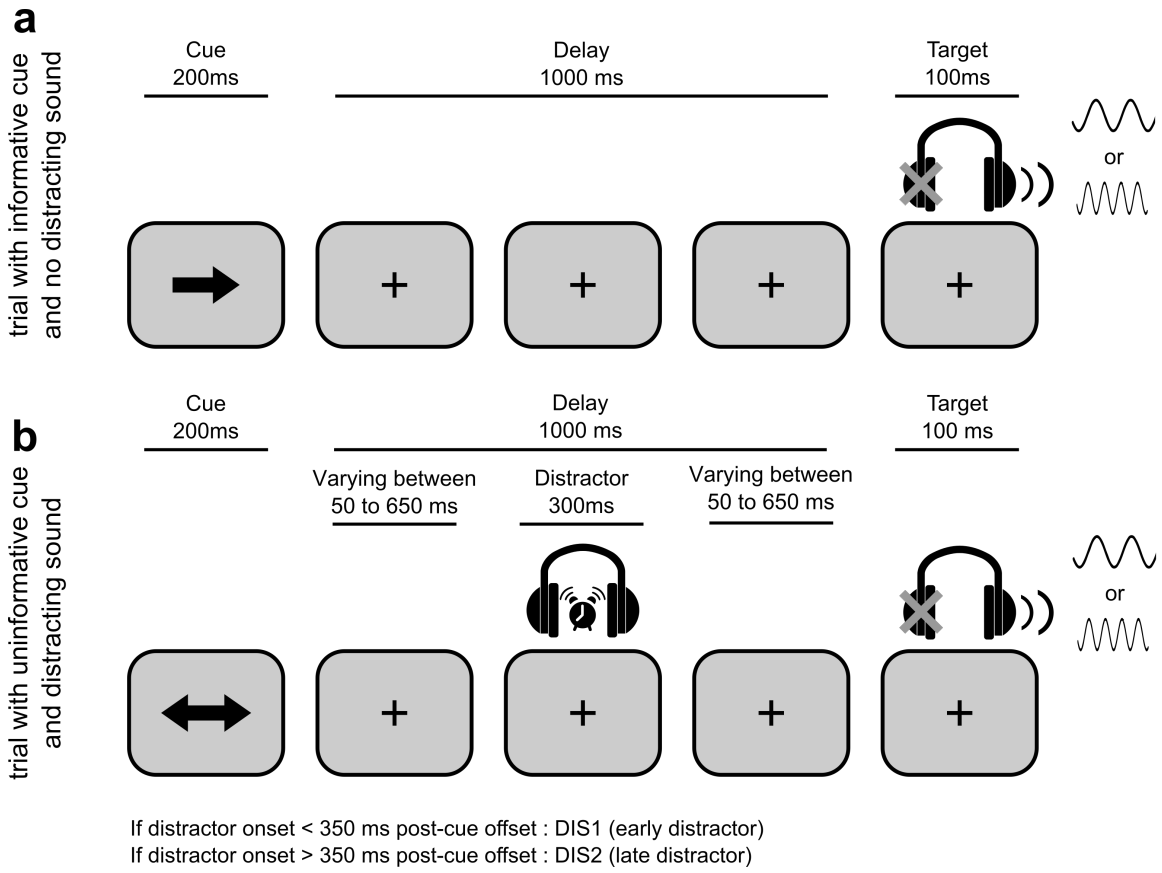


Figure 23: Adapted version for MEG. *Please note that the distracting sound can now randomly onset from 50 to 650 ms after cue offset and there is now only two distractors category (DIS1 & DIS2). The cue-target interval is fixed to 1000 ms. Participants were instructed to discriminate between high-pitched or low-pitched target sounds.*

2.1.2 Results

Behavioral results

In healthy young adults participants As expected, Bidet-Caulet et al. 2015 observed that participants presented shorter reaction times when the visual cue was informative, i.e. it indicated where the target sound would be presented. Therefore, the difference in reaction time between informative and uninformative trials (in trials with no distracting sound) was considered to index the engagement of top-down anticipatory processes, or in other words, the ability to voluntarily orient attention towards one aspect of the environment.

$$Topdown = RT_{uninformative,NoDIS} - RT_{informative,NoDIS}$$

Surprisingly, distracting sounds had different effects depending on the distractor-target delay (Figure 24). Early distractors (DIS1, far from the target) were followed by a drop in

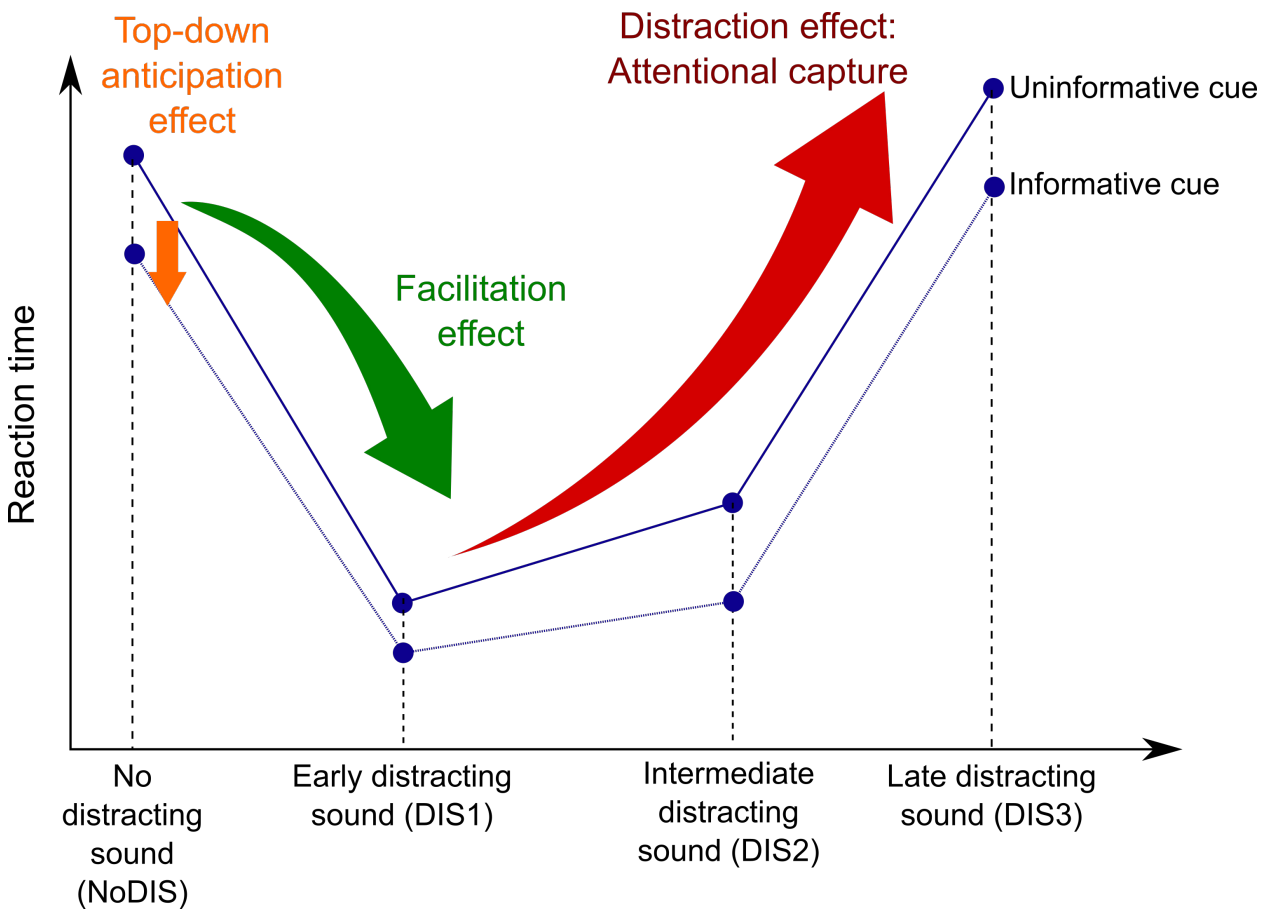


Figure 24: *Schematic representation of the behavioral effects obtained using the Competitive Attention Test, adapted from Bidet-Caulet et al. (2015).*

reaction time compared to the condition without distracting sounds (NoDIS). However, for late distractors (DIS3, close to the target), reaction times were similar than in the condition with no distracting sounds. Distracting sounds appear to elicit two distinct behavioral effects: a long-lasting facilitation effect and a short-lived distraction effect. The facilitation effect would be steady for at least 750 ms and would boost performance to the task. It is only visible for early (and intermediate) distractors which are remote from the target onset. When the distractor is close to the target, the behavioral benefit provided by the facilitation effect appears to be canceled out by the cost of bottom-up attention capture. This distraction effect seems to dissipate rather rapidly (in a few hundred milliseconds) as the behavioral facilitation is still clearly visible for intermediate distractors (DIS2) which are at least 550 ms away from the target onset (Figure 25). Therefore, the CAT provides both a measure of bottom-up attentional capture through the difference in reaction time between trials with late and early distracting sounds, and a measure of behavioral facilitation through the difference in reaction time between trials with no distracting sound and those with an

early distracting sound. It is likely that the facilitation effect reflects an increase in phasic arousal following salient, unexpected sounds, as it was proposed previously in the literature (Max et al. 2015; SanMiguel, Linden, and Escera 2010; Wetzel, Widmann, and Schröger 2012). However, other cognitive mechanisms might also account for this effect and further research is needed to conclude.

$Bottomup = RT_{DIS3} - RT_{DIS1}$

$Facilitation = RT_{NoDIS} - RT_{DIS1}$

Finally, there was no conclusive evidence of an interaction between the informational value of the cue and the behavioral effect of distracting sounds, suggesting that a superior top-down attentional load does not prevent distraction in the context of this task.

In healthy children Children are reputed to be more easily distracted than adults (Gumenyuk et al. 2001; Tipper et al. 1989; Wetzel and Schröger 2014). However, distractibility in childhood was mostly approached using attentional orienting (e.g. Posner tasks) and sustained attention paradigms (e.g. Continuous Performance Test). It is still unknown which cognitive mechanisms participate to the increased distractibility in children and what are the developmental trajectories of attentional functions during childhood. Distractibility in children may emerge from an imbalance between top-down and bottom-up attention.

Hoyer and collaborators used the CAT paradigm to investigate the development of distractibility from childhood to adulthood (Hoyer et al. 2019). Participants from 6 to 25 years performed the task. The task was slightly adapted to appeal more to young children: visual cues became dog cartoons indicating the side of presentation of auditory targets, auditory targets which were then dog barks. A plurality of indexes were extracted from behavioral data to investigate numerous dimensions of attention: they included those described above but also markers of sustained attention, impulsivity and motor control. Results showed that young children present enhanced distraction and reduced sustained attention, suggesting that the distractibility associated to childhood stems from dysfunctional top-down and bottom-up attention functions. This study also revealed that the developmental dynamics of the different attention functions were more complex than expected. Top-down attention orienting is mature among 6-years but bottom-up distraction remains particularly exacerbated at this age. On the other hand, teenagers were rather characterized by decreased motor control and increased impulsivity, both dissipating with adulthood.

Electrophysiological results Numerous event-related potentials (ERPs) are elicited during the CAT task, giving us a window on different attentional functions, as described in Bidet-Caulet et al. (2015) (Figure).

ERPs and bottom-up attention Distracting sounds elicited a well-known sequence of ERPs, identical to the one described in previous studies using the oddball paradigm (Escera et al. 1998; Horváth et al. 2011; McDonald et al. 2010; Yago et al. 2003). They were followed by a N1 and a biphasic P3 response. The early-P3 had a fronto-central topography and peaked around 240 ms, while the late-P3 had a fronto-parietal topography and peaked around 320 ms.

Distracting sounds also interacted with target processing as late distractors (DIS3) delayed the latency and decreased the amplitude of the N1 to the target sound. This interference effect may account for the behavioral distraction effect described previously. On the contrary, the processing of early distracting sounds (DIS1) appears to have ended a couple of hundred milliseconds before target onset, and they did not affect the latency or the amplitude of the N1 to the target. This absence of observable interference may explain why no behavioral cost is observed after early distractors.

ERPs and top-down attention Visual cues elicited a classical sequence of visual ERPs (P1, N1, P2, etc.), then followed by a negative slow wave, the Contingent Negative Variation (CNV), in anticipation of the target onset. The CNV is considered to reflect motor preparation and anticipatory processes when expecting an incoming stimulus (Brunia and van Boxtel 2001). An increased CNV was observed in *informative* trials compared to *uninformative* trials, suggesting that the CNV amplitude reflects (partly) top-down attention orienting.

Auditory targets elicited an auditory N1 and, as expected, a parietal P300. The precise function of the P300 (or P3b) is complex but it is considered to reflect the attention orienting towards a relevant stimulus and the allocation of cognitive resources to process it (Polich and Criado 2006; Polich 2007). The amplitude of the P300 was decreased in *informative* trials compared to *uninformative* trials. The authors interpretation was that *informative* cues decrease target uncertainty which is known to affect the amplitude of the P300 (Duncan-Johnson and Donchin 1977; Suwazono, Machado, and Knight 2000).

The top-down attention load also interacted with bottom-up attention as *informative* cues caused a decreased N1 and early-P3. The authors interpreted that "[...] the reduced N1 and early-P3 responses with more top-down attention load could be explained by a reduction in the available cognitive resources because the task is more resource consuming during informative trials as indicated by the enhanced CNV".

2.2 Second version (M/EEG)

2.2.1 Methods

A variant of the original paradigm was used for M/EEG studies (Figure 23). It was roughly identical except in the following aspects:

- Participants performed fewer blocks of trials in order to shorten the experiment. In order to maintain a sufficient number of trials in each condition for subsequent analyses:
  - The proportion of *informative* cues was decreased to 50%.
  - The delay between the distractor and the target is randomly chosen between 350 and 750 ms. Early distractors (DIS1) correspond to a distractor-target delay between 350 ms and 650 ms, late distractors (DIS2) correspond to a distractor-target delay between 50 ms and 350 ms.
- The cue-target interval is fixed at 1000 ms.
- Participants were now asked to perform a pitch discrimination task (and not a detection task), in order to increase the difficulty of the paradigm and engage more attentional resources.

MEG signals were recorded as well as EEG signals using 7 electrodes among young healthy participants and older adults. Analyses of oscillatory activities were conducted using MEG data.

2.2.2 Results

Behavioral results Behavioral results described above were replicated twice with independent samples of young healthy participants (ElShafei et al. 2018; ElShafei et al. 2020). There were two main differences with the original protocol. First, reaction times were generally higher because of the increased difficulty of the task. Second, the arousal effect was attenuated and contrary to the original protocol, reaction time in trials with a late distracting sounds was actually significantly higher compared to trials with no distracting sounds. It could also be due to the increased difficulty of the task which might have raised tonic arousal levels, leading to less pronounced phasic arousal increases.

Electrophysiological results

Alpha rhythms ElShafei and collaborators investigated the alpha-band oscillatory activities during the cue-target delay (ElShafei et al. 2018). In anticipation of the target sound, they observed distinct modulations of power in two sub-bands of alpha. Auditory target anticipation was associated to a desynchronization of "low-alpha" (7–11 Hz) and a synchronization of "high-alpha" (11–15 Hz) in the pre-target period. Source reconstruction revealed that the high-alpha synchronization emerged from visual areas and the magnitude of the synchronization correlated negatively with reaction time. On the other hand, the "low-alpha" desynchronization emerged from auditory cortices. Interestingly, top-down attention appeared to modulate alpha power. Within the right auditory cortex, the increase in high-alpha power was more pronounced when attending an ipsilateral sound; and a stronger decrease in low-alpha power was observed when attending a contralateral sound.

Alpha rhythms are considered to reflect inhibitory mechanisms which gate information towards relevant areas (Jensen, Kaiser, and Lachaux 2007). These phenomena described above would correspond to two distinct top-down anticipatory mechanisms. Facilitation mechanisms would be mediated by low-alpha desynchronization in relevant areas, here auditory cortices and especially the auditory cortex contralateral to the cued side; while inhibitory mechanisms would be mediated by high-alpha synchronization in irrelevant areas, here visual areas and the auditory cortex ipsilateral to the cued side. High-alpha synchronization in visual areas was the phenomenon most strongly linked to behavior. This study presented conclusive evidence of the presence of alpha rhythms in the auditory cortices using MEG, confirming recent observations (Mazaheri et al. 2014; Müller and Weisz 2012; Weisz et al. 2014).

Gamma rhythms ElShafei and collaborators also investigated gamma oscillations in response to distracting sounds (ElShafei et al. 2019). An increase in gamma (60–100 Hz) power is observable quickly after a distractor onset and emerges in the ventral attention network (VAN), including the temporo-parietal junction and the right ventro-lateral prefrontal cortex, a network whose functions are related to bottom-up attention (Corbetta et al. 2000; Corbetta and Shulman 2002). Moreover, top-down attention load (i.e. the informational value of the cue) modulated gamma activity in response to the distracting sound with a increase in gamma power in the medial prefrontal cortex in *informative* trials, suggesting an interaction between top-down attention and bottom-up attention. Finally, an increase in phase synchrony between the lateral prefrontal cortex and the auditory cortex after the presentation of the distracting sound has been observed, suggesting that the lateral prefrontal cortex plays a key role in the top-down inhibition of irrelevant stimuli.

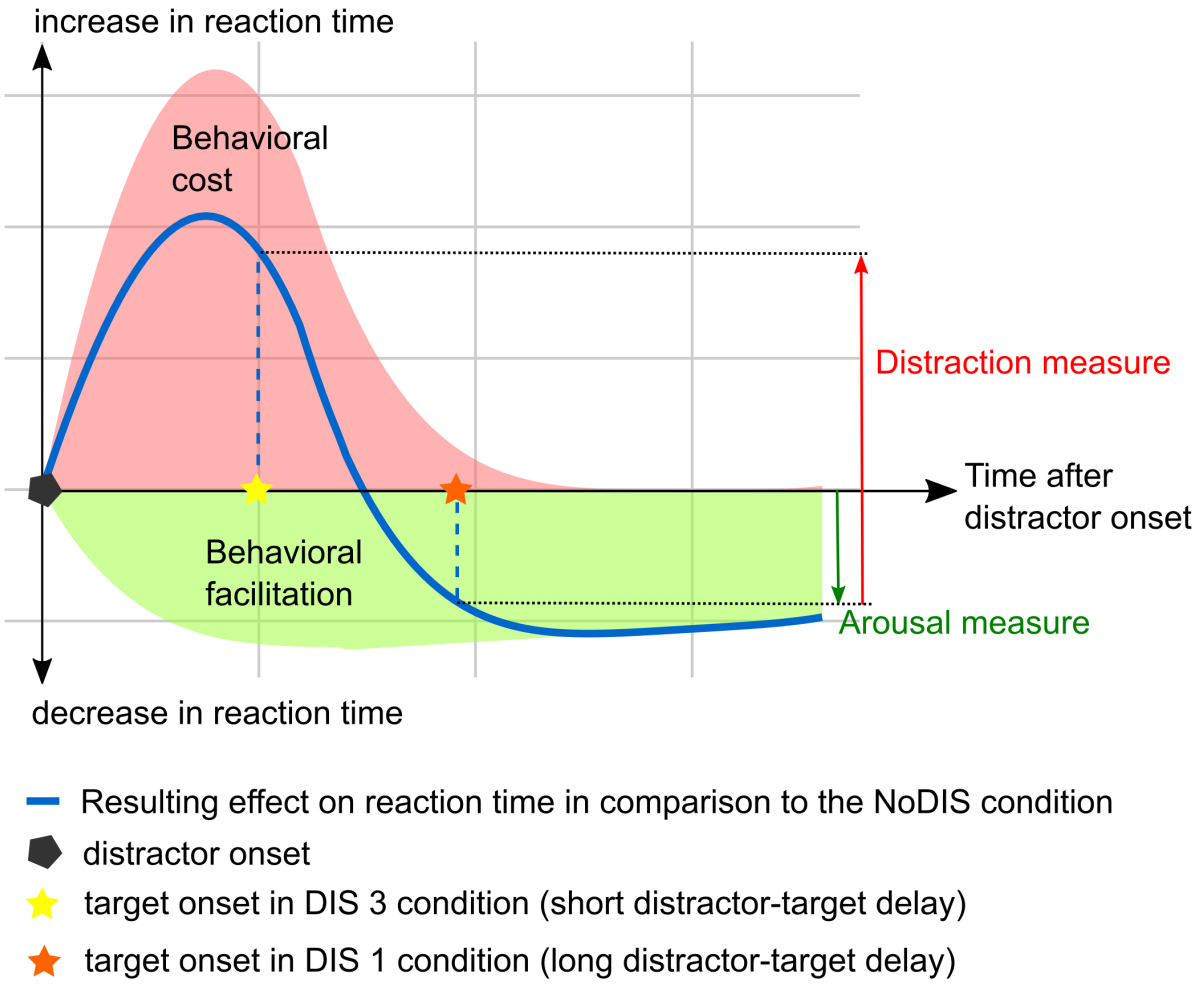


Figure 25: Model of the temporal dynamics of the distraction (red) and facilitation (green) effects following distracting sounds. *In DIS1 trials, the short-lived distraction effect has already vanished when the target is played, only remains the beneficial effect of facilitation. In DIS3 trials, the distraction effect is still persisting when the target is played, canceling out the beneficial effect of facilitation.*

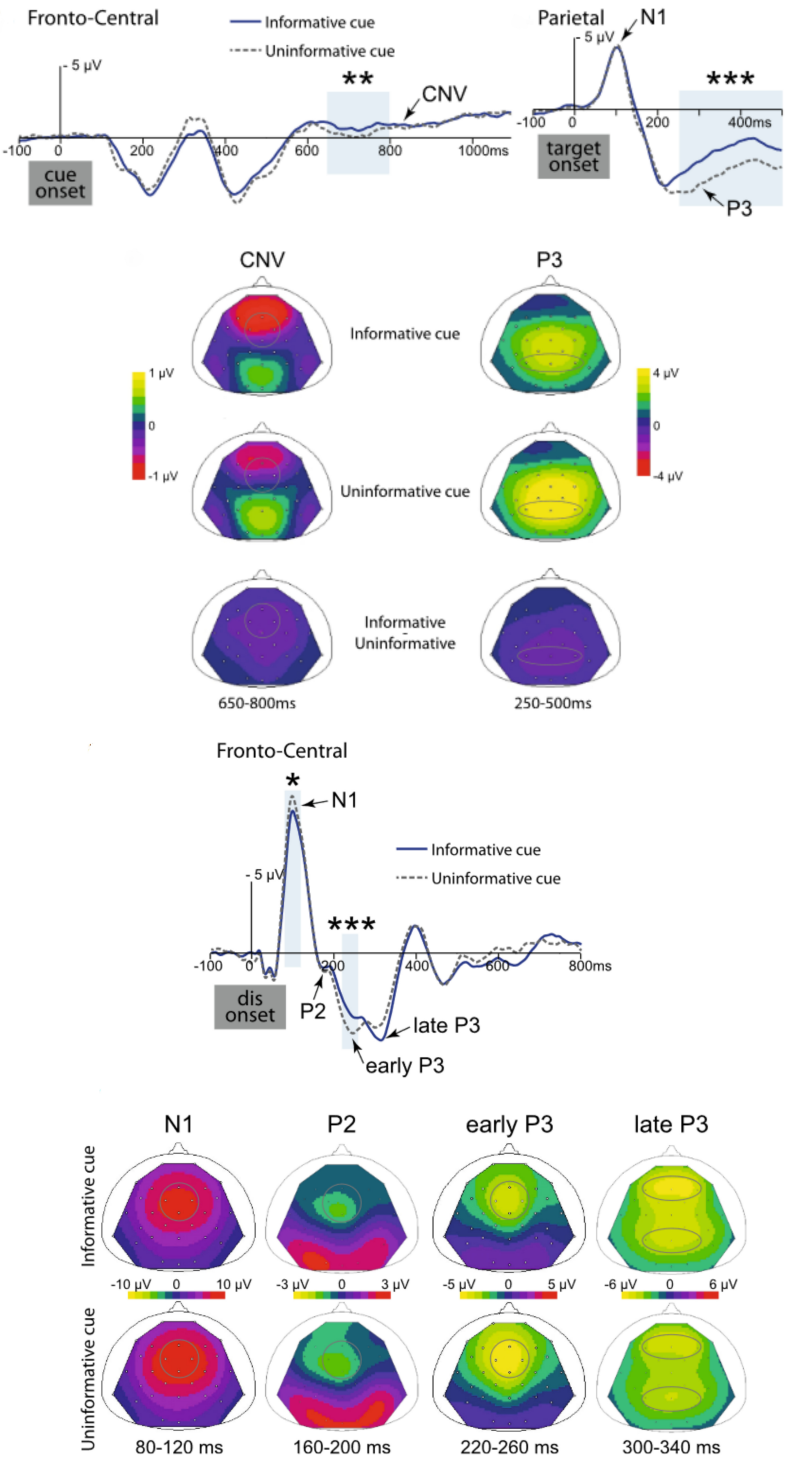


Figure 26: *Time-course and scalp topography of the event-related potentials to the cue, target and distracting sounds in Bidet-Caulet et al. (2015). The effect of the information value of the cue are also displayed.*

3 Conclusions

The Competitive Attention Test is a particularly useful tool to investigate attention in healthy and clinical populations. It consists in a more ecological examination of distractibility than other neurophysiological tests. It also provided distinct and robust behavioral and electrophysiological measures of top-down and bottom-up attention (and various cognitive functions), enabling to pinpoint the precise attentional alterations which may exist in a given population.

Part III

Hypotheses & Objectives

As I have developed above, there is a reasonable number of psychological studies in favor of the existence of attention difficulties in migraine. However, there is little data in the literature allowing to understand accurately which attentional processes are affected in migraine. Moreover, neuroimaging studies investigating attention in migraine are still very scarce and there is a poor understanding of which cortical networks involved in the disruption of attention in migraine. The Competitive Attention Test is a particularly adequate paradigm to fill the gaps left in the literature about migraine and attention. This task provides reliable behavioral measures of top-down and bottom-up attention and there are previous studies investigating the event-related responses and the oscillatory activities elicited during this specific task. However, before using this paradigm to investigate attention in migraine, there are still some clarifications to be made. Bidet-Caulet et al. (2015) observed that distracting sounds may trigger a facilitation effect when the delay between the distractor and the target is sufficient. However, if the authors speculated that it may due to an increase in phasic arousal, the actual nature of the behavioral facilitation has yet not been established. Also, the literature about distraction has interpreted distractor-elicited event-related potentials in the framework of attention capture. If distracting sounds elicit both facilitation and attention capture behaviorally, it is reasonable to imagine that both effects are reflected in the event-related response.

The first objective of this work is twofold and focuses on investigating phasic arousal in healthy adults participants.

- It is necessary to confirm that the facilitation effect observed in the CAT is indeed the reflection of an increase in phasic arousal. An alternative hypothesis would be that the distracting sound elicits an reorientation of attention towards the auditory modality even before the onset of the auditory target, facilitating target processing and boosting performance. In order to settle between these two hypotheses, we have designed alternative versions of the CAT in which the sensory modalities of the cue and the target are changed.

- It would be valuable to find an electrophysiological index of this increase in phasic arousal in order to have a better understanding of this cerebral process. We hypothesize that if a event-related response is associated, it should vary in amplitude according to the arousing properties of the sound. To this end, participants have rated all the distracting sounds used during the CAT for their arousing and emotional properties. Then we have attempted to correlate these ratings to the event-related responses recorded during the task.

The second objective of this work is also twofold and focuses on investigating attention

capacities in migraine.

- First, it has still not been established that attention difficulties are linked to the sensory disturbances observed in migraine. We hypothesize that a deficient attentional filtering of the environmental sources of sensory stimulation may lead to a state of sensory overload, in which migraineurs would have trouble to suppress irrelevant streams of stimuli in the background. To have a better understanding of the link between attention and hypersensitivity, a questionnaire has been designed in which healthy controls and migraine participants self-evaluate their attention difficulties and how sensitive they are to light, noise and odors.

- Then, we hypothesize that migraine is characterized by either deficient top-down attentional processes or exacerbated, hyper-responsive bottom attentional processes or both. To characterize and identify the precise attentional mechanisms at play in attention difficulties associated to migraine, healthy controls and migraineurs performed the CAT while MEG and EEG signals were recorded. On the other, the analyses of both event-related responses will shed light on top-down (e.g. with the contingent negative variation) and bottom-up processes (e.g. with the P3 responses) during the CAT as attention-associated event-related responses are particularly well-described in the literature. Our previous work on healthy participants will also be particularly helpful for the interpretation of the distractor-elicited event-related responses. On the other hand, the investigation of alpha rhythms during the target anticipation period will be useful to characterize the relative contribution of facilitatory and inhibitory attentional processes. Finally, the use of MEG will be crucial to identify the cortical networks potentially affected as its spatial resolution is far superior to EEG while retaining its fine-grained temporal resolution and its superior signal-to-noise ratio will be important for advanced analyses of high-frequency oscillations, namely distractor-induced gamma bursts during the task.

The third objective of this work focuses on investigating brain anatomy in migraine. We hypothesize that sensory symptoms and attention difficulties may be linked to abnormalities in brain structure. Recently developed morphometry techniques are novel computational approaches which provide a streamlined, automatic analysis of group differences in terms of brain anatomy. Voxel-based and surface-based morphometry (VBM & SBM) process images obtained through anatomical MRI and allow the investigation of macroscopic changes, namely differences in gray- and white-matter volume, in cortical thickness or in the geometry of cortical gyri and sulci. Tract-based spatial statistics (TBSS) process images obtained during diffusion tensor imaging (DTI) sequences and allow the investigation of microscopic

changes, namely the integrity of the white matter fascicles. To have a better understanding of migraine anatomy, we have performed morphometry techniques on newly acquired data and we have confronted to previous results through a systematic review and a meta-analysis of the literature.

Part IV

Experimental works

1 Towards electrophysiological markers of phasic arousal

1.1 General introduction

As I presented above, the first objective of this study is to better characterize the behavioral facilitation triggered by distracting sounds in the CAT. We hypothesize that it stems from a phasic increase of arousal but other alternative hypotheses have to be infirmed before we can confirm this theory. In this regard, we developed variants of the CAT to observe if the behavioral facilitation effect remains despite changes in the sensory modality of the cue or target stimulus or despite longer interval between the distractor and the target. The second objective is to detect a potential ERP component reflecting the phasic increase of arousal triggered by salient distracting sounds. With that in mind, participants have been asked to subjectively rate all the distracting sounds used in the task according to their arousal and emotional properties. Then, we re-analyzed previously acquired EEG data to find a statistical association between the arousal ratings and the amplitude of the ERPs.

1.2 Article 1: "Fronto-central P3a to distracting sounds: An index of their arousing properties"

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Fronto-central P3a to distracting sounds: An index of their arousing properties

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ABSTRACT

The P3a observed after novel events is an event-related potential comprising an early fronto-central phase and a late fronto-parietal phase. It has classically been considered to reflect the attention processing of distracting stimuli. However, novel sounds can lead to behavioral facilitation as much as behavioral distraction. This illustrates the duality of the orienting response which includes both an attentional and an arousal component. Using a paradigm with visual or auditory targets to detect and irrelevant unexpected distracting sounds to ignore, we showed that the facilitation effect by distracting sounds is independent of the target modality and endures more than 1500 ms. These results confirm that the behavioral facilitation observed after distracting sounds is related to an increase in unspecific phasic arousal on top of the attentional capture. Moreover, the amplitude of the early phase of the P3a to distracting sounds positively correlated with subjective arousal ratings, contrary to other event-related potentials. We propose that the fronto-central early phase of the P3a would index the arousing properties of distracting sounds and would be linked to the arousal component of the orienting response. Finally, we discuss the relevance of the P3a as a marker of distraction.

1. Introduction

Attentional processes enable us to selectively attend stimuli which are relevant to our goals, and to filter out irrelevant stimuli, to increase task-efficiency. However, unexpected salient stimuli tend to attract our attention away from the task at hand: this is commonly referred as distraction or involuntary attention. This distraction effect is usually transient and we are able to focus back on the task, unless the stimulus was evaluated as significant.

Auditory distraction has been mostly investigated using audio-visual oddball paradigms during which task-irrelevant standard or rare novel sounds precede visual targets to be discriminated (Escera et al., 2003, 2000; 1998; Schröger and Wolff, 1998). These studies have shown that novel sounds, compared to standard sounds lead to prolonged reaction times or decreased hit rates to visual (Andrés et al., 2006; Berti et al., 2004; Escera et al., 1998) or auditory (Berti and Schröger, 2003; Rinne et al., 2006; Schröger, 1996; Wetzel et al., 2006) targets. These novel sounds would elicit attentional capture, also referred as involuntary orienting of attention in the literature (Wetzel et al., 2013), and their processing would require resources that are then unavailable for the maintenance of attention on the task at hand (Escera et al., 2000; Näätänen, 1992).

At the electrophysiological level, novel distracting sounds elicit a well-described sequence of event-related potentials (ERPs) which includes the N1 and a P3 complex (Escera et al., 2003, 1998). The N1 response to unexpected sounds is deemed to index a transient detector mechanism (Berti, 2013; Escera et al., 1998) that would trigger an attention switch to salient stimuli (Näätänen, 1990; Näätänen and Picton, 1987; Näätänen and Winkler, 1999). The P3 complex, also called novelty-P3 or P3a (Friedman et al., 2001; Olofsson and Polich, 2007; Ranganath and Rainer, 2003), is composed of a fronto-central early phase peaking around 235 ms, referred as the early-P3 in the following, and a fronto-parietal late phase peaking around 320 ms referred as the late-P3 in the following (Escera et al., 2000, 2000; Escera and Corral, 2007; Yago et al., 2003). This dissociation has been recently confirmed using a Principal Component Analysis (PCA) compiling data from different oddball paradigms (Barry et al., 2016). The functions attributed to each phase are still under debate. Nevertheless, the P3a has been considered to reflect the attention processing of distracting stimuli (Polich and Criado, 2006) and has been frequently associated with impaired performances due to unexpected novel sounds (Berti and Schröger, 2003; Escera et al., 1998; Schröger and Wolff, 1998; Wetzel et al., 2006), leading to the assumption that this ERP would index distraction.

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However, in the last decades, a growing number of studies challenged the idea that unexpected rare novel sounds only yield distraction (for a review, see Parmentier, 2014). Indeed, a behavioral cost was not always observed after novels sounds (Li et al., 2013; Ljungberg et al., 2012; Parmentier et al., 2011, 2010; Wetzel et al., 2013, 2012). In some oddball paradigms, novel sounds could even enhance performances (SanMiguel et al., 2010b, 2010a; Wetzel et al., 2013, 2012). Several mechanisms can account for such facilitation effects in the oddball paradigms. Novel sounds could act as warning signals which trigger a top-down anticipation of the onset of the incoming target. They could also induce a phasic increase in unspecific arousal (SanMiguel et al., 2010b, 2010a; Wetzel et al., 2013, 2012), which results in enhanced readiness to process and respond to any upcoming stimulus. These findings led to propose that novel sounds generate a combination of facilitation and distraction effects which final effect on the performance of an unrelated task depends on the level of the task demands (SanMiguel et al., 2010a, see also Eysenck, 2012; Kahneman, 1973; Yerkes and Dodson, 1908 for the interaction of arousal with task demands) and the properties of the novel sounds (Parmentier et al., 2010; SanMiguel et al., 2010a; Wetzel et al., 2012). The "arousal hypothesis" is consistent with a model of the orienting response towards unexpected novel sounds which comprises an arousal component to account for behavioral benefits and an attentional component, a reflexive attentional switch to the eliciting stimulus, to explain behavioral costs (Näätänen, 1992). Nevertheless, only few studies have investigated the link between the behavioral benefit and the properties of the distracting sounds (Max et al., 2015; Wetzel et al., 2012). To our knowledge, the differential impact of arousal and emotional properties on the facilitation effect has not been explored. We define here arousal as a state of enhanced physiological reactivity that leads to a condition of unspecific sensory alertness and readiness to respond to any upcoming stimulus (Aston-Jones and Cohen, 2005; Coull, 1998; Näätänen, 1992; Nieuwenhuis et al., 2011; Sturm and Willmes, 2001), enabling improved performance, in this particular case target detection.

In the same line, the P3 complex has been observed in response to novel sounds resulting in facilitation effects (SanMiguel et al., 2010b; Wetzel et al., 2013), leading to alternative explanations of the cognitive functions underlined by this brain response. Wetzel and colleagues proposed that the P3 complex reflects novelty evaluation of the stimulus; whereas San Miguel and colleagues proposed that the P3 complex reflects the summation of different brain operations triggered by the novel event, such as arousing, orienting and executive control processes. Accordingly, if we consider the different P3a phases, the early-P3 has not been necessarily linked to distraction in the literature. In oddball paradigms, in contrast to the late-P3, the early-P3 amplitude remains unchanged when behavioral distraction increases (SanMiguel et al., 2008), leading the authors to propose that the early-P3 may reflect a process other than the involuntary orienting of attention. In a similar fashion, behavioral distraction by deviant sounds is not always associated with the elicitation of an early-P3 (Horváth et al., 2011). On the other hand, the late-P3 has been more consistently considered as a signature of involuntary attentional capture (Bidet-Caulet et al., 2015; Escera et al., 2000, 1998; Roye et al., 2007). This undermines the idea that the P3a indexes solely distraction. It is imaginable that other properties of novel or distracting sounds (such as their arousing value) are linked to the P3a and especially to its early phase, the early-P3.

The goal of this study is to characterize the facilitation effect triggered by unexpected salient stimuli at the behavioral and electrophysiological levels. The Bidet-Caulet et al. (2015) paradigm is particularly adapted to investigate the duality of effects by distracting sounds. In this task, unexpected task-irrelevant sounds, played between a visual cue and an auditory target in 25% of the trials (see Fig. 1a), resulted in two opposite effects, whose intensity was found to be dependent on the delay between the distractor and the target (see Fig. 2). Distracting sounds played long before the target induce a reduction of reaction times compared to a condition without distractor: this difference has been considered as a behavioral index of facilitation (Bidet-Caulet et al., 2015). Distracting sounds played just before the target induce an increase in reaction times compared to a condition with a distractor played earlier: this difference has been considered as a behavioral index of attentional capture (Bidet-Caulet et al., 2015). Moreover, this paradigm produces a robust sequence of event-related potentials including a biphasic P3a.

Two hypotheses can account for the facilitation effect observed using this paradigm. As mentioned above, distracting sounds could trigger an increase in unspecific arousal. Alternatively, the auditory distractors could result in an earlier attentional shift from the visual cue modality to the auditory target modality, facilitating the processing of the target. In a first behavioral experiment, we used adaptations of the paradigm to test these two propositions by changing the sensory modality of the cue or the target (see Fig. 1b and c). In a second behavioral experiment, we used another adaptation of the paradigm to characterize the durability of the facilitation effect by increasing the delay between the distractor and the target (see Fig. 1d). Finally, in an EEG experiment, we investigated the brain underpinnings of the facilitation effect by exploring the relationship between the arousing properties of distracting sounds and distractor-related ERPs.

2. First behavioral experiment

In a recent study, Bidet-Caulet and colleagues managed to temporally dissociate facilitation and distraction components elicited by unexpected task-irrelevant sounds (Bidet-Caulet et al., 2015). In this task, a visual cue indicated (or not) the side of an auditory target to detect. Between the cue and the target, a distracting sound was presented in 25% of the trials (Fig. 1a). Distracting sounds, played more than 500 ms before the target, induced a reduction in reaction times compared to a condition without distractor. Two hypotheses can account for this facilitation effect. (1) The facilitation effect is related to an unspecific burst of arousal triggered by the distracting sound because of its unexpectedness and its saliency. (2) Facilitation is due to the distracting sound inducing an earlier attentional shift from the cue modality (visual) to the target modality (auditory, same as the distractor).

In this first behavioral experiment, we created two adaptations of the Bidet-Caulet et al. (2015) paradigm to test these hypotheses (Fig. 1b and c). In a visuo-visual task, we used a visual target instead of an auditory target. In an audio-auditory task, we used an auditory cue instead of a visual cue. We hypothesized that (1) if the behavioral facilitation effect by distracting sounds is caused by an increase in phasic arousal, this effect should not be influenced by the sensory modality of the cue nor of the target. However, (2) if the behavioral facilitation effect stems from an earlier attentional shift towards the auditory modality following distracting sounds, it should be reduced with an auditory cue or a visual target.

2.1. Materials and methods

2.1.1. Participants

Fifteen paid participants (all right-handed, 9 females, mean age ± standard deviation (SD): 28.5 ± 8.9 years) took part to the first behavioral experiment. All participants were free from neurological or psychiatric disorder, and had normal hearing and normal or corrected-to-normal vision. All participants gave written informed consent.

2.1.2. Design of distracting sounds

Thirty ringing sounds (clock-alarm, door bell, phone ring, etc.) were used as distracting sounds in this study. These sounds were from several origins: Anne Guillaume's sound library (Guillaume et al., 2004); Michael Marcell's collection of environmental sounds (Marcell et al., 2000); audio CDs: sound library sonoteca, Mon imagier sonore (Olivier Tallec, Gallimard Jeunesse), Sound effects (DOM); and various websites: http://www.findsounds.com/, http://www.sound-effects-library.com/, and http://www.sounddogs.com/. When necessary, sounds were re-sampled

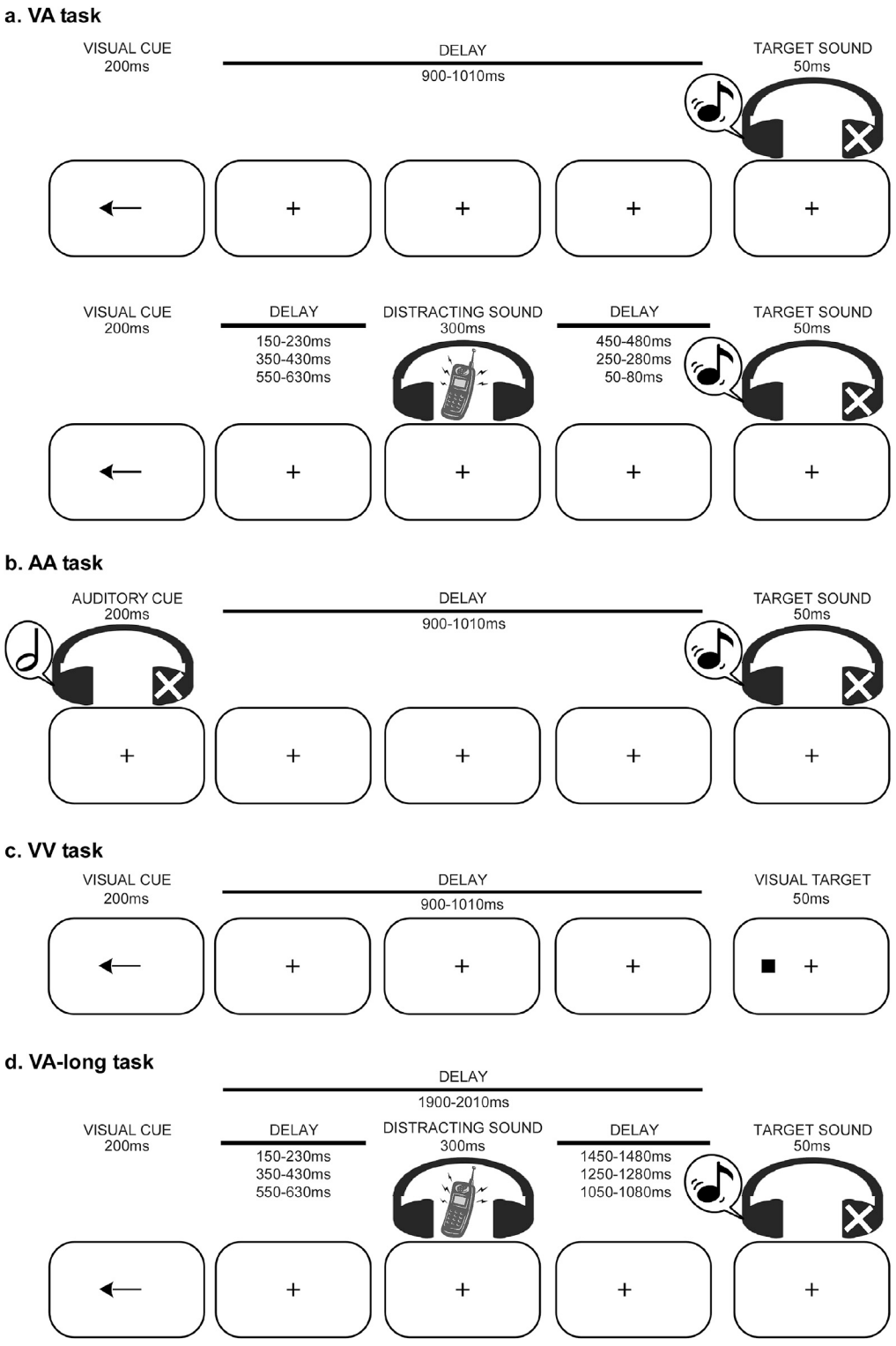

Fig. 1. Experimental paradigms. **a. VA task.** First row: Example of a distractor-free trial (75% of the trials). A visual cue (200 ms) precedes the onset of a monaural target sound (50 ms) by a random delay (900–1010 ms). In 66.6% of the trials, a one-sided cue indicates in which ear (left or right) the target sound will be played (informative trial). In the other 33.4% of the trials, a two-sided visual cue does not provide any indication in which ear (left or right) the target sound will be played (trial not depicted in the figure). Second row: Example of a trial with a distractor (25% of the trials). All parameters are identical to trials with no distracting sound, except that a binaural distracting sound (300 ms duration), such as a phone ring, is played during the delay between cue and target. The distracting sound can equiprobably onset in three different time periods after the cue offset: in the 150–230 ms range, in the 350–430 ms range, or in the 550–630 ms range. **b. AA task.** Example of a distractor-free trial. All parameters are identical to the VA task, except that the cue is a monaural (informative cue) or binaural (uninformative cue) 200 ms sound. **c. VV task.** Example of a distractor-free trial. All parameters are identical to the VA task, except that the target is a squared dot presented at the left or the right side of the screen. **d. VA-long task.** Example of a trial with a distractor. All parameters are identical to the VA task, except that the cue-target delay is comprised between 1900 and 2010 ms. VA: Visuo-auditory, AA: Audio-auditory, VV: Visuo-visual.

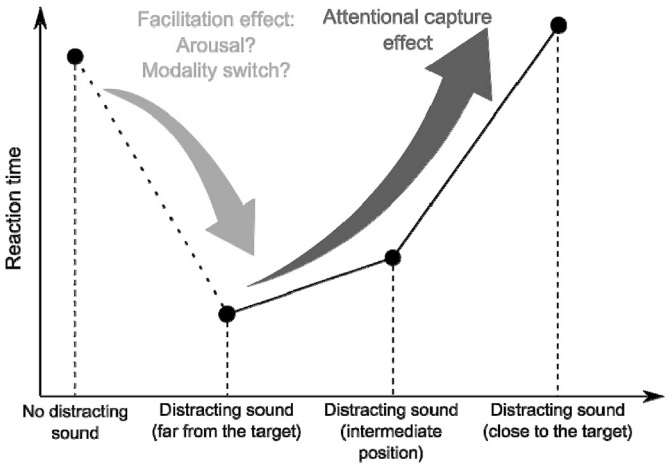

Fig. 2. Schematic representation of the effect of distracting sounds on reaction times in a target detection task according to Bidet-Caulet et al. (2015). In comparison with trials without distractor, when the distractor-target delay is large, the presence of a distracting sound results in shorter reaction times (facilitation effect). However, when the distractor-target delay is short, this enhancement of performances by the distracting sound is canceled out (attentional capture effect).

at 44 kHz on 16 bits and edited to last 300 ms (5 ms rise-time and 20 ms fall-time), with Adobe Audition software (Adobe). All sounds were then RMS normalized with MATLAB (Mathworks). Finally, loudness was subjectively equalized by two listeners. Sounds were delivered at an intensity level judged comfortable by the participants at the beginning of the experiment.

2.1.3. Stimuli and task

We manipulated the sensory modality of the cue and the target in three different cueing tasks (Fig. 1a,b,c). In the visuo-auditory task (VA, see Fig 1a), 75% of the trials (NoDIS trials) consisted in a visual cue (200 ms duration), a delay (randomly chosen between 900 and 1010 ms) followed by a target sound (50 ms duration). The cue was centrally presented on a screen (grey background) and could be a green arrow pointing to the left, to the right, or to both sides. The target sound was a monaural harmonic sound (fundamental frequency: 200 Hz, 5 harmonics; 5 ms rise-time, 5 ms fall-time) presented at 15 dB SL (mean ± SD: 52.2 ± 0.7 dBA) in earphones. In the other 25% (DIS trials), the same trial structure was used, but a binaural distracting sound at 35 dB SL (mean ± SD: 77.2 ± 0.7 dBA) was played during the delay. The cue and target categories were manipulated in same proportion for trials with and without distracting sound. In 33.3% of the trials, the cue was pointing left and the target sound was played in the left ear, and in 33.3% of the trials, the cue was pointing right and the target sound was played in the right ear, leading to a total of 66.6% of informative trials. In the last 33.4% of the trials, the cue was uninformative, pointing in both directions, and target sound was played in the left (16.7%) or right (16.7%) ear. The distracting sound could be equiprobably presented in three different time periods after the cue offset: in the 150–230 ms range (DIS1), in the 350–430 ms range (DIS2), or in the 550–630 ms range (DIS3).

Participants were instructed to perform a detection task by pressing a mouse button as fast as possible when they heard the target sound. They were asked to allocate their attention to the cued side in the case of informative cue. Participants were informed that informative cues were 100% predictive and that a distracting sound could be sometimes played. In the absence of the visual cue, a blue fixation cross was presented at the center of the screen. Participants were instructed to keep their eyes fixating on the cross and to minimize eye movements and blinks while performing the task.

Two other variants of the task were designed. The structure remained the same but the sensory modality of the cue or of the target was modified. In the audio-auditory task (AA, see Fig. 1b), the cue was a harmonic sound (200 ms duration, 25 dB SL (mean ± SD: 67.2 ± 0.7 dBA), fundamental frequency: 500 Hz, 5 harmonics; 5 ms rise-time, 5 ms fall-time) played at the left or at the right ear (informative trials) or in both ears (uninformative trials). In the visuo-visual task (VV, see Fig. 1c), the target was a gray squared dot presented at the left or at the right side of the screen (visual angle: 6°) displayed for 50 ms.

Effects of the informational value of the cue are beyond the scope of this article and will not be presented. For a discussion of top-down attention deployment during the VA task, see Bidet-Caulet et al. (2015).

2.1.4. Procedure

Participants were seated in a comfortable armchair in a sound attenuated room, at a 1.5 m distance from the screen. All stimuli were delivered using Presentation software (Neurobehavioral Systems, Albany, CA, USA). Sounds were delivered through earphones (SONY MDR-E819V). First, the auditory threshold was determined for the target sound, in each ear, for each participant using the Bekesy tracking method. This resulted in an average target threshold across subjects of 28.2 dBA (SD = 0.6). Second, participants were trained with a short sequence of the task for each task.

Participants performed 5 blocks (72 trials each) for each of the tasks. Participants were thus presented, in each task, with 270 NoDIS, 30 DIS1, 30 DIS2, 30 DIS3 trials, irrespective of the cue category. No EEG was recorded in this experiment. The order of the tasks was randomly chosen for each participant. Participants had 2500 ms to answer after targets.

2.1.5. Behavioral data

A button press before target onset was considered as a false alarm (FA). A trial with no button press after target onset and before the next cue onset was considered as a missed trial. A trial with no FA and with a button press after target onset was counted as a correct trial. Reaction-times (RTs) to targets were analyzed in the correct trials only. Based on previous results (Bidet-Caulet et al., 2015), the difference in RTs between the NoDIS and DIS1 conditions can be considered as a measure of the facilitation effect triggered by distracting sounds whereas the difference in RTs between the DIS3 and DIS1 conditions can be considered as a good approximation of the attentional capture effect.

2.1.6. Statistical analysis of behavioral data

Statistical analyses were conducted using the software JASP (Wagenmakers et al., 2018). RTs and percentages of correct trials were submitted to a Bayesian repeated-measure ANOVA with DISTRACTOR (four levels: NoDIS, DIS1, DIS2, DIS3) and MODALITY (three levels: AA, VA, VV) as within-participant factors. Post-hoc comparisons (based on the default t-test with a Cauchy prior) between levels of the MODALITY and of the DISTRACTOR factors were also conducted using the software JASP.

Effects of MODALITY on the facilitation effect ($RT_{NoDIS} - RT_{DIS1}$) and the attentional capture effect ($RT_{DIS3} - RT_{DIS1}$) were investigated as planned post-hoc analyses of the MODALITY by DISTRACTOR interaction, using Bayesian one-way ANOVA with MODALITY (three levels: AA, VA, VV) as the within-participant factor. Bayesian t-tests were also used to investigate the difference between the attentional capture effect and zero in each task.

We reported Bayes Factor (BF_{10}) as a relative measure of evidence. To interpret the strength of evidence **against the null model**, we considered a BF between 1 and 3 as weak evidence, a BF between 3 and 10 as positive evidence, a BF between 10 and 100 as strong evidence and a BF higher than 100 as a decisive evidence (Lee and Wagenmakers, 2014). Similarly, to interpret the strength of evidence **in favor of the null model**, we considered a BF between 0.33 and 1 as weak evidence, a BF between 0.1 and 0.33 as positive evidence, a BF between 0.01 and 0.1 as strong evidence and a BF lower than 0.01 as a decisive evidence. The

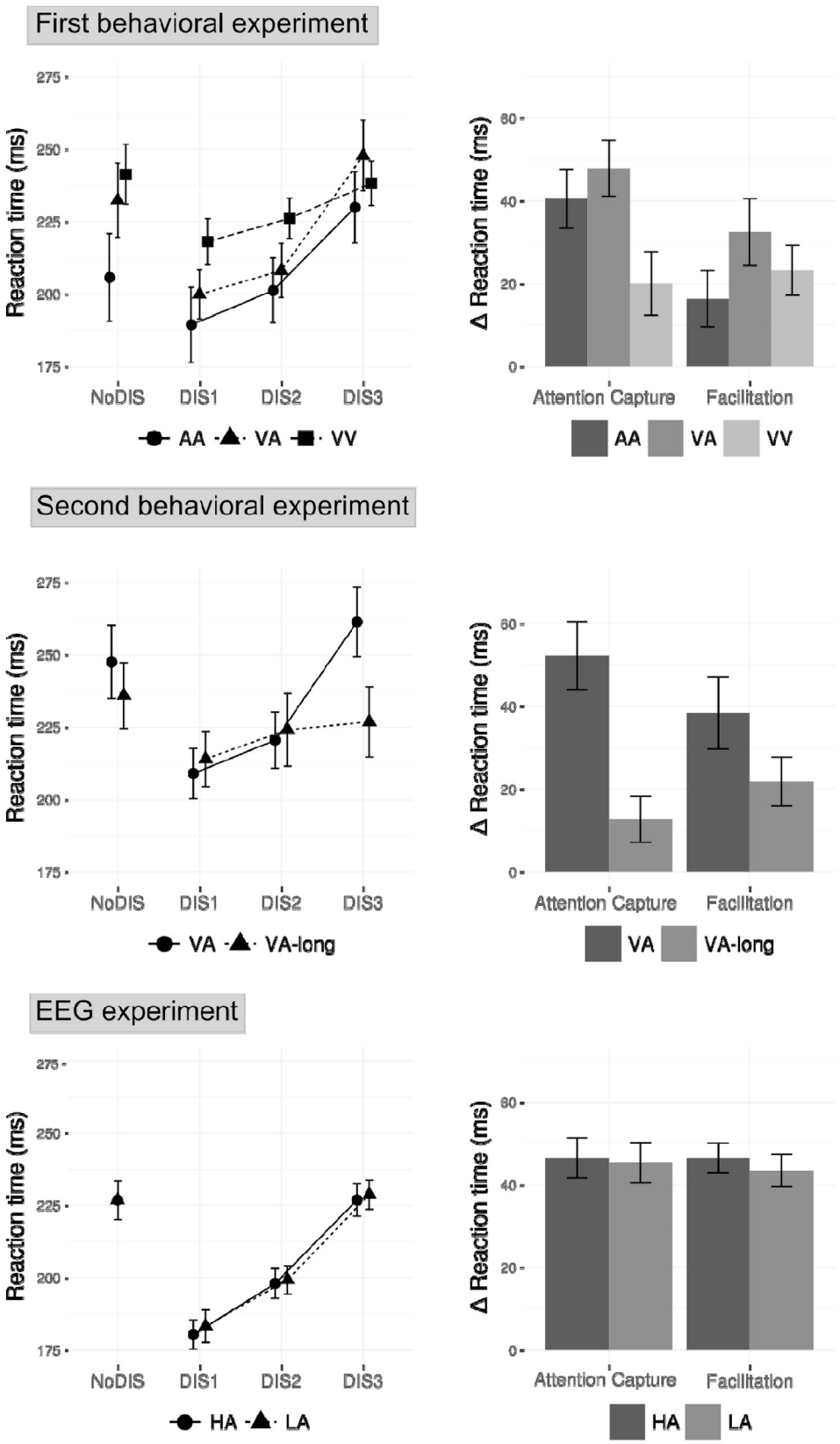

Fig. 3. Behavioral results for the three experiments. **Left.** Mean reaction time (RT) as a function of the distractor condition (NoDIS, DIS1, DIS2, DIS3). **Right.** Attentional capture (RT to DIS3 minus RT to DIS1) and facilitation (RT to NoDIS minus RT to DIS1) effects. Error bars represent ± 1 SEM. VA: Visuo-auditory, AA: Audio-auditory, VV: Visuo-visual, LA = low arousing sounds, HA = high arousing sounds.

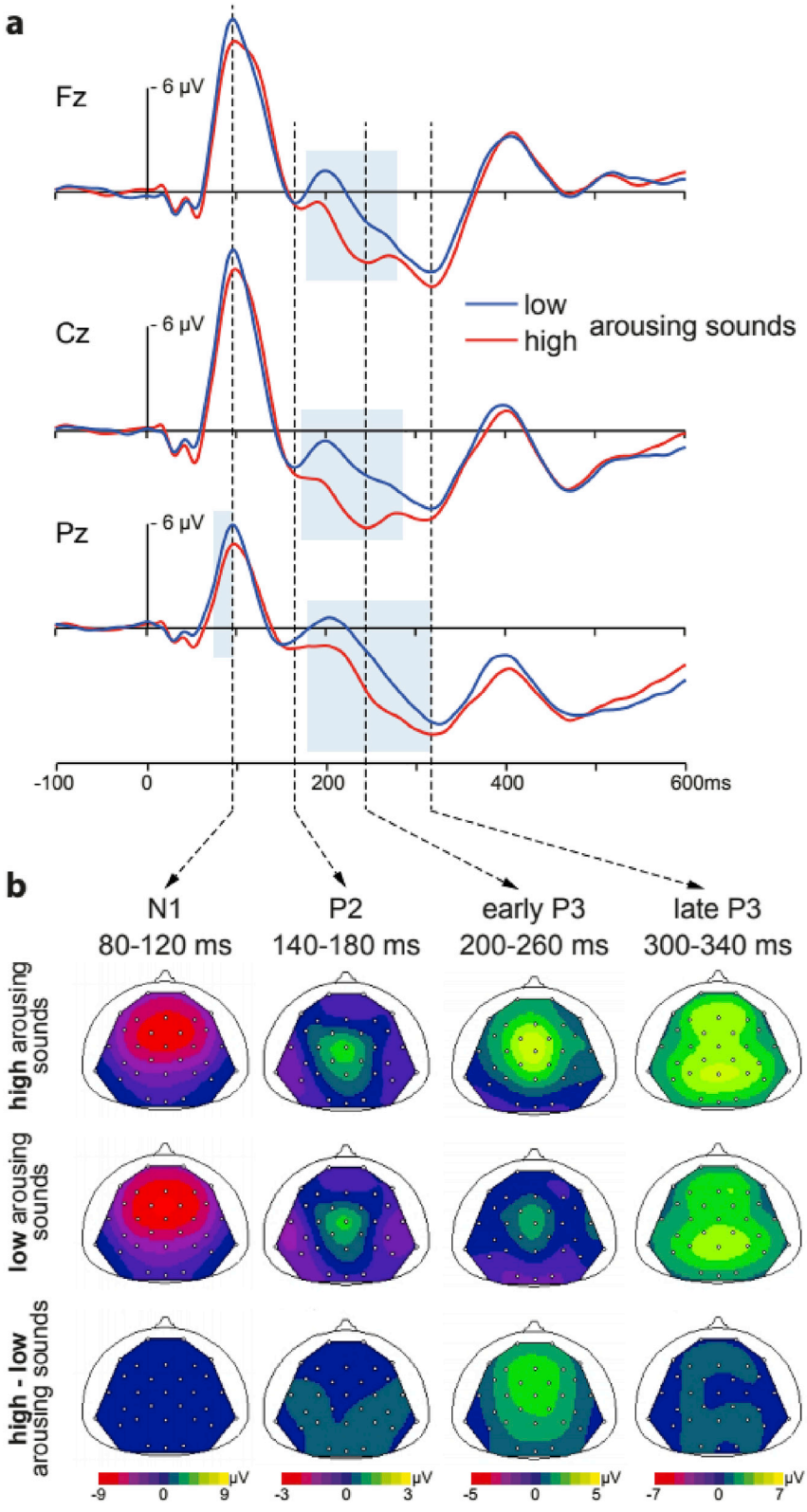

Fig. 4. ERPs to distracting sounds. **a.** Mean ERPs (after subtraction of surrogate ERPs in the NoDIS condition) at the Fz, Cz and Pz electrodes as a function of the arousal category (high-arousing or low-arousing). The blue square corresponds to latencies for which a significant effect of the arousal category is observed ($p < 0.05$). **b.** From left to right, scalp topographies (top views) of the N1, P2, early-P3 and late-P3, in the high and low arousing categories and their difference, in the 80–120, 140–180, 200–260 and 300–340 ms time-windows after distractor onset, respectively.

$BF_{inclusion}$ compares models that contain the effect to equivalent models stripped of the effect and was considered as a relative measure of evidence supporting the inclusion of a factor. Detailed output of the Bayesian ANOVA are reported in the Table 1. Unless stated otherwise, in the "Results'' section, mean values and standard errors of the mean are indicated.

2.2. Results

2.2.1. Percentage of correct responses (Table 1)

Participants correctly performed the detection task in 97.7% ± 1.1% of the trials. The remaining trials were either missed trials (0.1%) or trials with FAs (1.9% ± 0.3%).

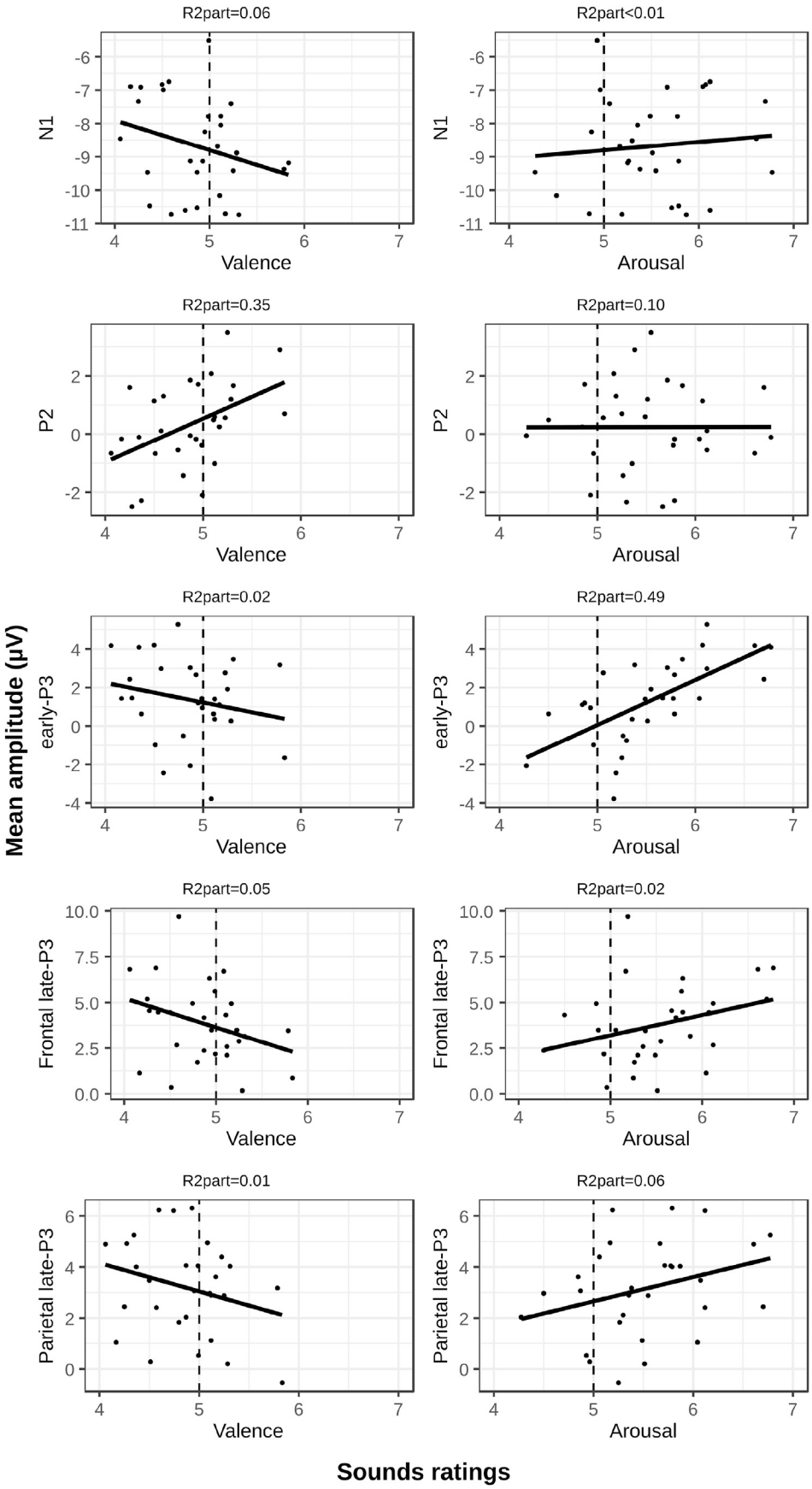

Fig. 5. Scatterplots of the mean amplitude of the N1, P2, early-P3 and late-P3 across subjects for each distracting sound as a function of the arousing ratings (left) or the valence ratings (right). Amplitudes were measured at the Cz electrode group for the N1, P2 and early-P3 and at the Fz and Pz electrodes for the late-P3. A dashed vertical bar separates sounds rated as negative (below 5 out of 10) and sounds rated as positive (above 5 out of 10). We report partial R-squared (calculated as described in paragraph 4.1.7).

Table 1
Results of Bayesian repeated-measure ANOVA on correct responses percentages, reaction times, facilitation effect and capture effect in the three experiments. The following outputs are specified: P(M) = prior model probability, P(M|data) = posterior model probability, BF_M = change from prior to posterior model, BF_{10} = Bayes Factor against the null model. The null model includes the subjects factor. For two-way Bayesian repeated-measure ANOVA, the following outputs are also specified: P(incl) = prior inclusion probability, P(incl|data) = posterior inclusion probability, $BF_{inclusion}$ = compares models that contain the effect to equivalent models stripped of the effect.

Experiment	Behavioral measure	Models	P(M)	P(M|data)	BF_M	BF_{10}	Effects	P(incl)	P(incl|data)	$BF_{inclusion}$
First experiment	Correct responses	Null model	0.20	0.11	0.48	1.00	MODALITY	0.40	0.16	0.21
		MODALITY	0.20	0.02	0.08	1.05	DIS	0.40	0.81	6.29
		DIS	0.20	0.67	8.00	6.10	MODALITY * DIS	0.20	0.06	0.44
		MODALITY + DIS	0.20	0.14	0.66	2.21				
		MODALITY + DIS + MODALITY * DIS	0.20	0.06	0.27	0.88				
	Reaction time	Null model	0.20	1.77E-16	7.08E-16	1.00	MODALITY	0.44	0.31	200057.16
		MODALITY	0.20	3.65E-13	1.46E-12	2062.80	DIS	0.40	0.31	8.38E+11
		DIS	0.20	1.53E-06	6.12E-06	8.65E+09	MODALITY * DIS	0.20	0.69	2.27
		MODALITY + DIS	0.20	0.31	1.76	1.73E+15				
		MODALITY + DIS + MODALITY * DIS	0.20	0.69	9.07	3.92E+15				
	Facilitation	Null model	0.50	0.38	0.62	1.00				
		MODALITY	0.50	0.62	1.62	1.62				
	Capture	Null model	0.50	0.05	0.05	1.00				
		MODALITY	0.50	0.95	19.71	19.71				
Second experiment	Correct responses	Null model	0.20	0.39	2.54	1.00	DELAY	0.40	0.43	0.72
		DELAY	0.20	0.28	1.53	0.71	DIS	0.40	0.31	0.47
		DIS	0.20	0.18	0.87	0.46	DELAY * DIS	0.20	0.02	0.18
		DELAY + DIS	0.20	0.13	0.61	0.34				
		DELAY + DIS + DELAY * DIS	0.20	0.02	0.10	0.06				
	Reaction times	Null model	0.20	1.66E-05	6.64E-05	1.00	DELAY	0.40	0.11	1.28
		DELAY	0.20	1.29E-05	5.14E-05	0.77	DIS	0.40	0.19	6379.94
		DIS	0.20	0.08	0.36	4965.79	DELAY * DIS	0.20	0.81	7.70
		DELAY + DIS	0.20	0.11	0.47	6356.66				
		DELAY + DIS + DELAY * DIS	0.20	0.81	17.29	48951.17				
EEG experiment	Correct responses	Null model	0.20	1.70E-17	6.82E-17	1.00	AROUSAL	0.40	0.11	0.13
		AROUSAL	0.20	2.10E-18	8.41E-18	0.12	DIS	0.40	0.96	4.99E+16
		DIS	0.20	0.86	23.70	5.02E+16	AROUSAL * DIS	0.20	0.04	0.36
		AROUSAL + DIS	0.20	0.11	0.47	6.22E+15				
		AROUSAL + DIS + AROUSAL * DIS	0.20	0.04	0.16	2.25E+15				
	Reaction times	Null model	0.20	1.35E-49	5.41E-49	1.00	AROUSAL	0.40	0.14	0.16
		AROUSAL	0.20	1.91E-50	7.63E-50	0.14	DIS	0.40	0.99	6.44E+48
		DIS	0.20	0.85	23.38	6.31E+48	AROUSAL * DIS	0.20	5.46E-03	0.04
		AROUSAL + DIS	0.20	0.14	0.65	1.04E+48				
		AROUSAL + DIS + AROUSAL * DIS	0.20	0.01	0.02	4.03E+46				

For the percentage of correct trials, the only model showing some evidence only included the effect of DISTRACTOR ($BF_{10} = 6.1$). There was positive evidence against a specific effect of MODALITY ($BF_{inclusion} = 0.2$) and there was positive evidence of a specific effect of DISTRACTOR ($BF_{inclusion} = 6.3$) on the percentage of correct trials. Post-hoc comparisons showed that participants had a slightly lower percentage of correct responses in the DIS1 condition (95.3% ± 1.5%) compared to the NoDIS condition (98.1% ± 0.4%) ($BF_{10} = 17.3$).

2.2.2. Reaction times (Fig. 3, Table 1)

The best model was the one with both main effects of DISTRACTOR and MODALITY and their interaction ($BF_{10} = 3.9 \cdot 10^{15}$), but it was only 2.3 times more likely than the model with only the two main effects of DISTRACTOR and MODALITY ($BF_{10} = 1.7 \cdot 10^{15}$). There was decisive evidence for specific effects of DISTRACTOR ($BF_{inclusion} = 8.4 \cdot 10^{11}$) and MODALITY ($BF_{inclusion} = 2.0 \cdot 10^{5}$), there was only weak evidence for a specific effect of the DISTRACTOR by MODALITY interaction ($BF_{inclusion} = 2.3$).

Post-hoc analysis of the MODALITY main effect showed that participants were faster in the AA task than in the VA (BF_{10}(AA vs. VA) = 1381.8) and VV (BF_{10}(AA vs. VV) = 21834.9) tasks.

Post-hoc analysis of the DISTRACTOR main effect showed that participants were faster in the DIS1 condition than in the NoDIS ($BF_{10} = 1.7 \cdot 10^{5}$) and DIS3 ($BF_{10} = 2.7 \cdot 10^{8}$) conditions, confirming the significance of a facilitation effect and an attentional capture effect. On average, between NoDIS and DIS1, RTs dropped by 9.5% ± 2.7%.

Planned post-hoc analyses of the DISTRACTOR by MODALITY interaction were performed to test the effect of MODALITY on the facilitation and attentional capture effects. Almost no evidence of an effect of MODALITY on facilitation ($BF_{10} = 1.6$) was found. A strong evidence of an effect of MODALITY on attentional capture ($BF_{10} = 19.7$) was found, with post-hoc comparisons showing strong evidence of a reduced attentional capture in the VV task compared to the VA task ($BF_{10} = 11.3$). No evidence of difference in attentional capture between VA and AA ($BF_{10} = 0.8$) was found. However, there were positive to decisive evidence of an attentional capture effect in all the tasks (Bayesian t-tests comparing the effect to zero: BF_{10}(AA) = 1270.6, BF_{10}(VA) = 9130.6, BF_{10}(VV) = 3.8).

2.3. Discussion

This first experiment confirms that distracting sounds can result in a facilitation effect at the behavioral level, and shows that this benefit is independent of the cue and target sensory modalities.

2.3.1. Facilitation and attentional capture effects of distracting sounds

With the present protocol, it has been possible to temporally dissociate facilitation and attentional capture effects of the same distracting sounds within the same task. Distracting sounds elicit a facilitation effect that improves performances especially with long distractor-target intervals (i.e. DIS1 and DIS2 conditions). However, the gain in RT is canceled out when the distractor onset is too close to the target sound (DIS3 condition), suggesting that distractors also trigger an attentional capture. This timing effect indicates that when the target occurs, the balance between cost and benefit differs according to the onset time of the distracting sound, suggesting that the facilitation and attentional capture effects triggered by the distracting sounds have different time courses. The facilitation effect would be stable for at least 750 ms (longest interval between distracting and target sound onsets) and induce a similar benefit on target processing irrespective of the distractor onset time. On the contrary, the attentional capture would be a transient powerful phenomenon that could interfere with target processing only when the distracting sound occurs within a few hundreds of ms before target onset, and that would be low or completed when the distractor is played long before target onset. A short duration of the attentional capture phenomenon is consistent with previous findings showing a detrimental effect of task-irrelevant deviant sound on target processing with onset-to-onset interval of 200 ms but not of 550 ms (Schröger, 1996). According to our results, the facilitation effect of novel sounds is less likely to be observed, at the behavioral level, in classical oddball studies because the typical sound-target delay is 300 ms, thus the attentional capture effect has not yet vanished and masks any potential facilitation effect.

These present results confirm that an unexpected salient sound triggers several phenomena that may produce opposite effects on the reaction time to a subsequent target: a cost related to a short-lasting attentional capture and the benefits of a more long-lasting facilitation effect. This duality in effects was previously observed in several recent studies (Ljungberg et al., 2012; Max et al., 2015; Parmentier et al., 2010; SanMiguel et al., 2010b, 2010a; Wetzel et al., 2013, 2012).

2.3.2. Nature of the facilitation effect

With this first experiment, we attempted to precise the nature of the facilitation effect. In the visuo-auditory task, two hypotheses may account for the gain in RT in distractor trials. (1) The facilitation effect is related to an unspecific burst of arousal triggered by the distracting sound because of its unexpectedness and its saliency and because of the low arousal level of the task, as proposed in previous studies (Bidet-Caulet et al., 2015; SanMiguel et al., 2010b, 2010a; Wetzel et al., 2013, 2012). (2) Facilitation is due to the facilitation by the distracting sound of the attentional shift from the cue modality (visual) to the target modality (auditory, same as the distractor). A distracting sound placed between a visual cue and an auditory target could result in an earlier attentional shift leading to better performances compared to a no distracting sound condition. According to this second hypothesis, we should expect a smaller behavioral benefit if the cue and the target are in the same sensory modality. We tested this hypothesis in a visuo-visual and an audio-auditory cueing tasks and found no clear evidence of a reduction of the facilitation effect triggered by distracting sounds, in comparison to the visuo-auditory task. This is in line with previous results that showed that auditory warning signals can trigger facilitation in both visual and auditory detection tasks (Posner et al., 1976). Therefore, the attentional reorientation towards the target modality cannot account for the facilitation effect of the distracting sound. Moreover, similar facilitation effects of the distracting sounds were found regardless of the target sensory modality, suggesting that the facilitation effect is independent of the sensory modality. These results rather support the first hypothesis that facilitation effect stems from a distractor-related burst of arousal.

Outside of the literature on the oddball paradigm, it has also been known for decades that auditory warning signals, also referred to as "accessory stimuli", played before or concurrent to the onset of the target visual stimulus facilitate the processing of such target stimulus (Hackley and Valle-Inclán, 1999, 1998; Posner et al., 1976; Valls-Solé et al., 1995). Interestingly, it has also been proposed that the speeding of reaction times by warning signals/accessory stimuli stems from an increase in phasic arousal (Hackley, 2009; Tona et al., 2016).

In conclusion and in agreement with previous studies (SanMiguel et al., 2010b; Wetzel et al., 2013), we show that performances after a distracting sound result from the combination of the benefits due to an increase in unspecific arousal and to the costs of attentional capture.

2.3.3. Effects of cue and target sensory modality on reaction times and attentional capture effects

On the one hand, subjects were faster in the audio-auditory task than in the visuo-auditory one. It could be easily explained by the fact that auditory cues are more arousing than the visual ones inducing a general gain in reactivity. On the other hand, subjects were slower overall in the visuo-visual task simply because the task was probably more difficult.

There was positive to decisive evidence of an attentional capture effect regardless of the sensory modality of the cue and target. This result does not support the hypothesis that, in cross-modal tasks, distraction stems from the time penalty caused by shifting attention from one

modality to the other (Parmentier, 2014; Parmentier et al., 2008). The attentional capture effect would be rather due to an involuntary capture of attention by the distracting event, diverting attention from the task at hand (Escera et al., 2000; Horváth et al., 2008; Näätänen, 1992).

We also found that the attentional capture effect is weaker in the visuo-visual task, but comparable in the visuo-auditory and audio-auditory tasks. In the visuo-visual task, the auditory modality is not relevant for the task: as a result, subjects may be more efficient at inhibiting sounds, and less sensitive to attentional capture by distracting sounds.

3. Second behavioral experiment

The aim of this second behavioral experiment is to test the endurance of the facilitation effect: a reduction or even an extinction of the facilitation effect could be expected with time. We created an adaptation of Bidet-Caulet et al. (2015) paradigm with twice longer cue-target intervals (in order to increase the delay between the distracting sound and the target by 1 s, see Fig. 1d).

3.1. Material and methods

3.1.1. Participants

Twelve paid participants (all right-handed, 4 females, mean age ± SD: 26 ± 5.4 years) took part to the second behavioral experiment. Six participants participated to both behavioral experiments.

All participants were free from neurological or psychiatric disorder, and had normal hearing and normal or corrected-to-normal vision. All participants gave written informed consent.

3.1.2. Stimuli and task

Participants performed the VA task and a variant of this task (VA-long, see Fig. 1d). The order of the tasks was randomized between subjects. The task structure remained the same however in the VA-long task, the cue-target delay was increased by 1000 ms (between 1900 and 2010 ms). Cue-distractor delays were unchanged: therefore, the distractor-target interval was increased by 1000 ms. The experimental procedure was identical than during the first experiment. The auditory threshold was determined for the target sound, in each ear, for each participant using the Bekesy tracking method. This resulted in an average target threshold of 28.2 dBA (SD = 0.7), in an average distractor loudness of 77.2 dBA (SD = 0.7) and in an average target loudness of 52.2 dBA (SD = 0.7).

3.1.3. Statistical analysis of behavioral data

RTs and percentages of correct trials were submitted to a Bayesian repeated-measure ANOVA with DISTRACTOR (four levels: NoDIS, DIS1, DIS2, DIS3) and DELAY (two levels: VA, VA-long) as within-participant factors. Post-hoc comparisons (based on the default t-test with a Cauchy prior) between levels of the DELAY factor were also conducted using the software JASP.

Effects of DELAY on the facilitation effect ($RT_{NoDIS} - RT_{DIS1}$) and the attentional capture effect ($RT_{DIS3} - RT_{DIS1}$) were investigated as planned post-hoc analyses of the DELAY by DISTRACTOR interaction, using Bayesian t-tests. Bayesian t-tests were also used to investigate the difference between the attentional capture effect and zero in each task. Detailed output of the Bayesian ANOVA are reported in the Table 1. Unless stated otherwise, in the "Results'' section, mean values and standard errors of the mean are indicated.

3.2. Results

3.2.1. Percentage of correct responses (Table 1)

Participants correctly performed the detection task in 98.3% ± 0.4% of the trials. The remaining trials were either missed trials (0.1%) or trials with FAs (1.6% ± 0.4%). No model showed any evidence of an effect on the percentage of correct trials (all $BF_{10} < 1$).

3.2.2. Reaction times (Fig. 3, Table 1)

The best model was the one with both main effects of DISTRACTOR and DELAY and their interaction ($BF_{10} = 48951.2$). There was a decisive specific effect of DISTRACTOR ($BF_{inclusion} = 6379.9$) and a positive specific effect of the DISTRACTOR by DELAY interaction ($BF_{inclusion} = 7.7$). However, there was no evidence for a specific effect of DELAY ($BF_{inclusion} = 1.3$).

Post-hoc analysis of the DELAY main effect did not show any evidence for a difference in RTs between the VA and VA-long task ($BF_{10} = 0.7$).

Planned post-hoc analyses of the DISTRACTOR by DELAY interaction were performed to test the effect of DELAY on the facilitation and attentional capture effects. We observed only weak evidence of an effect of DELAY on facilitation ($BF_{10} = 2.0$) but we observed strong evidence of an effect of DELAY on attentional capture ($BF_{10} = 17.1$). Attentional capture was lower in the VA-long task (13.6 ± 5.9 ms) compared to the VA task (50.0 ± 7.4 ms). There was not much evidence that attentional capture is different from zero in the VA-long task (Bayesian t-test: $BF_{10} = 1.9$), whereas there was decisive evidence that the effect is different from zero in the VA task (Bayesian t-test: $BF_{10} = 505.6$).

3.3. Discussion

In this second experiment, we wanted to characterize the durability of the facilitation effect triggered by distracting sounds. In the longer version of the experiment (VA-long), participants still responded faster to targets preceded by a distracting sound despite a distractor-target delay reaching up to 1750 ms. Even if a trend could be observed in the data, there is no positive evidence that the facilitation effect decreased with a longer delay. This increase in phasic arousal seems to remain sustained at a steady level for at least a couple of seconds. A facilitation effect of salient task-irrelevant sounds has already been observed for sound-target delay superior to 1000 ms (as well as for very short delays under 100 ms) in several studies (e.g. Posner et al., 1976; Ulrich, 1996). In a paradigm using auditory targets preceded by standard or novel pictures, novel pictures were found to reduce reaction times but only for picture-target delay of 0 and 200 ms and not for 800 ms (Schomaker and Meeter, 2014). This could be explained by the fact that the novel stimuli in the visual modality are less arousing than those in the auditory modality. Visual accessory stimuli trigger less facilitation than auditory accessory stimuli in both visual and auditory detection tasks (Posner et al., 1976).

These results also confirm that attentional capture is a transient phenomenon: when the distractor-target delay is superior to 1000 ms, no clear evidence could be found of a difference in reaction times between trials including early distractors and trials including late distractors. As discussed previously, this is consistent with results using the auditory oddball paradigm: a behavioral effect of attentional capture by deviant sounds can only be observed for short delays between the deviant and the target sound (200 ms) but not for longer delays (550 ms) (Schröger, 1996).

4. EEG experiment

In this EEG experiment, we investigated the influence of the arousing content of the distracting sounds on their respective event-related potentials during the Bidet-Caulet et al. original task (Fig. 1a). We hypothesize that the increase of phasic arousal following distracting sounds is reflected at some point in the cortical processing of the sound. In that case, we expected that there is at least one event-related response whose amplitude would be modulated by the perceived "arousingness" of the sound. In this purpose, distracting sounds were rated according to their arousing content and ERPs to high and low arousing sounds were compared. To dissociate the effect of "arousingness" from the impact of emotional valence, multiple regression were performed on ERPs with arousal and valence as regressors.

4.1. Materials and methods

4.1.1. Participants

Forty-one paid participants took part to the EEG experiment. Two of them were excluded from further analyses because of noisy EEG data, one because of low behavioral performances and one because of an issue with the experimental setup during the study. Consequently, only thirty-seven participants (21 females, all right-handed, mean age ± SD: 22.5 ± 2.7 years) were included in further analyses. Data from 17 out of the 37 included participants have been presented in a previous publication (Bidet-Caulet et al., 2015).

No participant participated in both EEG and behavioral experiments. All participants were free from neurological or psychiatric disorder, and had normal hearing and normal or corrected-to-normal vision. All participants gave written informed consent.

4.1.2. Stimuli, task and procedure

The task was identical to the VA task (Fig. 1a) in behavioral experiments and to the experiment in Bidet-Caulet et al. (2015). EEG was recorded while participants performed 15 blocks (72 trials each) of the VA task. Participants were thus presented, with 810 NoDIS and 270 DIS trials. The experimental procedure was identical than during the previous experiments. The auditory threshold was determined for the target sound, in each ear, for each participant using the Bekesy tracking method. This resulted in an average target threshold of 28.9 dBA (SD = 2.2), in an average distractor loudness of 77.9 dBA (SD = 2.2) and in an average target loudness of 47.9 dBA (SD = 2.2).

4.1.3. Behavioral ratings of distracting sounds

The same set of distracting sounds used in the behavioral experiments were used in the EEG experiment. Forty-one participants were asked to rate each sound for arousal (calm – exciting) and for valence (unhappy – happy) on a 9-point scale with the Self-Assessment Manikins (Bradley and Lang, 1994). Twenty of these participants were from the cohort of the EEG experiment and the twenty-one additional ones were only recruited for the sound rating. The thirty distracting sounds were presented in a different random order to each participant. After each sound, participants were successively presented with the arousal and the emotion scales. They had 5s to indicate their rating value by pressing the corresponding key on a keyboard for each scale.

High-arousing (HA) distracting sounds will comprise those rated above the median rating of all sounds, low-arousing (LA) distracting sounds will comprise those rated beneath the median rating of all sounds. Acoustic parameters (mean brightness, mean roughness, mean pitch and attack leap) were analyzed using the MATLAB MIRtoolbox 1.3.4 (Lartillot et al., 2008).

4.1.4. Statistical analysis of behavioral data

RTs and percentages of correct trials were submitted to a Bayesian repeated-measure ANOVA with DISTRACTOR (four levels: NoDIS, DIS1, DIS2, DIS3) and AROUSAL (two levels: HA, LA) as within-participant factors. Post-hoc comparisons (based on the default t-test with a Cauchy prior) between levels of the DISTRACTOR factor were also conducted using the software JASP. Detailed output of the Bayesian ANOVA are reported in the Table 1. Unless stated otherwise, in the "Results'' section, mean values and standard errors of the mean are indicated.

4.1.5. EEG recording

EEG was recorded from 32 active Ag/AgCl scalp electrodes mounted in an electrode-cap (actiCap, Brain Products, Gilching, Germany) following a sub-set of the extended International 10–10 System. Four additional electrodes were used for horizontal (external canthi locations) and vertical (left supraorbital and infraorbital ridge locations) EOG recording and two other electrodes were placed on earlobes. The reference electrode was placed on the tip of the nose and the ground electrode on the forehead. Data were amplified, filtered and sampled at 1000 Hz (BrainAmp, Brain Products, Gilching, Germany). Data were re-referenced offline to the average potential of the two earlobe electrodes.

4.1.6. EEG data analysis

EEG data were band-pass filtered (0.5–40 Hz). Prior to ERP analysis, eye-related activities were detected using independent component analysis (ICA) and were selectively removed via the inverse ICA transformation. Only 1 or 2 ICs were removed in each participant. Trials including false alarms or undetected target, and trials contaminated with excessive muscular activity were excluded from further analysis. For the purpose of the present study, only trials with distracting sounds were considered (see Bidet-Caulet et al., 2015 for analysis of the other trials). On average across participants, the number of considered trials for analysis was 119 ± 12 trials (mean ± SD) with HA and 119 ± 11 trials with LA distracting sounds.

ERPs were averaged locked to distractor onset and were baseline corrected to the mean amplitude of the −100 to 0 ms period before distractor onset. To analyze ERPs to distracting sound, for each distractor onset time-range, surrogate ERPs were created in the NoDIS trials and subtracted from the actual ERPs. The obtained ERPs were thus clear of cue-related activity.

ERP scalp topographies were computed using spherical spline interpolation (Perrin et al., 1989). ERPs were analyzed using the software package for electrophysiological analysis (ELAN Pack) developed at the Lyon Neuroscience Research Center (elan.lyon@inserm.fr; Aguera et al., 2011).

4.1.7. Statistical analysis of ERP data

Statistical analyses were performed on a frontal (Fz), a central (Cz) and a parietal (Pz) electrode from the distractor onset to 350 ms after onset as previously done in Bidet-Caulet et al. (2015). Later responses were not investigated because the shortest duration between the distracting sound and the following target sound onset was 350 ms.

To explore the effect of the arousing content on the ERPs to distracting sound (HA vs. LA), permutation tests based on randomization (Edgington, 2014) were used. Each randomization consisted in (1) the random permutation of the values of the 37 pairs of conditions (corresponding to the 37 participants), (2) the calculation of the sum of squared sums of values in each condition, (equivalent to the test statistic F in designs with paired conditions with equal sample size, for a demonstration see Edgington, 2014), and (3) the computation of the difference between these two statistic values. We performed 1000 such randomizations to obtain an estimate of the distribution of this difference under the null hypothesis. The analysis was performed from 0 ms to 350 ms after distractor onset, over 10 ms windows moving by step of 5 ms. To correct for multiple tests in the time dimension, a Bonferroni correction would have been over-conservative because it assumes that the data for each test are independent and does not take into account the temporal correlation of EEG data (Manly et al., 1986). To increase sensitivity while taking into account multiple testing in the time dimension, we used a randomization procedure proposed by Blair and Karniski (1993). For each permutation of the dataset, the maximum number of consecutive significant time-samples in the entire 0–350 ms time-window was computed. Over all the permutations, we thus obtained the distribution of this maximum number under the null-hypothesis. In this distribution, the 95th percentile corresponds to the maximum number of consecutive significant samples one can obtain by chance with a risk of 5%. We required all the effects to last at least this number of samples. This procedure was run separately for each channel. As the three electrodes were tested independently, a Bonferroni correction was applied on computed p-values to correct for family-wise errors (Weisstein, 2004).

Correlations across distracting sounds between ratings for arousal and valence and the median across participants of the mean amplitude of each of the ERPs mentioned below were conducted using Bayesian multiple linear regression. In our linear models, despite a correlation between arousal and valence ratings, the collinearity is not excessive

Table 2
Results of Bayesian multiple linear regression on the amplitude of the N1, P2, early-P3 and late-P3 (frontal and parietal components) across the distracting sounds. The predictive variables were the arousal ratings and the valence ratings of the distracting sounds. The following outputs are specified: P(M) = prior model probability, P(M|data) = posterior model probability, BF_M = change from prior to posterior model, BF_{10} = Bayes Factor against the null model. The null model includes the subjects factor. For two-way Bayesian repeated-measure ANOVA, the following outputs are also specified: P(incl) = prior inclusion probability, P(incl|data) = posterior inclusion probability, $BF_{inclusion}$ = change from prior to posterior inclusion probability.

Event-related response	Models	P(M)	P(M|data)	BF_M	BF_{10}	Effects	P(incl)	P(incl|data)	$BF_{inclusion}$
N1	Null model	0.25	0.40	2.03	1.00	Arousal	0.50	0.29	0.41
	Arousal	0.25	0.16	0.55	0.39	Valence	0.50	0.44	0.79
	Valence	0.25	0.30	1.31	0.75				
	Arousal + Valence	0.25	0.14	0.47	0.34				
P2	Null model	0.25	0.04	0.11	1.00	Arousal	0.50	0.52	1.10
	Arousal	0.25	0.51	3.14	0.34	Valence	0.50	0.95	19.46
	Valence	0.25	0.44	2.36	12.09				
	Arousal + Valence	0.25	0.01	0.04	14.06				
Early-P3	Null model	0.25	4.95E-04	1.48E-03	1.00	Arousal	0.50	0.99	1203.67
	Arousal	0.25	0.77	10.11	1558.71	Valence	0.50	0.26	0.30
	Valence	0.25	3.35E-04	1.01E-03	0.06				
	Arousal + Valence	0.25	0.23	0.89	460.87				
Frontal late-P3	Null model	0.25	0.31	1.32	1.00	Arousal	0.50	0.48	0.91
	Arousal	0.25	0.31	1.38	1.03	Valence	0.50	0.38	0.61
	Valence	0.25	0.22	0.84	0.71				
	Arousal + Valence	0.25	0.16	0.58	0.53				
Parietal late-P3	Null model	0.25	0.32	1.43	1.00	Arousal	0.50	0.50	0.98
	Arousal	0.25	0.34	1.54	1.05	Valence	0.50	0.34	0.51
	Valence	0.25	0.18	0.67	0.57				
	Arousal + Valence	0.25	0.16	0.55	0.48				

with a Variance Inflation Factor (VIF) equal to 1.29, under the commonly accepted cutoff value of 5 or 10 (O'brien, 2007). Therefore, multiple linear regression with ratings for arousal and valence as regressors could be conducted. Tests were applied to each transient ERP at the electrode of their maximum: the N1 mean amplitude in the 80–120 ms window at Cz electrode, the P2 mean amplitude in the 140–180 ms window at Cz electrode, the early-P3 mean amplitude in the 200–260 ms window at Cz electrode, and the late-P3 mean amplitude in the 300–340 ms window at Fz and Pz electrodes. We report the Bayesian Factor (BF), the multiple R-squared for the results of the multiple linear regression and the partial R-squared for arousal and valence ratings, separately. Detailed output of the Bayesian regressions are reported in the Table 2.

4.2. Results

4.2.1. Properties of distracting sounds

The median arousal rating of all distracting sounds was 5.5.15 high-arousing (HA) sounds (Mean ± SD = 6.0 ± 0.4) were found significantly more arousing than the 15 low-arousing (LA) sounds (Mean ± SD = 5.1 ± 0.3) (Mann-Whitney *U* test: $p < 0.001$). We found a trend for a significant difference in valence ratings of HA and LA (HA: 4.7 ± 0.4, LA: 5.0 ± 0.5, Mann-Whitney *U* test: $p = 0.056$). Ratings for arousal and valence were negatively (slope = −0.60) and significantly correlated (linear regression: $F_{1,28} = 7.8$, $p = 0.009$, $R^2 = 0.21$): negative sounds tended to be rated more arousing than neutral and positive sounds. Overall, sounds were rather neutral in valence (min = 4.0, max = 5.8, median = 4.9).

No significant difference in mean pitch, mean roughness, mean brightness and attack leap was found between HA and LA sounds (Mann-Whitney *U* test: all p-values > 0.35).

4.2.2. Percentage of correct responses (Table 1)

Participants correctly performed the detection task in 93.1% ± 0.9% of the trials. The remaining trials were either missed trials (1.5%) or trials with FAs (5.4% ± 0.9%).

The best model was the one with only the main effect of DISTRACTOR ($BF_{10} = 5.0{\cdot}10^{16}$). There was positive evidence against a specific effect of AROUSAL ($BF_{inclusion} = 0.1$) on RTs. There was no evidence in favor of the DISTRACTOR by AROUSAL interaction ($BF_{inclusion} = 0.4$), but there was decisive evidence of a specific effect of DISTRACTOR ($BF_{inclusion} = 5.0{\cdot}10^{16}$). Participants were less accurate in trials including distracting sounds (90.0 ± 1.4%) than in trials with no distracting sounds (95.6 ± 0.8%).

4.2.3. Reaction times (Fig. 3, Table 1)

The best model was the one with only the main effect of DISTRACTOR ($BF_{10} = 6.3{\cdot}10^{48}$). There was positive evidence against a specific effect of AROUSAL on RTs ($BF_{inclusion} = 0.2$) and a decisive specific effect of DISTRACTOR on RTs ($BF_{inclusion} = 6.4{\cdot}10^{48}$).

Post-hoc analysis of the DISTRACTOR main effect showed that participants were faster in the DIS1 condition than in the NoDIS condition ($BF_{10} = 5.9{\cdot}10^{23}$) and than in the DIS3 condition ($BF_{10} = 1.6{\cdot}10^{18}$).

4.2.4. EEG response to distracting sounds (Fig. 4)

In response to distracting sounds, the fronto-central N1 response (~100 ms) was followed by a small fronto-central P2 response (~160 ms), and a P3 complex that could be dissociated in two parts: an early-P3 (~240 ms) with a fronto-central distribution, and a late-P3 (~320 ms) with frontal and parietal components.

At the frontal electrode, the amplitude of the ERPs was significantly more positive for HA distractors from 180 ms to 280 ms (p-values ranging from <0.001 to 0.027), with the maximal difference at 221 ms. At the central electrode, the amplitude of the ERPs was significantly more positive for HA distractors from 175 ms to 290 ms (p-values ranging from <0.001 to 0.045), with the maximal difference at 223 ms. At the parietal electrode, the amplitude of the ERPs was significantly more positive for HA distractors from 80 ms to 100 ms (p-values ranging from <0.001 to 0.045) and from 180 ms to 300 ms (p-values ranging from <0.001 to 0.039), with the maximal difference at 253 ms. Please note that the amplitude of the ERPs at the parietal electrode were significant between 300 and 335 ms before Bonferroni correction but failed to reach significance after correction.

4.2.5. Relationships between EEG responses to distracting sounds and sound ratings (Fig. 5, Table 2)

There was no evidence of an effect of arousal ratings ($BF_{10} = 0.4$), nor valence ratings ($BF_{10} = 0.8$) on the amplitude of the N1 ($R^2 = 0.05$).

The best model of the P2 amplitude was the one including both effects of arousal and valence ratings ($BF_{10} = 14.1$) but it was only 1.2 times better than the model including only the effect of valence ratings ($BF_{10} = 12.1$). There was strong evidence of the specific effect of valence ratings ($BF_{inclusion} = 19.5$), but no evidence of a specific effect of arousal ratings ($BF_{inclusion} = 1.1$). The more positive the valence, the larger the P2 ($R^2_{valence} = 0.35$).

The best model of the early-P3 amplitude was the one only including the effect of arousal ratings ($BF_{10} = 1558.7$). It was only 3.4 times better than the model including both arousal and valence rating effects ($BF_{10} = 460.9$). There was decisive evidence of the specific effect of arousal ratings ($BF_{inclusion} = 1203.7$), but there was positive evidence against a specific effect of valence ratings ($BF_{inclusion} = 0.3$). The more arousing, the larger the early-P3 ($R^2_{arousal} = 0.49$).

There was no evidence of an effect of arousal ratings ($BF_{10} = 1.0$), nor of valence ratings ($BF_{10} = 0.7$), nor of both ratings ($BF_{10} = 0.5$) on the amplitude of the frontal late-P3 ($R^2 = 0.017$).

There was no evidence of an effect of arousal ratings ($BF_{10} = 1.1$), nor of valence ratings ($BF_{10} = 0.6$), nor of both ratings ($BF_{10} = 0.5$) on the amplitude of the parietal late-P3 ($R^2 = 0.061$).

4.3. Discussion

4.3.1. Behavioral results

We found that the behavioral facilitation effect was not modulated according to the arousing content of the distraction sounds. The absence of an effect may be explained by the fact that in our study, high-arousing and low-arousing distractors were quite close in their mean arousal rating. This result contrasts with a recent audio-visual oddball study in which it has been reported that negative arousing novel sounds can trigger a smaller increase in reaction times compared to neutral novel sounds (Max et al., 2015). The authors interpreted this facilitation effect as "an unspecific benefit of emotional arousal".

4.3.2. Influence of the arousal and valence contents on ERPs

In the present study, in response to distracting sounds, two phases of the P3 response could be separated: an early phase peaking fronto-centrally between 200 and 260 ms (early-P3) and a late phase peaking frontally and parietally between 300 and 340 ms (late-P3) in agreement with previous studies (Escera et al., 1998; Escera and Corral, 2007; Yago et al., 2003).

We assessed the impact of the arousing value of distracting sounds on these electrophysiological responses: high-arousing distracting sounds elicited a larger early-P3. The difference between responses to high-arousing and low-arousing sounds was maximal at the latency of the early-P3 at fronto-central electrodes. The finding of increased early and late P3 to high arousing sounds is quite consistent with previous studies in the literature. In the auditory modality, both the early-P3 and the late-P3 have been found enhanced after high-arousing negative sounds compared to less-arousing neutral novel sounds (Widmann et al., 2018). In the visual modality, high-arousing novels trigger larger P3a waves than low-arousing novels regardless of their valence (Olofsson and Polich, 2007; Rozenkrants and Polich, 2008). However, another study showed that only the P3b (and not the P3a) was enhanced when comparing responses to negative/positive high-arousing novel pictures compared to low-arousing neutral pictures (Delplanque et al., 2005).

The distinction between arousal and emotional effects on the P3 responses has been often ignored since previous studies compared responses to high-arousing negative and/or positive stimuli, to less-arousing neutral ones, leading to debatable conclusions as valence and arousal can interact (Cuthbert et al., 2000; Delplanque et al., 2006; Domínguez-Borràs et al., 2008; Olofsson and Polich, 2007; Widmann et al., 2018). Here, we aimed at disentangling the effects of the arousing content of distracting sounds from the effects of their emotional content. First, we used distracting sounds that were rather emotionally neutral. Second, multiple regression analysis indicated strong to decisive evidence that the ERP correlated with arousal ratings, and not with the valence ratings, at the latencies of the early-P3: the more arousing the sound is, the larger the early-P3. Moreover, at the latencies of the late-P3, no evidence of a correlation with the arousal ratings, nor with the valence ratings, could be found. Finally, the valence ratings were only found to correlate with ERP amplitude at the latencies of the P2, which amplitude was enhanced for negative sounds. This finding is consistent with previous studies in the visual modality which report enhanced P2 amplitude to disgusting and fearful stimuli compared to neutral ones (Carretié et al., 2011, 2004). The P2 remains one of the least investigated ERP in the auditory modality: very little is known about its functional significance (Crowley and Colrain, 2004). In the present study, it has proven to be sensitive to the valence of distracting sounds but not to their arousing value.

Taken together, these results suggest that the amplitude of the early-P3, only, is strongly related to the arousal rating of the distracting sounds.

5. General discussion

5.1. Distracting sounds and arousal

We showed that "distracting" sounds can trigger a facilitation effect on behavior when the distractor-target delay is superior to 300 ms. This facilitation effect was found not affected by the sensory modality of the target and to remain stable for at least 2 s, suggesting that salient task-irrelevant sounds can increase general reactivity to any incoming stimulus.

All these results converge towards the idea that distracting sounds, on top of the behavioral costs related to attentional capture, can trigger a burst of arousal, which can result in a behavioral benefit. Phasic increases of arousal correspond to a state of enhanced physiological reactivity that leads to a condition of increased unspecific alertness and improved readiness to respond, which enables better performances. In tasks with low attentional demands, distracting sounds would temporarily increase arousal to a more optimal level enhancing reactivity during the task. This is consistent with a model of the orienting response which comprises an arousal component (Näätänen, 1992). Few studies investigating distraction have taken into account the arousal component provided by distracting sounds. In audio-visual oddball paradigms, distraction is measured as the difference in reaction time to targets preceded by a novel/deviant sounds compared to targets following a standard sound (Escera et al., 2000; Escera and Corral, 2007). It is important to note that since novel sounds can trigger both an attentional capture and an increase in phasic arousal, the behavioral costs and benefits resulting from each process, respectively, are both contributing to the so-called distraction measure in oddball paradigms.

In summary, distracting sounds can be followed by an increase in phasic arousal and, depending on the sound properties and the participant's current level of tonic arousal, can lead to a substantial behavioral benefit. The effects of the arousal burst persist for a couple of seconds but decline with time.

5.2. The role of the fronto-central P3a in phasic arousal

The P3a has been frequently associated with distraction as its elicitation often coincided with impaired performances (Berti and Schröger, 2003; Escera et al., 2003; SanMiguel et al., 2008; Schröger and Wolff, 1998). P3a amplitude and the increase of RT due to deviant sounds is also moderately correlated (Berti et al., 2004). Furthermore, in an oddball paradigm, if deviant sounds become task-relevant, the P3a decreases and performances improve compared to task-irrelevant deviant sounds (Hölig and Berti, 2010). These results have been interpreted as an implication of

the P3a in both involuntary and voluntary attention switching.

However, in the present study, the elicitation of both P3a phases was associated with improved performances (early distractors) but also with unchanged performances (late distractors). This is consistent with previous studies reporting a dissociation between the P3a and observable behavioral distraction (Rinne et al., 2006; SanMiguel et al., 2010b; Wetzel et al., 2013). As demonstrated earlier, salient task-irrelevant sounds trigger an orienting response which comprises both attentional capture and arousal components. These sounds can lead to improved, stable or impaired performances depending on task demands, distractor-target delays, the psychological state of the participant, etc. In other words, distracting sounds elicit both components of the orienting response, the final behavioral outcome depend on the balance between benefits and costs related to these two components. Therefore, linking the P3a solely to distraction may be reductive. In the light of our results and previous findings, the P3a can be seen as a more complex response which encompasses both components of the orienting response as it has been proposed by San Miguel and colleagues (2010).

In this line, previous results suggest that the early-P3 is not an adequate marker of attention reorientation. Contrary to the late-P3, the amplitude of the early-P3 is unchanged in a passive oddball paradigm compared to an active paradigm in which sounds precede the onset of visual targets (Escera et al., 2000, 1998). The authors concluded that as the early-P3 was insensitive to attentional manipulations, it was unlikely to reflect attentional reorientation. Sounds with personal significance (such as one's own first name spoken by a familiar voice or one's own ringtone) are expected to trigger stronger attentional capture but unlike the late-P3, the early-P3 is impervious to personal significance (Holeckova et al., 2006; Roye et al., 2007). In contrast to the late-P3, the early-P3 is observable only for high magnitude deviant sounds and not for low-magnitude deviant sounds even if both result in behavioral distraction (Horváth et al., 2011). In clinical studies, the early-P3 does not appear to be a reliable index of distraction. In a study using an auditory oddball in children with ADHD, enhanced distractibility of the children was associated with a smaller early-P3 to novel sounds but also with a larger late-P3 (Gumenyuk et al., 2005). Similar results were observable among schizophrenic patients who displayed a smaller early-P3 to novel sounds in association with an increased behavioral distraction (Cortiñas et al., 2008). Different interpretations of the functional role of the early-P3 have emerged: the early-P3 was proposed to reflect an alerting process governing the direction of the attentional move (Ceponiene et al., 2004), a stimulus-specific process (Horváth et al., 2011), or the violation of the regularity registered by the automatic deviance detection system (Escera et al., 2000, 1998).

In the present study, we found that the amplitude of the early-P3 is strongly related to the arousal rating of the distracting sounds. Therefore, we propose that the early-P3 is an index of the phasic arousal increase triggered by unexpected salient sounds. In agreement with previous articles, we hypothesize that the attentional capture is more likely to be reflected by the late-P3 as already proposed in several previous articles (Barry and Rushby, 2006; Bidet-Caulet et al., 2015; Escera et al., 2000, 1998; Roye et al., 2007).

Nomenclature of the P3-complex has been inconsistent throughout the literature. In active and passive oddball paradigms, infrequent target or non-target deviant sounds trigger a fronto-central P3a (Escera et al., 1998; 2000; Schröger and Wolff, 1998; Squires et al., 1975). In "novelty oddball" paradigms, it has been observed that novel environmental sounds were followed by an erp coined as "novelty-P3" (Courchesne et al., 1975; Friedman et al., 2001; Gaeta et al., 2003). In an influential study, the authors described the novelty-P3 and the P3a as indistinguishable and that the two labels could be used interchangeably (Simons et al., 2001). This result has been widely accepted in the literature (Polich, 2007) but it has not prevented both nomenclatures to persist in subsequent articles (Escera and Corral, 2007; SanMiguel et al., 2010b). Moreover, both the P3a and the novelty-P3 have been found to comprise two phases: a fronto-central early phase peaking around 235 ms and a fronto-parietal late phase peaking around 320 ms (Escera et al., 1998; Escera and Corral, 2007; Yago et al., 2003). A recent study has run a principal component analysis (pca) compiling data from different oddball paradigms (Barry et al., 2016). Based on latency, topography and conditions of elicitation, the authors suggest that the early P3a reflects the genuine P3a and that the late-P3a reflects the genuine novelty-P3. in numerous articles, a monophasic fronto-central erp peaking around 240 ms is referred to as "P3a": this would be equivalent to the early-P3 observed here and in previous studies.

In the light of previous and present findings, it seems important to consider, in future studies, the different phases of the P3 complex in response to novel or distracting sounds. The investigation of their link with the distinct arousal and attentional components of the orienting response should provide new insight on the contradictory effect observed at the behavioral level.

5.3. Relationships between the fronto-central P3a and arousal

From now on, "P3a" will refer specifically to the positive fronto-central ERP peaking around 240 ms, named early-P3 in the present study.

Both P3a and arousal have been linked to the locus coeruleus-norepinephrine (LC-NE) system in the literature. The locus-coeruleus is a brainstem neuromodulatory system that sends noradrenergic innervation to all cortical regions and to the amygdala and notably influences the cortical control of attention through arousal (for a review, see Sara and Bouret, 2012). It has been proposed that the interaction between the NE system and the prefrontal cortex is crucial for attentional regulation (Arnsten, 1998). Excessive release of norepinephrine coincides with amplified responses to distracting stimuli and degraded task performance in monkeys (Rajkowski et al., 1997). The LC-NE would be closely linked to the orienting response: unexpected and/or arousing stimuli trigger a phasic activation of the LC-NE which consequently facilitates sensory processing (Aston-Jones and Cohen, 2005; Nieuwenhuis et al., 2005). P3a response and phasic activation of the LC-NE system share common antecedent conditions as both of them are elicited by motivationally significant stimuli such as novel stimuli in oddball tasks. In a passive auditory oddball study in monkeys, surgical lesions of the locus coeruleus were associated to decreased P3a-like response to deviant sounds (Pineda et al., 1989). It has been proposed that the LC-NE system phasic activation mediates both the P3a response and the behavioral facilitation effect following novel stimuli but such direct evidences in humans are still lacking (Schomaker and Meeter, 2015).

However, indirect evidences have accumulated. Autonomic components of the orienting responses such as the skin conductance response (SCR) and the pupil dilation response (PDR) are concomitant with the elicitation of the P3a and both would reflect the coactivation of the LC-NE system and the peripheral sympathetic nervous system (for a review, see Nieuwenhuis et al., 2011). In a recent oddball study, comodulation of the PDR response and the early- and late-P3a have been reported: both were enhanced in concert by high-arousing negative novel sounds compared to low-arousing neutral novel sounds (Widmann et al., 2018). However in another oddball study, at the single trial level, P3a did not correlate with the PDR amplitude (Kamp and Donchin, 2015). In oddball studies, a tendency towards a larger P3a has been observed in trials in which a SCR has been elicited (Lyytinen et al., 1992; Marinkovic et al., 2001) but other studies fail to link the SCR to any of the ERPs triggered by novel sounds (Barry et al., 2013; Rushby and Barry, 2009). In a recent auditory oddball study, large SCR to novel sounds were associated to large late-P3 amplitudes but no such association could be drawn with the early-P3 (Berti et al., 2017). Studies using drugs to modulate noradrenergic activity can also be useful to understand the links between the P3a and the LC-NE system. A drug facilitating noradrenergic neurotransmission has been found to increase specifically the P3a in an auditory oddball, and had no effect on the P3b (Missonnier et al., 1999). Clonidine, a drug which attenuates baseline noradrenergic activity, has been found to decrease the amplitude of the P3a (but to

increase P3b) during an auditory oddball task (Brown et al., 2015). Further research will be necessary to corroborate the hypothesis of a causal link between the phasic increase of physiological arousal and the fronto-central early-P3 response after unexpected salient stimuli.

5.4. An arousal model

This model proposes that the fronto-central P3a reflect the phasic increase in arousal triggered by novel or distracting sounds. This alternative interpretation of the processes underlying the fronto-central P3a is in line with the Näätänen model of the orienting response including an arousal and an attentional components, and with a link between the P3a and the LC-NE system (see previous paragraph). In monkeys, the locus coeruleus is activated around 100 ms after stimulus onset (Aston-Jones et al., 1994; Rajkowski et al., 1994). It is imaginable that the P3a elicitation (whose peak is around 240 ms after stimulus onset) is the result of the general increase of cortical excitability following the LC-NE activation by novel stimuli.

This model is consistent with previous results and can help to shed light on them. First, it has been observed repeatedly that novel sounds trigger a larger fronto-central P3a than deviant sounds (e.g. Escera et al., 1998; Fabiani and Friedman, 1995; Gaeta et al., 2003; Spencer et al., 1999). This effect cannot be explained simply by deviance (both deviant and novel sounds deviate from the context of the standard sound sequence), nor by novelty (here understood as the association of rareness and unfamiliarity) because white noise distractors trigger a larger P3a than variable environmental novel sounds (Frank et al., 2012) and identical environmental sounds trigger a similar P3a than variable environmental novel sounds (Barkaszi et al., 2013). The difference in fronto-central P3a amplitude between novel and deviant sounds could, however, be explained by the fact that novel sounds are more salient due to their complexity and therefore more arousing, resulting in a steeper increase in phasic arousal and a larger fronto-central P3a. Second, one of the main characteristics of the P3a is to quickly decrement with repeated exposure (Barry et al., 2016; Courchesne et al., 1975; Debener et al., 2002). This is compatible with the observations that the locus coeruleus neural response to novel sounds or to novel environments quickly decreases after few presentations in rats (Hervé-Minvielle and Sara, 1995; Vankov et al., 1995). Therefore, the arousal model of the P3a fits the classic theory of the orienting response and can account for the main properties of the P3a that have been highlighted in the literature.

P3a has been widely considered as an index of distractibility and used as such in numerous clinical studies including for example healthy old adults (Getzmann et al., 2013), participants under the influence of alcohol (Marinkovic et al., 2001), patients with closed head injury (Kaipio et al., 2000), Alzheimer (Correa-Jaraba et al., 2018) or dyslexia (Rüsseler et al., 2002), healthy children (e.g. Gumenyuk et al., 2001; Wetzel and Schröger, 2007) and children with ASD (Ferri et al., 2003), depression (Lepistö et al., 2004) or ADHD (e.g. Gumenyuk et al., 2005; Keage et al., 2006; van Mourik et al., 2007). Misunderstanding the complexity of the P3a signal could lead to erroneous interpretations of data in clinical studies. An increased arousability (in the sense of a propensity to increased phasic arousal responses) could be mistaken for an enhanced distractibility. This arousal model of the P3a may help to make sense to seemingly paradoxical results such as the association of a reduced P3a with increased behavioral distraction (van Mourik et al., 2007; Keage et al., 2006) or opposite modulations of the early- and late-P3 (Cortiñas et al., 2008; Gumenyuk et al., 2005). It will be essential for further studies about distractibility to dissociate the two phases of the P3 complex to improve medical diagnosis.

6. Conclusions

In summary, the present findings show that unexpected salient sounds during a task trigger two distinct processes: a short-lived attentional capture and a more lingering phasic increase in arousal. Consequently, performances are conditioned to both facilitation by phasic arousal and impairment by attentional capture. Whether unexpected salient sounds will have detrimental or beneficial effects on performances partly depends on the design of the task (the sound-target delay in the present study but also the informational value or task-relevance of the sound, the task demand, etc.). Unexpected salient sounds trigger a biphasic P3, we found that the amplitude of the early-P3 is strongly related to the arousal rating of the distracting sounds. Therefore, we propose that both the attention and arousal components of the orienting response are reflected in the P3 but that the phasic arousal response is more associated to the fronto-central early-P3, often named P3a in the literature.

Declarations of interest

None.

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2 Attentional alterations in migraine

2.1 General introduction

The aim of this project is to investigate the attention function in migraine by integrating different research methods. Previous literature has identified that migraine is likely to be associated with a moderate impairment of attention (Vallesi 2020; Vuralli, Ayata, and Bolay 2018). However, the neuropsychological tests used in these studies do not provide precise information on the specific attention mechanisms which might be altered. Also, there is not much scientific literature reporting that this attentional alterations have actually an impact on the everyday life of migraineurs during the headache-free phase. The underlying motivation to investigate attention in migraine is that we hypothesize that a deficient attention filter may participate to the sensory disturbances, especially interictally. Impaired top-down attentional mechanisms and/or exacerbated bottom-up attentional processes may lead to poorly monitored sensory processing and to an overload of irrelevant sensory information.

In the article 2, migraineurs and healthy participants responded to a questionnaire evaluating their attention difficulties in the everyday life, along with their sensitivity to light, noise and odors. For migraineurs, sensory sensibility was evaluated both during and outside migraine attacks. This study aims to establish that migraineurs self-report increased distractibility and to link these attentional difficulties to the intensity of their sensory sensibility.

In the article 3 and 4, migraineurs and healthy participants performed the CAT while EEG and MEG signals were recorded. The attention function will be assessed through behavioral effects and event-related responses in the article 3 and through alpha and gamma activities in the article 4. As I discussed in the first part of this manuscript, event-related responses and brain rhythms are particularly well-suited for the investigation of the attention processing of sensory information.

2.2 Article 2: “Self-perceived attention difficulties are associated with sensory hypersensitivity in migraine”

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Original article

Self-perceived attention difficulties are associated with sensory hypersensitivity in migraine

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ABSTRACT

Background. – Attention is the process which enables to preferentially select salient or relevant stimuli and to attenuate the response to irrelevant incoming stimuli. Migraine is characterized by both attentional alterations and an abnormal sensory processing to external stimulations. The aim of the study was to investigate potential interactions between self-perceived attentional difficulties and sensory hypersensitivity in migraine patients.

Methods. – Forty-six episodic migraineurs without aura and 46 healthy controls filled out questionnaires on self-perceived attention difficulties and self-reported sensitivity to visual, auditory and olfactory stimulations.

Results. – Compared to controls, migraineurs reported significantly higher levels of attention difficulty and sensory sensitivity. Sensory hypersensitivity correlated significantly with self-perceived attentional difficulties in migraineurs ($P = 0.002$), but not with migraine disability or levels of anxiety or depression. Ictal and interictal sensory sensitivities were significantly correlated in migraineurs within visual ($P < 0.001$), auditory ($P < 0.001$) and olfactory ($P = 0.001$) modalities.

Conclusion. – This study shows for the first time an association between self-reported attentional difficulties and multimodal sensory hypersensitivity. Studies combining behavioral and physiological measures of sensory processing and attention processes are necessary to further understand the peculiar vulnerability of migraineurs to sensory stimuli.

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1. Introduction

Migraine is characterized by an abnormal sensory processing [1,2]. Enhanced sensitivity to uni- or multi-modal stimuli, such as an exacerbation of headache or discomfort, is a striking feature of migraine which varies over the migraine cycle [3,4]. Neurophysiological and neuroimaging studies also suggest that the migraine brain is hyperresponsive to sensory stimuli as evidenced by impaired habituation to stimuli and increased BOLD fMRI responses to photic stimuli [5].

In parallel, recent research has pinpointed attentional alterations in interictal migraineurs. Attention is the process which enables to preferentially select salient or relevant stimuli and to attenuate the response to irrelevant incoming stimuli. Neurophysiological and neuroimaging studies suggest an altered top-down attentional control of the visual cortex [6] and an enhanced orienting response towards acoustic stimuli [7,8] in migraineurs. Behavioral and neuropsychological studies also report attentional impairments in migraineur children and adults (for a review, see [9]). However, distinction between executive functions and attention, or hyperactivity symptoms and attention, is not always possible given the tests employed [10,11] and results are not always consistent overall. For instance, Gil-Gouveia et al. [12] and Lo Buono et al. [13] found no difference between migraineurs' and controls' performance in the Trail Making Test-A and -B. The study of Han et al. suggested that some components of attention may be impaired in migraineurs without aura, whilst other components are intact [14].

To our knowledge, no study has investigated the potential link between migraine enhanced sensory sensitivity and attentional alterations. Both point to abnormal sensory processing in migraine patients. The aim of our study was to investigate the interactions between sensitivity to light, sound, odor, and self-perceived attentional difficulties by means of questionnaires, in episodic migraineurs without aura and control participants.

2. Methods

2.1. Participants

Forty-six migraine patients without aura and forty-six healthy control participants matched for sex, age, education and music training participated in this study (Table 1). All migraine patients fulfilled the criteria of episodic migraine according to the International Headache Society [15], were aged 18 to 75 years and suffered from at least one attack per month. Exclusion criteria were migraine with aura, chronic migraine (>15 days of headache per month), other neurological or psychiatric disease, and use of preventive medication. Attack frequency was 3.8 ± 1.9 per month. Twenty-three migraineurs and eleven control subjects were concomitantly participants in a magnetoencephalography (MEG) study investigating auditory attention [16]. Participants gave their written informed consent, according to the Declaration of Helsinki.

2.2. Material

We created one questionnaire assessing self-perceived attentional difficulties in daily life. This questionnaire was inspired from the Attention self-assessment questionnaire [17] and the Wender Utah Rating Scale [18]. For each item, the participants rated on a 4-point scale the frequency with which they encounter difficulties in a particular situation. We also created three questionnaires to assess visual, auditory, and olfactory hypersensitivity. Each item presented a behavioral or emotional response to a sensory stimulation and a 4-point scale from 1 ''Rarely'' to 4 ''Very often''. These questionnaires were divided into two sections: ''between attacks'' and ''during an attack'' (see Appendix for the full French version, with an English translation). The ''between attacks'' auditory questions were selected from the auditory sensitivity questionnaire of Khalfa (1999, French clinical test, published in English under the name HQ – Hyperacusis Questionnaire – [19]). The visual questions were adapted from Choi et al. [20]. The olfactory questions were inspired from the Glasgow Sensory Questionnaire [21,22].

Finally, migraineurs were requested to fill the HIT (Headache Impact Test, [23]) and the MIDAS scale (Migraine Disability Assessment, [24]) as a measure of migraine general severity, functional impact of migraines and migraine frequency. The 34 participants who underwent an additional MEG experiment also completed the HAD (Hospital Anxiety and Depression Scale [25]) to assess anxiety and depression levels.

2.3. Procedure

Participants ($n = 92$) completed the attention and hypersensitivity questionnaires. For the hypersensitivity questionnaires,

Table 1 – Demographic characteristics of the participants.

	Patients	Controls	Group comparison	P-value
	($n = 46$)	($n = 46$)	Statistics	
Sex (n)				
Male	10	13	$\chi^2(1) = 0.52$	0.471
Female	36	33		
Age (years)				
Mean (SD)	29.4 (9.4)	27.4 (11.2)	$t(90) = 0.93$	0.355
Education (years)				
Mean (SD)	15.5 (2.4)	15 (1.7)	$t(90) = 1.18$	0.240
Music training (years)				
Mean (SD)	3.4 (4.9)	3.4 (4.2)	$t(90) = 0.50$	0.964

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controls were asked to answer only the ''between attacks'' sections. The migraine patients also completed the HIT and the MIDAS ($n = 46$). The HAD was completed only by the subjects participating in the MEG study ($n = 23$ migraineurs).

2.4. Statistical analysis

Responses ''rarely'' were recoded as ''1'', ''sometimes'' as ''2'', ''often'' as ''3'' and ''very often'' as 4. Missing data in questionnaires were replaced by the group average score for the item. By averaging item scores, we got a total score for each questionnaire. Separate scores were computed for the sections ''between attacks'' and ''during an attack'' for the hypersensitivity questionnaires. Internal coherence of each questionnaire was assessed using Cronbach's alpha.

Group differences in the scores from the self-perceived attentional difficulties and the visual, auditory and olfactory interictal hypersensitivity questionnaires were assessed using independent *t*-tests. Pearson correlations between ictal and interictal scores and between modalities were then conducted on migraine patient data. Finally, a multiple linear regression assessed the relationship between interictal sensory hyperactivity with self-perceived attention difficulties, including age, sex, education level, MIDAS and HIT scores as covariates to control for confounding effects. Modeling assumptions were verified using the gvlma R-package [26]: data fulfilled the statistical assumptions of independence, normality and homogeneity of variances ($P > 0.05$). The multicollinearity was not excessive with a Variance Inflation Factor (VIF) always less than 0.69, under the commonly accepted cut-off value of 5 or 10 [27].

Causality questions (''Is your headache worsened by…?'' and ''Is your headache triggered by…?'') were analyzed separately, with the aim to examine the link between the perception of a stimulation as a trigger and interictal hypersensitivity in migraineurs.

All the computed *P*-values were two-tailed and the cut-off for statistical significance was 0.5.

3. Results

There were no missing data across the questionnaires for the control group. In the migraine group, the rate of unanswered items was < 2% for all questionnaires. Internal coherence was high within each questionnaire (interictal part), as measured by Cronbach's alpha computed on the 92 participants: 0.73 for the attention questionnaire, 0.85 for the visual questionnaire, 0.84 for the auditory questionnaire. The olfactory questionnaire comprised only one question in the interictal part. Three migraineurs out of 23 tested showed an anxiety score greater than the pathological cut-off according to the HAD norms, but the depression score was not pathological and their data were retained for the main analyses.

3.1. Group comparisons

Migraineurs showed significantly higher scores of self-perceived attention difficulties than control participants ($t(90) = 2.64$, $P = 0.010$, $d = 0.53$), as illustrated on Fig. 1A.

Between attacks, migraineurs showed significantly higher scores of sensory hypersensitivity than controls in the visual ($t(90) = 3.84$, $P < 0.001$, $d = 0.75$), auditory ($t(90) = 3.22$, $P = 0.002$, $d = 0.64$), and olfactory modalities ($t(90) = 2.18$, $P = 0.032$, $d = 0.45$), as illustrated on Fig. 1 (panels B, C, and D).

Ratings by items are illustrated in Fig. 2.

3.2. Correlations in migraineurs

Visual and auditory hypersensitivity were correlated in migraineurs, slightly in interictal periods ($r(44) = 0.30$, $P = 0.043$)[1], more strongly in ictal period ($r(44) = 0.432$, $P = 0.003$). Olfactory hypersensitivity did not correlate with the other modalities in interictal period ($r(44) < 0.22$, $P > 0.141$). In ictal period, the correlation of olfactory hypersensitivity with auditory hypersensitivity was significant ($r(44) = 0.315$, $P = 0.033$), but the correlation with visual hypersensitivity failed to show significance ($r(44) = 0.24$, $P = 0.102$). Note however that the olfactory questionnaire was shorter and hence likely to be less robust than the auditory and visual questionnaires.

In the analyses that follow, we used a composite score of interictal sensory hypersensitivity across visual and auditory modalities by averaging visual and auditory scores for each migraineur participant.

The multiple linear regression revealed a significant correlation between interictal sensory hypersensitivity and self-perceived attention difficulties ($t = 3.47$, $P = 0.001$) with no significant contribution of the covariates (see Table 2). The model had a multiple R^2 of 0.38 and an adjusted R^2 of 0.28 ($F(6,39) = 3.95$, $P = 0.003$). The relationship between sensory hypersensitivity and attention is illustrated in Fig. 3.

Tested in a separate analysis because of a sample of lower size ($n = 23$), the correlation between the anxiety and depression score (HAD total score) and self-perceived attentional difficulties revealed a significant association between the two variables ($r(21) = 0.45$, $P = 0.033$). However, the anxiety and depression score was not significantly correlated with interictal sensory hypersensitivity ($r(21) = 0.09$, $P = 0.674$).

3.3. Attack-related questions in migraineurs

Sensory hypersensitivity was strongly enhanced during ictal periods compared to interictal periods (during attack composite score: 2.8 ± 0.6; between-attack composite score: 2.30 ± 0.6; $t(45) = -7.8$, $P < 0.001$). Ictal and interictal scores were also significantly correlated within each modality (visual: $r(44) = 0.57$, $P < 0.001$; auditory: $r(44) = 0.72$, $P < 0.001$; olfactory: $r(44) = 0.47$, $P = 0.001$).

To the question ''Is your headache worsened by…?''(see Appendix), 70% of migraineur participants answered ''often'' or ''very often'' for lights, 65% for sounds, 43% for odors. To the question ''Is your headache triggered by…?'', 15% of migraineur participants answered ''often'' or ''very often'' for lights, 11% for sounds, 22% for odors. Scores to the question ''Is your headache triggered by…?'' were significantly correlated to interictal sensory hypersensitivity for visual and auditory

[1] While visual and auditory sensitivity did not correlate in control participants: $r(44) = 0.08$; $P = 0.61$.

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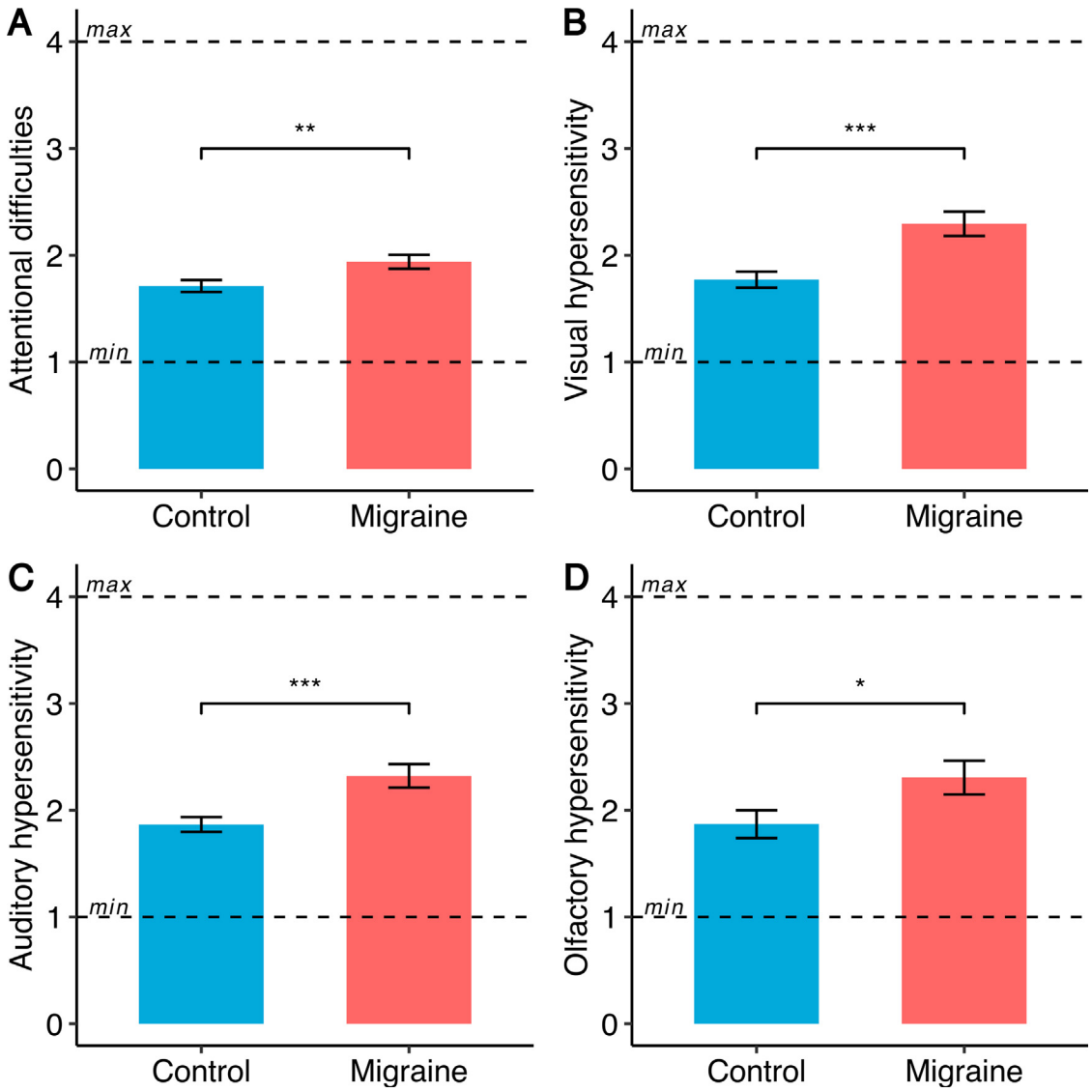

Fig. 1 – Average score from the attention questionnaire (panel A) and the sensory hypersensitivity questionnaires ("between attacks" questions) in control and migraine participants (panels B, C, D). *P < 0.05, ** P < 0.01, *** P < 0.001.

modalities (visual: $r(44) = 0.43$; $P = 0.003$; auditory: $r(44) = 0.38$; $P < 0.010$), and marginally for olfactory modality ($r(44) = 0.26$; $P = 0.077$).

4. Discussion

Compared with controls, migraine patients reported significantly higher levels of sensory sensitivity and attention difficulties. Both variables were positively correlated among migraineurs, after controlling for background variables (age, sex, education, HIT and MIDAS scores). Ictal and interictal sensory sensitivities were significantly correlated in migraineurs within visual, auditory and olfactory modalities. The correlation between visual and auditory hypersensitivity was slight in interictal period in migraineurs, and reinforced in ictal periods.

4.1. *Multimodality of sensory hypersensitivity*

In this study, migraine patients reported a higher self-reported sensitivity to light, sound and odor between and during migraine attacks. A recent study showed that patients with ictal photophobia were more likely to complain about interictal photosensitivity as well as visual stimuli as triggers than headache patients without ictal photophobia or controls [28]. Our results corroborate this finding within the visual modality and show that these correlations between ictal and interictal states are also observed within auditory and olfactory modalities. A limit of the current study is that ictal and interictal allodynia was not evaluated.

Migraineurs reporting interictal hypersensitivity to a given modality also complained that these stimulations could trigger migraine attacks. This link is however difficult to draw up since answers to the hypersensitivity questionnaires may

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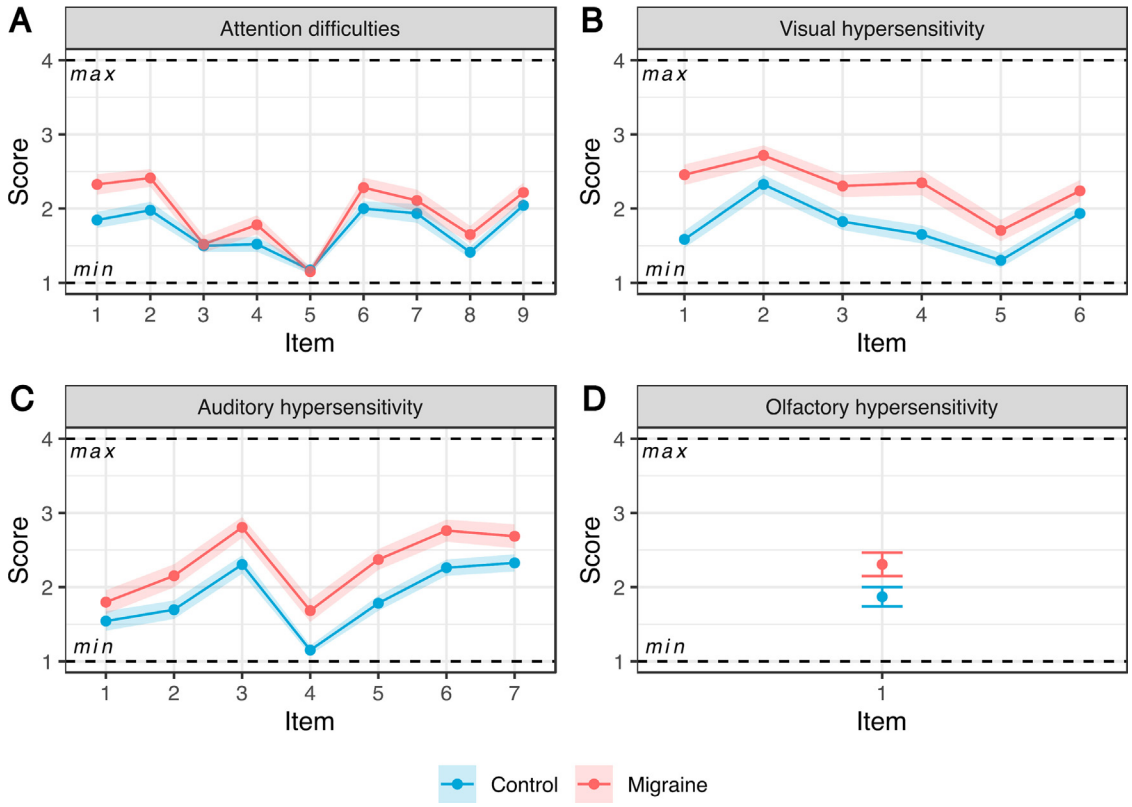

Fig. 2 – Profile of average rating (shaded area represents the standard-error) by item and group for the attention questionnaire (panel A) and the sensory hypersensitivity questionnaires ("between attacks" questions) in control and migraine participants (panels B, C and D).

Table 2 – Results of the multiple linear regression in migraineurs data ($n = 46$) with the interictal audiovisual hypersensitivity as the dependent variable.

	Estimate	Standard-error	t-value	P
(Intercept)	0.854875	1.070402	0.799	0.42933
Attention	**0.610242**	**0.175795**	**3.471**	**0.00128**
Age	−0.003425	0.008243	−0.415	0.68006
Sex	−0.196746	0.175242	−1.123	0.26842
Education level	−0.041456	0.032653	−1.270	0.21175
HIT	0.016227	0.011846	1.370	0.17858
MIDAS	0.005301	0.007090	0.748	0.45915

Self-perceived attention difficulties were significantly linked to hypersensitivity, while the demographic and migraine variables were not. Characters in bold: statistically significant factor.

reflect preventive behaviors set up by patients toward a supposed trigger. Moreover, attribution of a causal role to certain sensory stimulations may be misinterpretation by patients of a simple co-occurrence of hypersensitivity and migraine attacks. Indeed, patients pay exacerbated attention to certain stimuli in the premonitory phase of the attack [29].

Correlation between self-reported visual and auditory sensitivity in migraineurs is in line with a set of data linking sensitivities across modalities. For instance, lower sound aversion thresholds were observed in patients with allodynia compared with non-allodynic patients [30] and patients with olfactory hypersensitivity were more likely to complain of photophobia [31]. This multimodal sensitivity would reflect the hypothesis that migraine is "a paroxysmal disorder of pan-sensory gain" [2].

4.2. *Self- reported attentional difficulties in migraine*

The present findings of self-reported attentional difficulties in migraineurs complement a set of studies objectivating complex attentional alterations between attacks [16] for electrophysiology; and more contrasting results for behavioral performances [14,32]. Our results suggest that attentional difficulties are not only detected by fine electrophysiology measures in experimental set-ups, but are consciously experienced by migraineurs in daily life, even in patients with episodic migraine. Recently, a cross-sectional study among university students showed an association between self-perceived attention difficulties and hyperactivity symptoms levels in students suffering from migraine [11]. Attention deficit is also reported in both children and adult patients with migraine (see [9] for a review). A comorbidity between migraine and Attention Deficit and Hyperactivity Disorder (ADHD) has been described, possibly because the same neurotransmitters might be involved in both conditions (see [33] for a review and meta-analysis; in particular migraine with aura [34]; see also [35]). However, the item in our attention questionnaire which could be considered as typical of ADHD (distraction at school during childhood), did not yield a difference in rating by

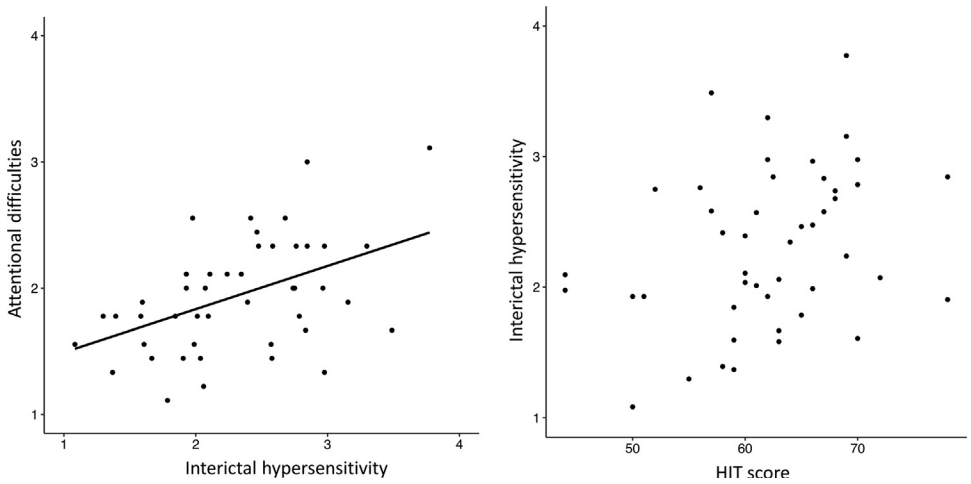

Fig. 3 – Interictal sensory hypersensitivity correlated significantly with self-perceived attentional difficulties in migraineurs (left) but not with migraine disability (HIT score, right).

migraineurs and controls (questionnaire in annex and Fig. 2). Items revealing the greatest group differences concerned sensitivity to exogeneous and endogenous distractors, fatigability in sustained attention tasks and attention to detail. Migraineurs did not report making more errors than did controls when divided attention or sustained attention was required. Migraineurs might pay a higher cost in attention to reach the same performance level, leading to fatigue. More detailed explorations of the different components of attention are needed to better understand this attentional profile.

4.3. *Correlations between self-reported attentional difficulties and sensory sensitivity in migraine*

The pathophysiological mechanism of ictal and interictal non-painful symptoms in migraine is still poorly understood. Three hypotheses may be proposed as possible explanations for the association we found between self-perceived attentional difficulties and sensory hypersensitivity.

First, attentional difficulties may be caused by an increased sensitivity to environmental stimuli. Migraine is characterized by sensory amplification that occurs both during and between attacks and that implies multimodal sensory systems (see above). External stimuli may engage attention in an exacerbated manner in migraineurs [7], yielding distraction, and thus attentional difficulties in daily life. According to this hypothesis, migraine would generate sensory hypersensitivity, which, as a consequence, would disturb attentional processes.

Second, hypersensitivity could be caused by attentional difficulties linked to migraine. Altered bottom-up (involuntary capture of attention by an unexpected salient stimulus) and/or top-down (voluntary attention to sensory stimuli) processes could lead to abnormal sensory modulation management. For instance, an association between attentional deficit and abnormal sensitivity to sensory stimuli has been reported in patients with ADHD [36,37]. According to this hypothesis, migraine generates attentional imbalances, which expose patients to multimodal sensory hypersensitivity. However, migraine disease is not primarily an attention deficit disorder.

Third, both self-reported attentional difficulties and enhanced sensory responsiveness could originate from individual predisposition to develop migraine. Neurochemical imbalances (noradrenaline, dopamine) could underly the attentional difficulties as well as the ictal and interictal pathophysiology of the migraineur brain (e.g. [38]). This hypothesis could explain that both sensory and attentional anomalies have been reported in adults but also in children with migraine (see above): they would not be consequences of several years of migraine damaging the cognitive functions, but reflects of a source dysfunction. Longitudinal studies are required to enlighten causal relationships and disentangle anomalies which are at the core of migraine disease, and anomalies secondary to the source dysfunctions. One could for instance investigate engagement of attention in external stimuli processing in children, and how predictive it is for later migraine disease.

Importantly, the association we found here between self-perceived attentional difficulties and sensory hypersensitivity cannot be explained by anxiety and depression nor by the severity of migraine, as both variables were not correlated with sensory hypersensitivity. A personality factor as neuroticism [39] could underlie a higher level of complaint in migraineurs than controls and association between both complaints (hypersensitivity and attention difficulties). However, in that case, we would probably have observed a level of complaint across all scales (including HAD score) proportional to the migraine severity (HIT score), which was not the case. In line with these observations, interictal photosensitivity has been found to be unrelated to duration of migraine, frequency of attacks and mood disorder [40,41].

5. Conclusion

This study highlights the association between multimodal hypersensitivity and self-perceived attentional difficulties in migraine patients. Studies combining behavioral and physiological measures of sensory processing and attention pro-

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cesses are necessary to further understand the peculiar vulnerability of migraineurs to sensory stimuli.

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Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Questionnaires

The French version was used in the present study. The English translation is provided between brackets for the readership of this article. The scale is the same across the questionnaires: ''rarely'', ''sometimes'', ''often'' or ''very often''.

Echelle d'attention *[Attention scale]*	Très rarement	Parfois	Souvent	Très souvent
1. Au cours de mes activités (lecture, télévision, conversation,.), je perds le fil parce que je suis distrait(e) par les bruits extérieurs et/ou le va-et-vient autour de moi. *[During/throughout my activities (reading, television, conversation,. . .), I lose the thread because I get distracted by external noises and/or coming and going around me.]*	◯	◯	◯	◯
2. Au cours de mes activités (lecture, télévision, conversation,.), je perds le fil parce que mon esprit vagabonde et que je ne peux pas m'empêcher de penser à autre chose. *[During/throughout my activities (reading, television, conversation,. . .), I lose the thread because my mind wanders and I cannot keep from thinking about something else.]*	◯	◯	◯	◯
3. Quand je mène une activité simple, répétitive et monotone de longue durée, je commets beaucoup d'erreurs. *[When I'm doing a simple, repetitive, monotonous activity for a long time, I make a lot of mistakes.]*	◯	◯	◯	◯
4. Quand je mène une activité et que je suis interrompu(e) par quelque chose d'imprévu, j'oublie d'y revenir pour la terminer. *[When I'm doing an activity and I get interrupted by something unexpected, I forget to come back and finish.]*	◯	◯	◯	◯
5. Quand je mène une activité qui comporte plusieurs étapes (comme faire du café), j'en omets une. *[When I'm doing an activity that includes several steps (like making coffee), I forget to do one.]*	◯	◯	◯	◯
6. Je me fatigue lors d'un effort soutenu d'attention. *[I get tired when trying to focus my attention on something for a long time.]*	◯	◯	◯	◯
7. A l'école j'avais tendance à rêvasser plutôt qu'à suivre les cours *[At school, I tended to daydream rather than pay attention in class.]*	◯	◯	◯	◯
8. Je ne prête pas attention aux détails. *[I don't pay attention to details.]*	◯	◯	◯	◯
9. Quand je mène une activité, je commets des erreurs si on me parle en même temps. *[When I am doing something, I make mistakes if someone talks to me at the same time.]*	◯	◯	◯	◯

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Questionnaire de gêne au bruit *[Phonophobia questionnaire]* *Si vous présentez des migraines, répondez aux questions suivantes en vous basant sur votre vécu en dehors des crises :* *[If you have migraines, answer the following questions based on your experience between attacks:]*	Très rarement	Parfois	Souvent	Très souvent
1. Vous arrive-t-il d'utiliser des bouchons (boules Quiès) pour limiter votre perception du bruit ? *[Do you ever use earplugs to keep the noise down?]*	◯	◯	◯	◯
2. Avez-vous des difficultés à ne plus faire attention aux sons qui vous entourent dans les situations de la vie quotidienne ? *[Is it hard to not pay attention anymore to sounds around you in everyday situations?]*	◯	◯	◯	◯
3. Etes-vous gêné(e) pour vous concentrer dans un environnement bruyant ? *[Is it hard for you to concentrate in noisy surroundings?]*	◯	◯	◯	◯
4. Si l'on vous propose une activité (sortie, cinéma, concert), pensez-vous tout de suite au bruit que vous aurez à supporter ? *[When someone suggests doing something (going out, to the cinema, to a concert), do you immediately think about the noise you are going to have to put up with?]*	◯	◯	◯	◯
5. Est-ce que le bruit vous fatigue ? *[Does noise make you tired?]*	◯	◯	◯	◯
6. Trouvez-vous certains bruits ou sons agaçants, irritants ? *[Are certain sounds or noises irritating?]*	◯	◯	◯	◯
7. Est-ce que les bruits forts vous dérangent ? *[Do loud noises bother you?]*	◯	◯	◯	◯
Ne répondez aux questions suivantes que si vous présentez des migraines : *[Answer the following questions only if you have migraines:]*	◯	◯	◯	◯
8. Lorsque vous avez la migraine, vous arrive-t-il d'utiliser des bouchons (boules Quiès) pour limiter votre perception du bruit ? *[During your headache, do you ever use earplugs to keep the noise down?]*	◯	◯	◯	◯
9. Lorsque vous avez la migraine, avez-vous des difficultés à ne plus faire attention aux sons qui vous entourent dans les situations de la vie quotidienne ? *[During your headache, is it hard to not pay attention anymore to sounds around you in everyday situations?]*	◯	◯	◯	◯
10. Lorsque vous avez la migraine, est-ce que les bruits forts vous dérangent ? *[During your headache, do loud noises bother you?]*	◯	◯	◯	◯
11. Lorsque vous avez la migraine, trouvez-vous certains bruits ou sons agaçants, irritants ? *[During your headache, are certain sounds or noises irritating?]*	◯	◯	◯	◯
12. Votre migraine empire-t-elle quand il y a du bruit ou certains sons ? *[Is your headache worsened by noise or certain sounds?]*	◯	◯	◯	◯
13. Votre migraine est-elle déclenchée par le bruit ou certains sons ? *[Is your headache triggered by noise or certain sounds?]*	◯	◯	◯	◯

Questionnaire de gêne à la lumière *[Photophobia questionnaire]* *Si vous présentez des migraines, répondez aux questions suivantes en vous basant sur votre vécu en dehors des crises :* *[If you have migraines, answer the following questions based on your experience between attacks]*	Très rarement	Parfois	Souvent	Très souvent
1. Est-ce que la lumière vous fatigue ? *[Does light make you tired?]*	◯	◯	◯	◯
2. Quand la lumière est vive, vous sentez-vous ébloui(e) ou aveuglé(e) ? *[Do bright lights bother you (glare, blurred vision)?]*	◯	◯	◯	◯
3. Etes-vous dérangé(e) par des lumières vacillantes ou éblouissantes, certaines couleurs, ou des rayures très contrastées ? *[Do flickering lights, glare, specific colors or high contrast striped patterns bother you?]*	◯	◯	◯	◯
4. Vous arrive-t-il d'éteindre des lumières ou de tirer des rideaux pour éviter une trop grande luminosité ? [*Do you ever turn off the lights or draw the curtains to avoid bright light?*]	◯	◯	◯	◯
5. Portez-vous des lunettes de soleil même lorsque les conditions lumineuses sont normales ? *[Do you wear sunglasses even in normal daylight?]*	◯	◯	◯	◯
6. Avez-vous mal aux yeux lorsque la lumière est vive ? *[Do bright lights hurt your eyes?]*	◯	◯	◯	◯

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(Continued)

Questionnaire de gêne à la lumière *[Photophobia questionnaire]* *Si vous présentez des migraines, répondez aux questions suivantes en vous basant sur votre vécu en dehors des crises :* *[If you have migraines, answer the following questions based on your experience between attacks]*	Très rarement	Parfois	Souvent	Très souvent
Ne répondez aux questions suivantes que si vous présentez des migraines : *[Answer the following questions only if you have migraines]*	◯	◯	◯	◯
7. Lorsque vous avez la migraine, vous sentez-vous plus ébloui(e) ou aveuglé(e) que d'habitude par les lumières vives ? *[During your headache, is the glare or blurred vision worse than usually caused by bright light?]*	◯	◯	◯	◯
8. Lorsque vous avez la migraine, êtes-vous dérangé(e) par des lumières vacillantes ou éblouissantes, certaines couleurs, ou des rayures très contrastées ? *[During your headache, do flickering lights, glare, specific colors or high contrast striped patterns bother you?]*	◯	◯	◯	◯
9. Lorsque vous avez la migraine, vous arrive-t-il d'éteindre des lumières ou de tirer des rideaux pour éviter une trop grande luminosité ? *[During your headache, do you ever turn off the lights or draw the curtains to avoid bright light?]*	◯	◯	◯	◯
10. Lorsque vous avez la migraine, portez-vous des lunettes de soleil même lorsque les conditions lumineuses sont normales ? *[During your headache, do you wear sunglasses even in normal daylight?]*	◯	◯	◯	◯
11. Lorsque vous avez la migraine, avez-vous mal aux yeux lorsque la lumière est vive ? *[During your headache, do bright lights hurt your eyes?]*	◯	◯	◯	◯
12. Votre migraine empire-t-elle quand la lumière est vive ? *[Is your headache worsened by bright lights?]*	◯	◯	◯	◯
13. Votre migraine est-elle déclenchée par une lumière vive ? *[Is your headache triggered by bright lights?]*	◯	◯	◯	◯

Questionnaire de gêne aux odeurs *[Osmophobia questionnaire]* *Si vous présentez des migraines, répondez à la question suivante en vous basant sur votre vécu en dehors des crises :* *[If you have migraines, answer the following questions based on your experience between attacks:]*	Très rarement	Parfois	Souvent	Très souvent
1. Cherchez-vous à éviter les lieux avec des odeurs fortes ? (odeurs de cuisine, de friture, de parfum, d'essence). *[Do you try to avoid places with strong odors (kitchen, frying, perfume, petrol smells)?]*	◯	◯	◯	◯
Ne répondez aux questions suivantes que si vous présentez des migraines : *[Answer the following questions only if you have migraines]*	◯	◯	◯	◯
2. Pendant votre migraine, les odeurs fortes (odeurs de cuisine, de friture, de parfum, d'essence) vous dérangent-elles ? *[During your headache do strong odors (kitchen, frying, perfume, petrol smells) bother you?]*	◯	◯	◯	◯
3. Votre migraine empire-t-elle en présence d'odeurs fortes ? *[Is your headache worsened by strong odors?]*	◯	◯	◯	◯
4. Votre migraine est-elle déclenchée par une odeur forte ? *[Is your headache triggered by strong odors?]*	◯	◯	◯	◯

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2.3 Article 3: "Auditory attention alterations in migraine: a behavioral and MEG/EEG study"

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Auditory attention alterations in migraine: A behavioral and MEG/EEG study

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HIGHLIGHTS

- Migraineurs performed as well as healthy participants in an attention task.
- However, EEG markers of both bottom-up and top-down attention are increased.
- Migraine is also associated with a facilitated recruitment of the right temporo-parietal junction.

ABSTRACT

Objectives: To evaluate alterations of top-down and/or bottom-up attention in migraine and their cortical underpinnings.
Methods: 19 migraineurs between attacks and 19 matched control participants performed a task evaluating jointly top-down and bottom-up attention, using visually-cued target sounds and unexpected task-irrelevant distracting sounds. Behavioral responses and magneto- and electro-encephalography signals were recorded. Event-related potentials and fields were processed and source reconstruction was applied to event-related fields.
Results: At the behavioral level, neither top-down nor bottom-up attentional processes appeared to be altered in migraine. However, migraineurs presented heightened evoked responses following distracting sounds (orienting component of the N1 and Re-Orienting Negativity, RON) and following target sounds (orienting component of the N1), concomitant to an increased recruitment of the right temporo-parietal junction. They also displayed an increased effect of the cue informational value on target processing resulting in the elicitation of a negative difference (Nd).
Conclusions: Migraineurs appear to display increased bottom-up orienting response to all incoming sounds, and an enhanced recruitment of top-down attention.
Significance: The interictal state in migraine is characterized by an exacerbation of the orienting response to attended and unattended sounds. These attentional alterations might participate to the peculiar vulnerability of the migraine brain to all incoming stimuli.
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1. Introduction

Migraine is the most common neurological disorder with a prevalence around 10% in the worldwide population (Stovner et al., 2007). Migraine is mainly characterized by recurrent headache attacks often accompanied by nausea and vomiting, all of which can be disabling and have a vast impact on quality of life. Migraine attacks are strongly associated with photophobia, phonophobia, osmophobia (aversion to visual, auditory and olfactory stimuli, respectively), and allodynia (pain sensitization to non-painful somatosensory stimuli) (Headache Classification Committee of the International Headache Society (IHS), 2013). These "phobias" encompass both a heightened sensitivity to external stimulation and an exacerbation of pain by those same stimulations. Sensory alterations persist, to a smaller extent, during the

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attack-free period. Interictally, thresholds for light-induced discomfort or pain (Main et al., 1997; Vanagaite et al., 1997) were found decreased in migraine (i.e., hypersensitivity), and intensity of light-induced pain was found exacerbated (Drummond, 1986). Similar results were reported in the auditory modality (Main et al., 1997; Vingen et al., 1998) and migraineurs describe a general over-responsiveness to everyday non-noxious stimuli in subjective questionnaires (Granovsky et al., 2018; Lévêque et al., 2020).

EEG is a particularly useful technique to investigate sensory processing with its high temporal resolution which allows a fine understanding of transient responses to sensory stimulation (Schoenen et al., 2003). Regarding the interictal period, the main result reported by previous EEG studies was a lack of habituation of brain responses to repeated visual stimulation (for a review, see Coppola et al., 2009). Deficits of habituation in migraine were described for various event-related potentials (ERPs): mostly for sensory components such as the visual P1 and N1 (Áfra et al., 2000; Ozkul and Bozlar, 2002; Schoenen et al., 1995), but also for later cognitive ERPs such as the P3b (Evers et al., 1999; Siniatchkin et al., 2003) and the contingent negative variation (CNV) (Kropp et al., 2015; Kropp and Gerber, 1993; Schoenen and Timsit-Berthier, 1993). Interestingly, those habituation impairments normalize before and during migraine attacks (Evers et al., 1999; Judit et al., 2000; Kropp and Gerber, 1995), even though hypersensitivity climaxes during attacks. Impairment of habituation in migraineurs is considered a hallmark of migraine neurophysiology and a biomarker of the interictal state in migraine. However, these results have not been replicated in recent studies (Omland et al., 2016, 2013; Sand and Vingen, 2000) and characterization of a lack of habituation in other sensory modalities have yielded less robust results than those obtained in the visual modality (Coppola et al., 2009; Demarquay and Mauguière, 2016). In the auditory modality, studies investigating habituation deficits in migraine are much scarcer and produced negative results (Morlet et al., 2014; Sand and Vingen, 2000; Wang and Schoenen, 1998). Other EEG responses have also been investigated, notably steady-state visual evoked potentials (SSVEP), electrical brain responses to repeated visual stimulations at specific frequencies. Results strongly suggest that the excitability of the occipital cortex is abnormal among migraineurs (de Tommaso, 2019; de Tommaso et al., 2014).

Magnetoencephalography (MEG) is also a powerful tool for the investigation of sensory processing. It provides a superior signal-to-noise ratio which allows for precise source reconstruction and a better sensitivity to sources tangential to the scalp (Ahlfors et al., 2010). In addition, MEG studies of sensory processing migraine are still very scarce because of the few available MEG systems and experts in the world. Nevertheless, the few existing MEG studies appear to confirm results obtained using EEG (Chen et al., 2013; Korostenskaja et al., 2011). Further investigating migraine using MEG could provide new insights in migraine pathophysiology as it enables to localize precisely from which cortical areas functional alterations emerge.

It is still unclear if the sensory dysfunction in migraine is only rooted in alterations of "low-level" stages of sensory processing or if the impairment of cognitive processing of sensory inputs also plays a part. It has been established that poor cognitive performance is associated with migraine attacks and sometimes persists during the interictal period (Vuralli et al., 2018). During a passive auditory oddball task, enhanced amplitudes of the N1 orienting component (Morlet et al., 2014) and of the P3a (Demarquay et al., 2011) have been reported among migraineurs. These two ERPs have been associated with the involuntary orienting of attention (Näätänen and Picton, 1987; Polich, 2007). In the visual modality, migraineurs were also found to present a heightened involuntary attentional orienting, a decreased ability to suppress unattended stimuli in the periphery, and abnormalities in top-down attentional processes (Mickleborough et al., 2011a). This is corroborated by reports of self-perceived attentional difficulties by migraineurs (Carpenet et al., 2019; Lévêque et al., 2020; Sacks, 1992). Furthermore, some clinic-based studies using neurophysiological tests revealed that migraine had a moderate effect on attentional performances during the interictal period (reviewed in Vuralli et al., 2018). However, attention impairment was not consistently detected in clinical studies (Burker et al., 1989; Conlon and Humphreys, 2001; Koppen et al., 2011) and the precise attentional mechanisms altered in migraine remain to be characterized.

The present study aims to better characterize which attentional brain mechanism is potentially impaired in migraine. In a world saturated with sensory information, the allocation of our limited cognitive processing resources is guided by two main attentional processes. Top-down (or voluntary) attention enables to selectively attend stimuli which are relevant to our goals, and to filter out irrelevant stimuli. It operates through inhibitory and anticipatory mechanisms (Bidet-Caulet et al., 2010), underpinned by the dorsal attention network (Corbetta et al., 2000; Corbetta and Shulman, 2002) and reflected in EEG by specific ERPs such as the Contingent Negative Variation (CNV, Brunia and van Boxtel, 2001) or the Negative Difference (Nd, Alcaini et al., 1994a; Giard et al., 2000; Näätänen, 1982). As for bottom-up (or involuntary) attention, it is the ability to have our attention captured by unexpected salient events in one's environment. It is mediated by the ventral attention network (Corbetta et al., 2008; Corbetta and Shulman, 2002) and reflected in EEG by the ERPs such as the orienting component of the N1 and the P3a (orienting of the attention towards the unexpected stimulus, see Alcaini et al., 1994b; Escera et al., 2000; Simons et al., 2001; Yago et al., 2003) and the reorienting negativity (RON, reorienting of the attention back to the task at hand, see Munka and Berti, 2006; Schröger and Wolff, 1998a). Based on previous studies, we hypothesize that migraine is associated with exacerbated bottom-up and/or deficient top-down attention processes, resulting in the inability to filter out irrelevant information and possibly participating to the sensory disturbances associated with this disorder. To this day, very few electrophysiological studies (see above) have attempted to investigate attention in migraine.

Migraineurs and control participants were recruited to perform an adapted version of the Competitive Attention Task (Bidet-Caulet et al., 2015) while brain activity was monitored using EEG and MEG. This paradigm enables to conjointly evaluate top-down and bottom-up attention, using visually-cued target sounds and unexpected task-irrelevant distracting sounds. The Competitive Attention Task has been successful in investigating specifically both facets of attention in healthy young adults (Bidet-Caulet et al., 2015; ElShafei et al., 2018, 2020b; Masson and Bidet-Caulet, 2019), in children (Hoyer et al., 2019) and in the elderly population (ElShafei et al., 2020a). We focused on evaluating attention during the pain-free period in an attempt to detect long-term functional alterations, and not alterations contingently linked to the state of pain and distress associated with migraine attacks. Analyses of behavioral performances, event-related potentials, and event-related fields both at the sensor and source levels were conducted to detect any attention alterations in migraine. According to our aforementioned hypotheses, we posit that migraine participants may present during this task: (1) elevated markers of bottom-up attention such as an increased impact of distracting sounds on performances, exacerbated event-related responses to distracting sounds and intensified recruitment of the ventral attention network; (2) degraded markers of top-down attention such as a decreased ability to anticipate target stimuli, a lower magnitude of attention-related event-related responses (e.g. CNV, Nd) and a decreased recruitment of the dorsal attention network.

2. Materials and methods

2.1. Participants

Migraine with and without aura are postulated to be distinct clinical entities (e.g. Russell et al., 1996) and they present different patterns of electrophysiological abnormalities (Demarquay and Mauguière, 2016). Consequently, this study focuses on migraine without aura, the most common of the two subtypes of migraine. Several EEG studies have reported a normalization of electrophysiological markers of the interictal period of migraine during the peri-ictal period, a normalization which peaks during the migraine attack (Chen et al., 2009; Evers et al., 1999; Judit et al., 2000; Kropp and Gerber, 1995; Mulder et al., 1999). As we were interested in studying attention during the interictal state, if the patient had a migraine attack during the 72 hours before the testing session, the session was postponed to an ulterior date. If the patient had a migraine attack during the 72 hours after the session, collected data were not used in the analyses, as it is common practice in neuroimaging studies of migraine (Demarquay and Mauguière, 2016). Also, it was crucial to recruit participants who presented an attack frequency sufficiently low so they were unlikely to have a migraine attack just after our experiment (e.g. chronic migraine).

25 migraine patients (17 female, 8 male) suffering from migraine without aura were included in this study. Inclusion criteria were age between 18 and 60 years (Table 1) and have a diagnosis of migraine with a reported migraine frequency between 2 to 5 days per month. Exclusion criteria comprised migraine with aura, chronic migraine, and migraine preventive medication. Every patient was examined by a neurologist (GD, Hospices Civils de Lyon). Migraine patients filled out the Hospital Depression and Anxiety scale (Zigmond and Snaith, 1983), the HIT-6, a short questionnaire aiming to evaluate headache impact on everyday life (Kosinski et al., 2003) and the Migraine Disability Assessment Questionnaire (MIDAS) (Stewart et al., 1999). Data from 19 patients (13 female, 6 male) were usable in this study: data from 5 patients were discarded because a migraine attack happened in the 72 hours following the recording session and data from 1 patient because the patient failed to perform the task correctly.

19 control participants free of migraine and matched to the patients for sex, age, handedness, education level, and musical practice[2] were included in this study. Exclusion criteria for all subjects included a medical history of psychological or neurological disorders, ongoing background medical treatment other than contraceptive medication, pregnancy, and hearing disability. Data from 10 out of the 19 control participants have been also included in previous articles (ElShafei et al., 2020b, 2020a). All subjects gave written informed consent and received a monetary compensation for their participation.

2.2. Task and procedure

In order to evaluate attentional functions among our participants, we used Bidet-Caulet's Competitive Attention Test. Participants were asked to discriminate between a low-pitched and a high-pitched target sound and to respond as fast and as correct as possible using a joystick. Target sounds were monaural and were randomly presented either at the left or right side. A visual cue always appeared 1000 ms before the target sound onset.

Top-down attention was evaluated through modulation of the cue informational value (Fig. 1a). *Informative* cues (single arrow) allowed the participant to predict the side of the presentation of the target in order to respond faster and more correctly; *uninformative* cues (double arrow) did not give information on the side of presentation of the target sound.

Bottom-up attention was evaluated through the effects of distracting sounds (Fig. 1b). In 25% of the trials, a salient task-irrelevant binaural sound was played at some point between the cue offset and the target onset. If the distracting sound onset was early (50 ms to 350 ms after cue onset), the trial was categorized as *DIS1*; if the distracting sound onset was late (350 ms to 650 ms after cue onset), the trial was categorized as *DIS2*. In the 75% remaining trials, no distracting sound was played; trials were categorized as *NoDIS*.

For full details on the task and procedure, please see ElShafei et al., 2020b. For an in-depth discussion of the Competitive Attention Test, please see Bidet-Caulet et al., 2015 and Masson and Bidet-Caulet, 2019.

Table 1
Demographics and headache profile of the control and migraine groups. Two control participants did not filled the Hospital Anxiety and Depression (HAD) scale. Mean and standard deviation are provided. Group differences are tested using a non-parametric Mann-Whitney U test. NA: not applicable.

	Migraine	Control	p-value
Sample size	19	19	–
Age (years)	32.7 (8.7)	31.2 (7.8)	0.53
Sex (number of female participants)	13 (68%)	13 (68%)	–
Education level (years)	15.8 (3.1)	15.8 (2.2)	0.99
Musical practice (years)	2.8 (3.3)	2.8 (3.5)	0.74
Laterality (number of right-handed)	19	19	–
Anxiety score	5.7 (3.5)	4.6 (2.5)	0.42
Depression score	2.6 (2.6)	1.8 (2.0)	0.31
Migraine duration (years)	16.8 (7.4)	NA	–
HIT-6 score	64.2 (7.1)	NA	–
MIDAS score	12.8 (12.1)	NA	–

2.3. MEG and EEG recording and preprocessing

Simultaneous EEG and MEG data were recorded with a sampling rate of 600 Hz during task performance. A 275-channel whole-head axial gradiometer system (CTF-275 by VSM Medtech Inc., Vancouver, Canada) was used to record electromagnetic brain activity (0.016–150 Hz filter bandwidth and first-order spatial gradient noise cancellation). Head movements were continuously monitored using 3 coils placed at the nasion and the two preauricular points. EEG was recorded continuously from 7 scalp electrodes placed at frontal (Fz, FC1, FC2), central (Cz), and parietal (Pz) sites, and at the two mastoids (TP9, TP10). The reference electrode was placed on the tip of the nose, the ground electrode on the forehead. One bipolar EOG derivation was recorded from 2 electrodes placed on the supra-orbital ridge of the left eye and infra-orbital ridge of the right eye.

For each participant, a 3D MRI was obtained using a 3T Siemens Magnetom whole-body scanner (Erlangen, Germany), locations of the nasion and the two preauricular points were marked using fiducials markers. These images were used for reconstruction of individual head shapes to create forward models for the source reconstruction procedures (see part 2.6).

MEG and EEG data were processed offline using the software package for electrophysiological analysis (ELAN Pack) developed at the Lyon Neuroscience Research Center (Aguera et al., 2011).

MEG data was processed as followed: (1) Raw signals were band-stop-filtered between 47 and 53 Hz, 97 and 103 Hz, and 147 and 153 Hz (zero-phase shift Butterworth filter, order 3) to remove power-line artifacts. (2) An independent component analysis (ICA) was performed on MEG signals filtered between 0.1 and 40 Hz. (3) Component topographies and time courses were visually

[2] Pitch discrimination is required in the task described below, and is an ability increasing with musical practice.

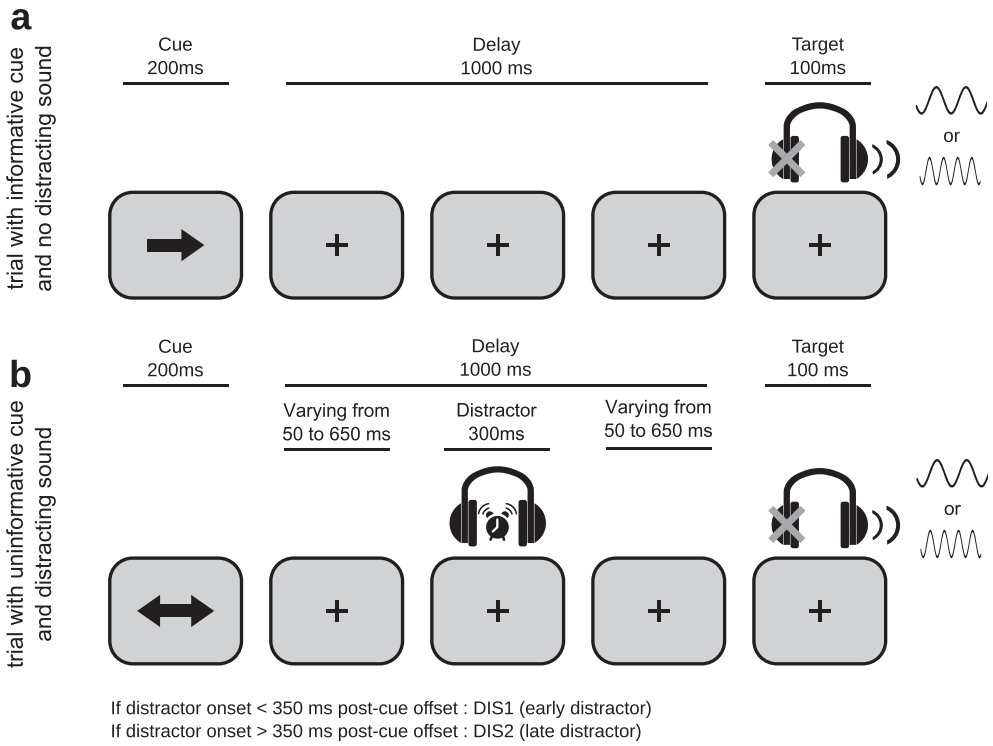

Fig. 1. Protocol. The task was to discriminate between a low- and a high-pitched sound, presented monaurally. A visual cue initiated the trial, and was either informative (50%) or non-informative (50%) about the target ear. 25% of the trials included a distracting sound. **(a)** Example of an *informative* trial with no distracting sound: a one-sided visual cue (200 ms duration) indicates in which ear (left or right) the target sound (100 ms duration) will be played after a fixed 1000 ms delay. **(b)** Example of an *uninformative* trial with a distracting sound: a two-sided visual cue (200 ms duration) does not provide any indication in which ear (left or right) the target sound will be played. The target sound can be a high- or low-pitched sound indifferently of the cue informational value. In 25% of all trials (with *informative* or *uninformative* cues), a loud binaural distracting sound (300 ms duration), such as a clock ring, is played during the cue-target interval at a random delay after the cue offset: the *DIS1* condition corresponds to early distracting sounds (starting 50–350 ms after cue offset), the *DIS2* condition corresponds to late distracting sounds (starting 350–650 ms after cue offset).

inspected to determine which components were to be removed (eye-movements and heartbeat artifacts) through an ICA inverse transformation. (4) The ICA inverse transformation was applied to the band-stop filtered MEG signals (resulting from step 1), 2 to 5 components were removed in each participant. (5) Trials contaminated with muscular activity or any other remaining artifacts were excluded automatically using a threshold of 2200 femtoTesla (maximum dynamic range allowed for the duration of a trial).

EEG data was processed as followed: (1) It was band-pass filtered between 0.1 and 40 Hz (zero-phase shift Butterworth filter, order 3). (2) Eye artifacts were removed from the EEG signal by applying a linear regression based on the EOG signal, because of the small number of recorded EEG channels which prevented to use ICA. (3) Trials contaminated with muscular activity or any other remaining artifacts were excluded automatically using a threshold of 150 microvolts (maximum dynamic range allowed for the duration of a trial).

Only trials for which the participant had answered correctly were retained. Trials for which the head position differed of more than 10 mm from the median position during the 10 blocks were also excluded from the analyses. For all participants, more than 80 % of trials remained in the analyses after rejection. Finally, both MEG and EEG data were band-pass filtered between 0.2 and 40 Hz (zero-phase shift Butterworth filter, order 3).

2.4. Event-related responses in the sensor space

Event-related fields (ERFs) and potentials (ERPs) were obtained by averaging filtered MEG and EEG data locked to each stimulus event: cue-related responses were locked to cue onset, target-related responses were locked to target onset, and distractor-related responses were locked to distractor onset. A baseline correction was applied based on the mean amplitude of the −100 to 0 ms period before the event. To analyze ERFs/ERPs to distracting sounds, for each distractor onset time-range, surrogate distractor ERFs/ERPs were created in the *NoDIS* trials and subtracted from the actual distractor ERFs/ERPs. The obtained distractor ERFs/ERPs were thus free of cue-related activity. Time-courses and topographies of ERFs/ERPs were plotted using ELAN software. Please note that regarding distractor-related responses, only responses to early distracting sounds (*DIS1*) were considered here in order to analyze late components unaffected by target-related responses.

2.5. Source localization of event-related fields

Conventional source reconstruction of MEG data was performed using the Statistical Parametric Mapping (SPM12) toolbox (Wellcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk/spm). Previously processed ERF data were converted in a SPM-compatible format. Regarding forward modelling, we considered a three-layer realistic Boundary Element Model (BEM), using canonical meshes provided with SPM12 (scalp, inner skull and cortical sheet) and warped to individual MRI to account for each participant anatomy (Mattout et al., 2007). Forward models were computed with the software OpenMEEG (OpenMEEG Software, https://openmeeg.github.io/, Gramfort et al., 2010). The estimation of sources was subsequently computed separately for each participant using a LORETA method (Pascual-Marqui et al., 2002), as implemented in SPM12. We performed inversions on the time-windows of interest defined using the time-courses of ERFs for each studied event (concatenation of conditions) (see Supplementary Figure A1). Regarding cue-related responses, we recon-

structed the contingent magnetic variation (CMV, 650–1200 ms post-cue onset). Regarding distractor-related responses, we reconstructed the magnetic N1 (N1m, 80–130 ms), the magnetic early-P3 (early-P3m, 200–250 ms), the magnetic late-P3 (late-P3m, 290–340 ms) and the magnetic reorienting negativity (RONm, 350 to 500 ms). Regarding target-related responses, we reconstructed the magnetic N1 (N1m, 70–150 ms) and the magnetic P300 (P3m, 250–400 ms).

2.6. Statistical analyses

2.6.1. Behavioral data

Trials with response before target (false alarm, FA), trials with incorrect responses and trials with no response after target onset and before the next cue onset (miss) were discarded. Percentages of correct responses and median reaction-times (RTs) in the correct trials were computed for each participant and were submitted to three-way repeated-measures ANOVA (rmANOVAs) with CUE category (2 levels: *uninformative, informative*) and DISTRACTOR condition (3 levels: *NoDIS, DIS1, DIS2*) as within-subject factors and GROUP category (2 levels: *controls*, *migraineurs*) as a between-subject factor. To correct for possible violations of the sphericity assumption, Greenhouse-Geisser correction was applied to resulting p-values. Post-hoc comparisons were conducted using t-tests followed by a Bonferroni correction. Statistical analyses were conducted using the software JASP (version 0.9).

2.6.2. ERP – Sensor-level data

For each ERPs, every sample in each electrode within a time-window of interest (650–1200 ms for cue-related ERPs, 0–650 ms for distractor-related ERPs, and 0–500 ms for target-related ERPs) was submitted to a two-way repeated-measures ANOVA (rmANOVAs) with CUE category (2 levels: *uninformative, informative*) as a within-subject factor and GROUP category (2 levels: *controls*, *migraineurs*) as a between-subject factor. Effects were considered significant if p-values remained lower than 0.05 over a 15 ms interval (corresponding to 9 consecutive samples, see Guthrie and Buchwald, 1991).

In case of a GROUP by CUE interaction, post-hoc unpaired t-tests were performed to assess group difference on the ERP difference *informative* minus *uninformative,* for every sample within the time-windows that had been found significant with the rmANOVA. Again, effects were considered significant if p-values remained lower than 0.05 over a 15 ms interval (corresponding to 9 consecutive samples).

2.6.3. ERF – source-level data

All statistical analyses regarding the activity of cortical sources were conducted using built-in statistical tools in SPM12. To investigate the GROUP and CUE main effects and the CUE by GROUP interaction, a two-way repeated-measure ANOVA was conducted on the value of source activity for each and every cortical vertex. Significance threshold was 0.05 at the cluster level (p-values corrected for family-wise error, cluster forming threshold = 0.05). In order to correct for multiple testing (as several time-windows are inspected, see 2.5 above), a subsequent Bonferroni correction has been applied.

3. Results

Demographics and results of the HAD, HIT-6 and MIDAS questionnaires are displayed in Table 1. The control and migraine group did not significantly differ in terms of age, education, musical education, anxiety and depression scores (all $p > 0.3$). The control and migraine group did not significantly differ in terms of the pitch difference between the two target sounds (Control & Migraineurs: 1.4 ± 0.2 semi-tones, Controls: 1.4 ± 0.2 semi-tones).

3.1. Behavior

Behavioral data are depicted Fig. 2. Participants responded correctly in 95.2% of trials. Remaining trials were either incorrect responses (4.3%), false alarms (0.3%) or misses (0.1%).

The two groups did not significantly differ in terms of percentage of correct responses (Migraineurs: 94.2 ± 1.0%, Controls: 95.4 ± 0.7%, $F_{1,36} = 0.92$, $p = 0.34$). The percentage of correct responses was not found significantly modulated by the CUE category ($F_{1,36} = 1.8$, $p = 0.18$). The DIS category significantly modulated the percentage of correct responses ($F_{2,72} = 4.8$, $\varepsilon = 0.99$, $p = 0.011$), with a significant decrease in the *DIS2* condition (93.8% ± 0.8%) compared to the *NoDIS* condition (95.5% ± 0.6%, $p = 0.006$), and a marginal decrease compared to the DIS1 condition (95.2% ± 0.7%, $p = 0.028$ – does not resist to Bonferroni correction). No interaction effect was found significant (all $p > 0.25$).

Concerning the median reaction times, both groups did not significantly differ in their performances (Migraineurs: 515 ± 11 ms, Controls: 520 ± 11 ms, $F_{1,36} = 0.013$, $p = 0.91$). A significant main effect of CUE ($F_{1,36} = 16.1$, $p < 0.001$) was observed with participants responding faster in the *informative* condition than in the *uninformative* condition. A significant main effect of DISTRACTOR ($F_{2,72} = 43.8$, $\varepsilon = 0.69$, $p < 0.001$) was observed with participants responding faster in trials with an early distracting sound (*DIS1*) ($p < 0.001$) and slower in trials with a late distracting sound (*DIS2*) ($p = 0.001$) compared to trials without distracting sound (*NoDIS*) (for information, *DIS1* vs. *DIS2*, $p < 0.001$). No interaction effect was found significant (all $p > 0.5$).

3.2. Event-related responses

3.2.1. Cue-related responses

Regarding source reconstruction, for every time-window of interest, inversions resulted in an explained variance superior to 95% (average across the 38 participants).

In response to visual cues (Fig. 3), participants presented occipital ERPs (obligatory visual ERPs) followed by a fronto-central slow negative wave, the contingent negative variation (CNV), which slowly builds up from around 650 ms to 1200 ms post-cue (corresponding to the target onset). The magnetic counterpart of the CNV, the CMV, was visible at the same latencies (Supplementary Figure A1). The time-window of interest for subsequent analyses was 650–1200 ms post-cue onset.

In EEG sensor-level data, neither GROUP nor CUE main effect nor CUE by GROUP interaction were found significant during the time-window of interest.

In MEG source-related data, no GROUP main effect was found significant during the CMV (650–1200 ms). Regarding the CUE main effect, a larger activation of the left occipital, motor and frontal cortices, the bilateral temporo-parietal junctions, and the right parietal and temporal cortices (Brodmann area (BA) 6, 19, 22, 39, 44) was found for *informative* trials compared to *uninformative* trials (Supplementary Figure A2). Regarding the GROUP by CUE interaction effect, the effect of the cue information (*informative* – *uninformative*) was stronger among migraineurs in a cluster including right associative visual areas (BA 7, 19).

3.2.2. Distractor-related responses

In response to distracting sounds (Fig. 4), participants presented an expected sequence of ERPs. It includes the fronto-central N1, the fronto-central early-P3 (~270 ms), the fronto-parietal late-P3 (~330 ms) and the frontal reorienting negativity (RON, ~410 ms). The fronto-central N1 comprises two subcomponents: the sensory

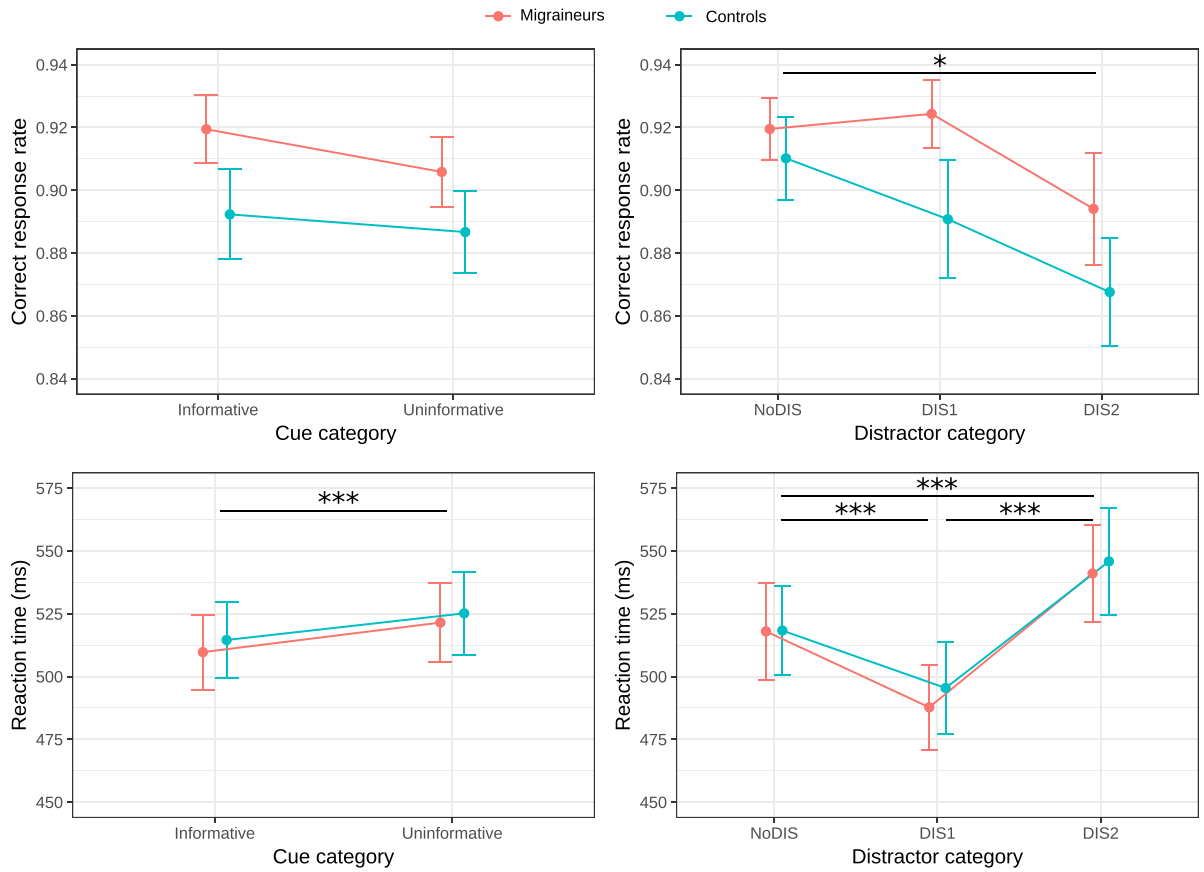

Fig. 2. Behavioral results. Mean correct response rate (top) and mean reaction times in milliseconds (bottom) to the target as a function of the GROUP (migraineurs or controls), and as a function of (left) the CUE category (*informative, uninformative*) or (right) the DISTRACTOR category (*NoDIS, DIS1 and DIS2*). ***: $p < 0.001$, *: $p < 0.05$, error bars represent the standard error of the mean.

component of N1 (~95 ms, with polarity inversion at the mastoids) and the orienting component of the N1 (~130 ms, with no polarity inversion at the mastoids). Their magnetic counterparts, respectively labelled in the following as N1m, early-P3m, late-P3m and RONm, were visible at similar latencies (Supplementary Figure A1).

In EEG data, the orienting component of the N1 (138–153 ms) and the RON (440–487 ms then 572–590 ms) were found significantly larger in migraineurs than in controls at Fz. A non-significant trend towards a decreased early-P3 in migraine could be observed. The GROUP by CUE interaction was significant on FC1 in the P50 latency range, prior to the N1 (38–60 ms). Post-hoc analyses confirmed that migraineurs show an increased cueing effect (*informative – uninformative*) during those latencies, with a more positive deflection in *uninformative* trials compared to the control group. Regarding the CUE main effect, during the first 150 ms and during the RON from 380 to 550 ms, responses were found significantly more negative in *informative* trials than in *uninformative* trials at fronto-central electrodes.

In MEG source-related data, at the latencies of the early-P3m (200–250 ms), migraineurs presented an increased cueing effect (*informative – uninformative*) in the left superior and middle temporal gyri (BA 21, 22). At the latencies of the RONm (350–500 ms), migraineurs presented a greater activation of the right angular gyrus (BA 39) which is part of the right temporo-parietal junction (rTPJ), and an increased cueing effect (*informative – uninformative*) in the right dorsolateral prefrontal cortex (BA 9), right frontal eyes fields (BA 8) and right superior parietal lobule and motor cortex (BA 4, 7).

3.2.3. Target-related responses

In response to target sounds (Figs. 5 and 6), in terms of ERPs, participants presented a fronto-central N1 composed of the sensory component of N1 (~95 ms) and the orienting component of the N1 (~130 ms), followed by a parietal P300 (after 250 ms). Their magnetic counterparts, respectively labelled in the following as N1m and P3m, were observed at similar latencies (Supplementary Figure A1).

In EEG data, the orienting component of the N1 on frontal electrodes (Fz, FC1, and FC2) was found larger in migraineurs than in controls (around 130 ms). The GROUP by CUE interaction was significant on fronto-central electrodes around 125 ms and 300 ms (with a significant CUE main effect between 278 and 317 ms at FC2). Difference ERPs (*informative – uninformative*, see Fig. 6) showed that contrary to controls participants, migraineurs displayed a frontal negative wave (Negative difference, Nd) comprising two mains peaks (~130 ms and ~300 ms). Post-hoc analyses showed that these two negatives peaks were significantly more negative among migraineurs on frontal electrodes (Fz, FC1, and FC2).

In MEG source-related data, at the latencies of the N1m (70–150 ms), migraineurs presented a larger activation of the right operculum (BA 40). At the latencies of the P3m (250–400 ms), migraineurs presented a larger activation of the right TPJ. Moreover, at the same latencies, a larger activation of the right frontal cortex (BA 9, 47) and of a cluster comprising the right angular gyrus and right occipital gyri (BA 7, 39) was found significant in uninformative trials compared to informative trials (Supplementary Figure A2).

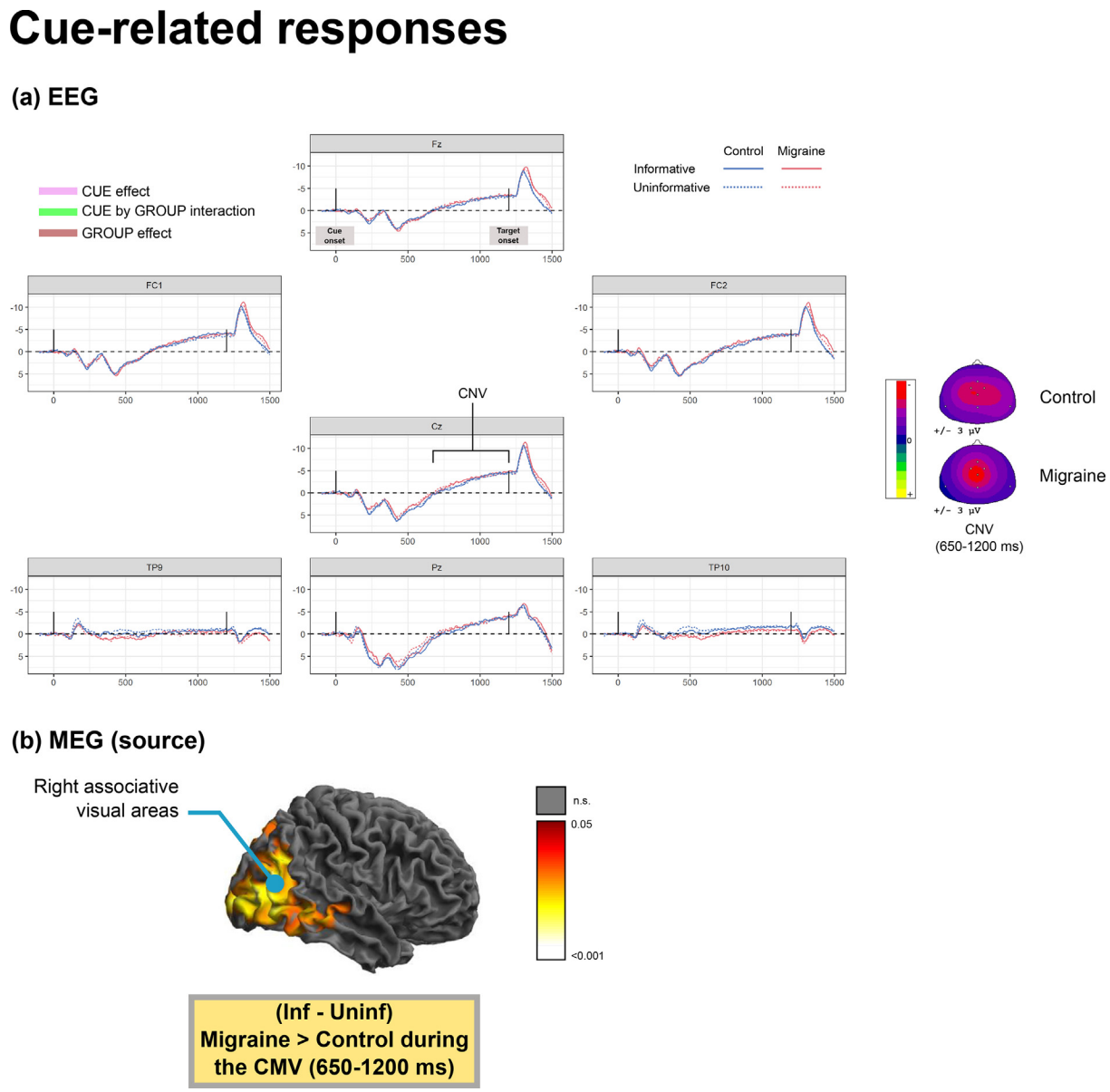

Fig. 3. **(a)** Event-related potentials (ERPs) in response to the visual cues as a function of the cue category (informative or uninformative, plain vs. dashed lines) and the group (control or migraine, blue vs. red lines). Time-courses are presented for all EEG sensors. Scalp topographies of the main cue-related responses are presented on the right. The first vertical bar corresponds to the cue onset, the second to the target onset. Statistical analysis of the ERPs during the contingent negative variation (CNV) time-window (650–1200 ms after cue onset) showed no significant effect. **(b)** P-value map (masked for corrected $p < 0.05$, the whiter the more significant) of the pattern of increased cueing effect on brain activation (source-reconstructed MEG data) in the migraine group during the contingent magnetic variation (CMV) time-window (650–1200 ms).

4. Discussion

Attention in migraine was investigated here using complementary methods. Behavioral data provided us three independent measures of top-down attention, bottom-up attention and phasic arousal in both the patient and control groups. Event-related potentials and fields provided complementary information on brain dynamics. On the one hand, EEG data helped to identify precisely which attentional process is potentially dysfunctional in migraine as event-related potentials (ERPs) to distractor, target and cue stimuli are particularly well-described in the literature (e.g. Brunia and van Boxtel, 2001; Näätänen and Picton, 1987; Polich, 2007). However, EEG has a poor spatial resolution which hinders precise cortical localization of functional alterations (especially when the number of electrodes is low). On the other hand, description and interpretation of event-related fields (ERFs) is less developed than their EEG counterparts. However, MEG data, thanks to its superior spatial resolution (and its equally high temporal resolution) (Hämäläinen et al., 1993), enabled through source reconstruction to pinpoint some of the cortical correlates underlying those alterations. If no behavioral differences were observable between migraineurs and healthy participants, migraine was here associated with elevated responses following distracting sounds (orienting component of the N1 and Re-Orienting Negativity, RON) and following target sounds (orienting component of the N1), conjoined with an increased recruitment of the right temporo-parietal junction. In addition, migraineurs presented an increased effect of the cue informational value on target processing resulting in the elicitation of a negative difference (Nd).

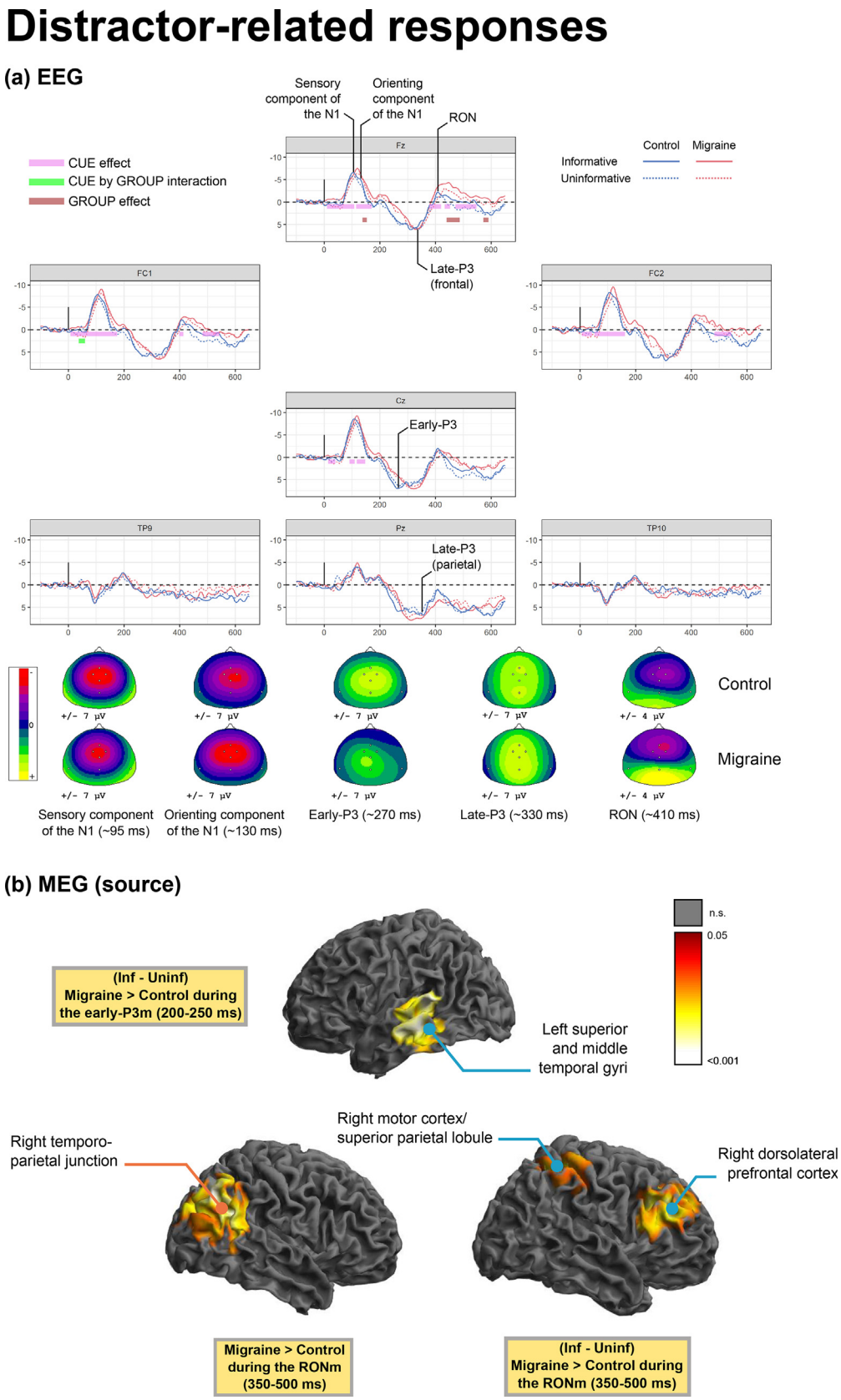

Fig. 4. **(a)** Event-related potentials (ERPs) in response to the distracting sounds as a function of the cue category (*informative* or *uninformative*, plain vs. dashed lines) and the group (control or migraine, blue vs. red lines). Time-courses are presented for all EEG sensors. Scalp topographies of the main distractor-related responses are presented below time-courses. GROUP by CUE repeated-measures ANOVA (rmANOVA) was applied to ERPs: significant effects ($p < 0.05$ over 15 consecutive ms) correspond to the colored boxes. **(b)** P-value map (masked for corrected $p < 0.05$, the whiter the more significant) of the pattern of increased brain activation in the migraine group during the magnetic reorienting negativity (RONm) time-window (350–500 ms) and the patterns of increased cueing effect on brain activation in the migraine group during the early-P3m (200–250 ms) and the RONm time-windows.

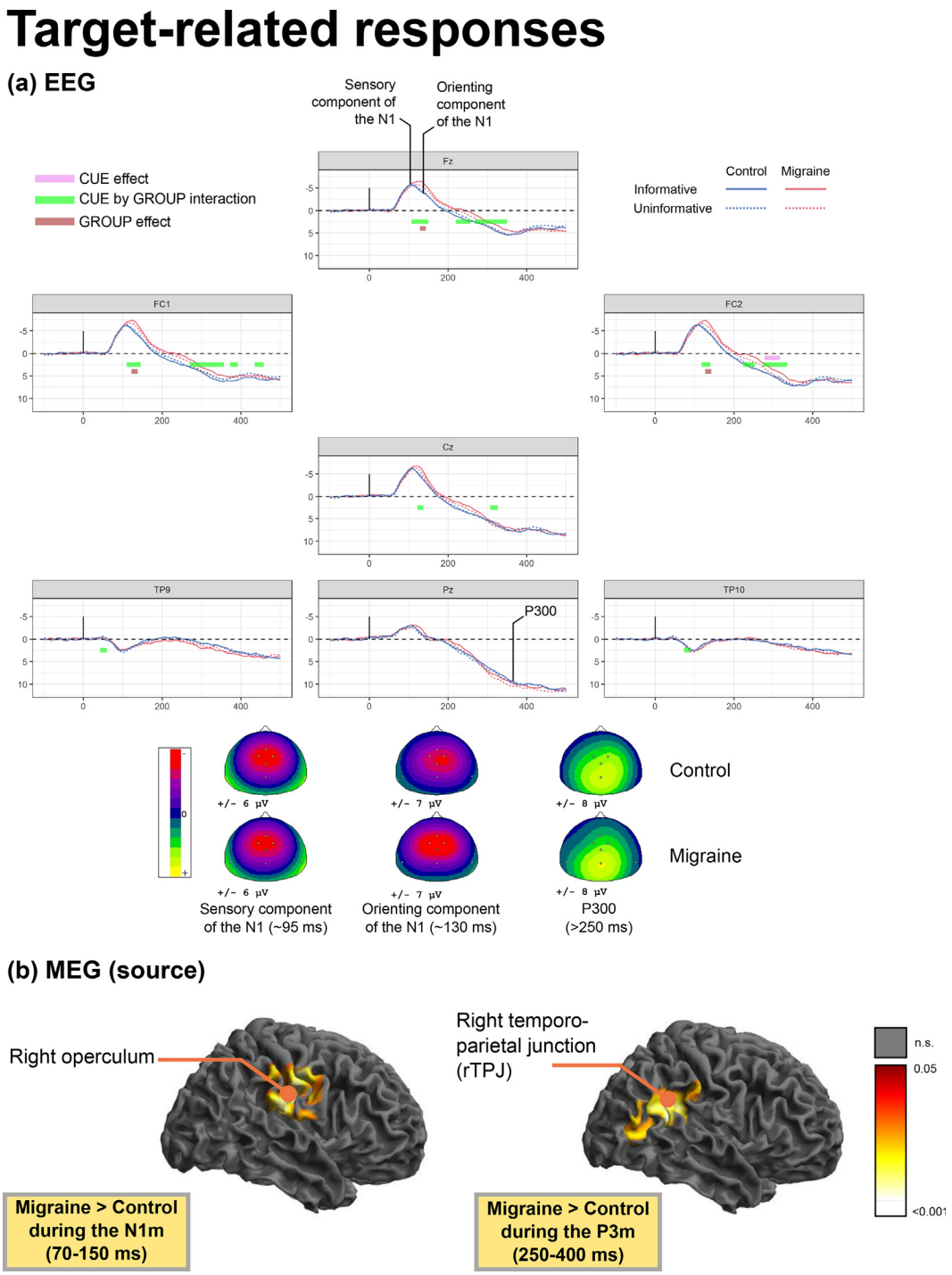

Fig. 5. **(a)** Event-related potentials (ERPs) in response to the target sounds as a function of the cue category (informative or uninformative, plain vs. dashed lines) and the group (control or migraine, blue vs. red lines). All EEG sensors are presented. Scalp topographies of the main target-related responses are presented below time-courses. GROUP by CUE repeated-measures ANOVA (rmANOVA) was applied to ERPs: significant effects ($p < 0.05$ over 15 consecutive ms) correspond to the colored boxes. **(b)** P-value map (masked for corrected $p < 0.05$, the whiter the more significant) of the pattern of increased brain activation in the migraine group during the N1m and P3m time-window (respectively 70–150 ms and 250–400 ms).

4.1. Exacerbated bottom-up attentional effects in migraine

In both participant groups, distracting sounds had opposite behavioral effects depending on the distractor-target interval. Early distracting sounds (*DIS1*) decreased reaction times compared to the condition without distractor (*NoDIS*). This facilitation effect has been previously interpreted as an increase in phasic arousal which improves readiness to respond to any incoming stimulus (Bidet-Caulet et al., 2015; Masson and Bidet-Caulet, 2019). However, late distracting sounds (*DIS2*) resulted in a deterioration of performances (increase of reaction times) compared to early distracting sounds (*DIS1*). This has been previously interpreted as the transient effect of attentional capture by the distracting sound (Bidet-Caulet et al., 2015; Masson and Bidet-Caulet, 2019). Both

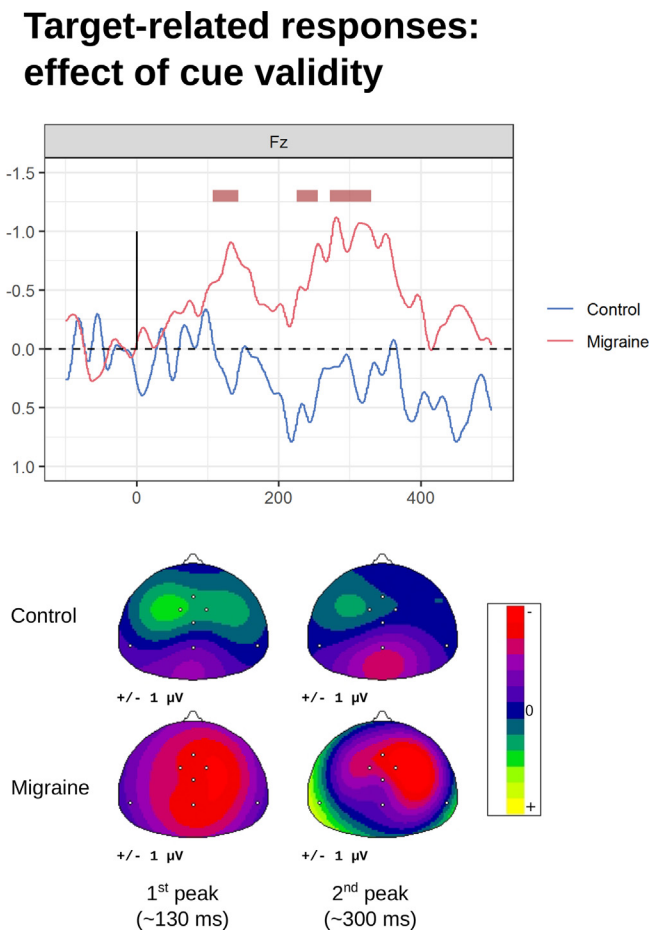

Fig. 6. Difference event-related potentials (ERPs) in response to the target (*informative* minus *uninformative* trials), only Fz is presented here. Significant group effects ($p < 0.05$ over 15 consecutive ms) correspond to the brown boxes. Please note the two peaks of the negative difference (Nd) present in the migraine group but absent for the control group.

"attention capture" and "phasic arousal" effects have been shown to be independent from the sensory modalities of the cue and target stimulus.

There is no observable evidence that the attentional capture and arousal effects of the distracting sounds were different among migraineurs compared to control participants at the behavioral level. This result is in line with a previous study finding no increased impact over performance of visual distractors during a visual cueing task in migraine (Mickleborough et al., 2016).

However, at the cortical level, migraineurs presented an increased orienting component of the N1 to distracting sounds while the sensory component remained unaltered. The orienting component of the N1 corresponds to the orienting component III described by Näätänen and Picton (Näätänen and Picton, 1987) and is only elicited by infrequent stimuli (Alcaini et al., 1994b). It follows the obligatory sensory component of the N1 and it is considered to be linked to the orienting response to unexpected incoming stimuli (Alcaini et al., 1994b). Increased N1 has been previously reported in migraine interictally (Sable et al., 2017) and also specifically its orienting component (Demarquay et al., 2011; Morlet et al., 2014). These results suggest that the orienting response to distractors is increased in migraine. Unaltered sensory component of the N1 (or earlier responses such as the P50) to the distractor or the target sound argues against an early dysfunctional sensory gating in migraine.

The reorienting negativity (RON) was also increased among migraineurs. The RON is considered to reflect the reorienting of attention towards task-relevant stimuli after distraction (Munka and Berti, 2006; Schröger and Wolff, 1998b) but the exact cognitive function of this response is still a matter of debate (Horváth et al., 2008). Source reconstruction of MEG data during the RONm time-window revealed an increased activation of the right temporo-parietal junction (rTPJ) in migraineurs. The rTPJ is part of the ventral attentional network considered to be implicated in stimulus-driven attentional control (for a review, see Corbetta and Shulman, 2002) and is activated by salient unexpected sounds (Salmi et al., 2009). Therefore, enhanced rTPJ activation could reflect an exacerbated bottom-up attentional capture by the distracting sounds in migraine. The rTPJ has also been proposed to play a crucial role in both voluntary and involuntary shifts of attention (Corbetta et al., 2008). In this line, its increased recruitment could also be the necessary consequence of a disproportionate orienting response towards the distracting sound which calls for a more powerful reorientation process towards the task.

Migraineurs also presented an increased orienting component of the N1 to target sounds compared to control participants. Target sounds appear to induce strong orientation responses in migraineurs despite their predictability and low salience. This is consistent with a previous auditory oddball study which reported increased orienting component of the N1 in migraine even for standard sounds (Morlet et al., 2014). Moreover, an increased activation of the rTPJ in migraine could be observed during the P300m time-window, confirming the exacerbation of the orienting response towards target sounds among migraineurs.

These results suggest that migraineurs present an increased orienting response towards both expected relevant and unexpected irrelevant sounds, indicating exacerbated bottom-up attentional processes in migraine. This effect would be mediated, at least in part, by the increased recruitment of the rTPJ, a major node of the ventral attention network (Corbetta and Shulman, 2002). Using fMRI, atypical activation during a visual task (Mickleborough et al., 2016) and functional connectivity profile (Lisicki et al., 2018b, 2018a) of the rTPJ were found in migraine.

4.2. Increased top-down attentional effects in migraineurs

Participants responded faster when the visual cue was informative of the auditory target location, in agreement with previous studies using the Competitive Attention Task (Bidet-Caulet et al., 2015; ElShafei et al., 2018). This effect has been considered to reflect enhanced anticipatory attention and has been shown to be independent from the sensory modality of the cue or the target stimulus (Masson and Bidet-Caulet, 2019).

The effect of the cue informational value on reaction times was not significantly different between the migraine and the control groups, suggesting no difference in top-down attention at the behavioral level in migraine using this paradigm. To our knowledge, three publications have investigated top-down attention in migraine using visual cueing tasks. None of them observed that migraineurs had a greater top-down attentional enhancement in valid cue trials, which is consistent with our results (Mickleborough et al., 2016, 2011a, 2011b). However, at the cortical level, differences in top-down attentional processes were observed between control participants and migraineurs. During target-related responses, the migraineurs presented a frontal slow negative wave in *informative* trials compared to *uninformative* trials, unlike control participants. This resembles the negative difference (Nd), also referred to as the processing negativity (PN). The Nd has been associated with the active selection of relevant information (Alcaini et al., 1994a; Giard et al., 2000; Näätänen, 1982), sug-

gesting enhanced recruitment of voluntary attention in migraineurs.

Moreover, the effect of the cue information was found more pronounced among migraineurs in visual association areas during the CMV preceding targets and in temporal areas during the early-P3m to distracting sounds. Interestingly, a similar effect was found during the RONm to distractors in the dorsolateral prefrontal cortex and the superior parietal lobule, two major nodes of the dorsal attentional network implicated in voluntary top-down attention (Corbetta et al., 2000; Corbetta and Shulman, 2002).

However, no clear evidence of an increased CNV/CMV in migraine could be found using this paradigm. The CNV reflects both attentional anticipation and motor preparation to an imperative stimulus (for a review on the CNV, see Brunia and van Boxtel, 2001, for the CMV, see Elbert et al., 1994; Gómez et al., 2004). These results are inconsistent with previous studies which considered that a wider CNV is a clinical marker of migraine (Kropp et al., 2015; Kropp and Gerber, 1995, 1993; Schoenen and Timsit-Berthier, 1993), which correlates with disease duration (Kropp et al., 2015, 2000) and fails to habituate (Kropp et al., 2015; Siniatchkin et al., 2003). This discrepancy could result from differences in the methods. Previous studies used a simple protocol with a warning signal and an imperative stimulus, separated by a 3-second inter-stimulus interval (while we used here only a one second delay), and the tasks only required motor preparation (while here also attentional processes were at play during the anticipation period).

These results suggest that migraineurs engaged more top-down attentional processes during target processing and anticipation, but also during distractor processing, compared to control participants.

4.3. Attention dysfunction in migraine

We hypothesized that migraine is associated with exacerbated bottom-up and/or deficient top-down attention processes, resulting in increased responsiveness to irrelevant information. In consideration of the present data, the reality appears more complex than our hypothesis:

(1) Increased brain responses to target and distracting sounds do suggest that the orienting response to attended and unattended sounds is exacerbated in migraine. This is quite consistent with anecdotal reports from migraineurs where they mention being easily distracted by their environment (Sacks, 1992). Migraineurs report higher self-perceived levels of attention difficulty than healthy controls (Carpenet et al., 2019; Lévêque et al., 2020). It is noteworthy that there exists a comorbidity of migraine with attention deficit and hyperactivity disorder (ADHD) (Fasmer et al., 2012; Paolino et al., 2015; Salem et al., 2017).

(2) However, at the behavioral level, contrary to our hypothesis, distracting sounds did not have a more pronounced effect on performance in migraine, nor did *informative* cues have a weaker effect in migraineurs. Literature about cognition and attention in migraine is quite contrasted. Neuropsychological evaluations of migraine patients in the literature did not report any major cognitive impairment during the interictal period (Gil-Gouveia et al., 2016; Pearson et al., 2006) but some psychometric tests have linked migraine with diverse minor cognitive alterations (Annovazzi et al., 2004; Calandre et al., 2002; Hooker and Raskin, 1986; Mongini et al., 2005; Zeitlin and Oddy, 1984). Attention in general has been investigated in migraine using specific psychometric tests (for a review, see Vuralli et al., 2018): some studies did not find any interictal attentional alterations in adults (Burker et al., 1989; Conlon and Humphreys, 2001; Koppen et al., 2011); while others have reported moderate impairment of attention during the interictal state (Mulder et al., 1999; Pellegrino Baena et al., 2018; Pira et al., 2000). Conflicting findings in the literature about attention in migraine could be explained by (a) the wide range of psychometrics tests used in the aforementioned studies suggesting that the precise cognitive and attentional processes investigated may vary from study to study, (b) the magnitude of attentional alterations in migraine might be small to moderate.

(3) Finally, top-down effects were found increased in migraine as evidenced by event-related potentials and source reconstruction. To our knowledge, increased top-down attentional effects have never been reported in past articles, whether these consisted in behavioral or neuroimaging studies. During attention tasks, migraineurs show either worse or equal performances compared to healthy participants (Vuralli et al., 2018). The present results do not necessarily suggest that migraineurs have superior, more effective top-down attentional mechanisms: they more likely reflect that, in the context of our task, migraineurs have voluntarily engaged more attentional resources in order to be task-efficient.

A good balance between top-down and bottom-up attention is essential to remain task-efficient while still being aware of one's own environment. The stronger involvement of top-down attentional functions may be seen as a compensatory strategy that migraineurs have developed to cope with heightened bottom-up orienting responses for each and every incoming sound. An increased recruitment of top-down attention would maintain the top-down/bottom-up balance at an operational state, preventing any behavioral impairment. However, it is likely that maintaining such an equilibrium in migraine would be costlier in terms of cognitive resources.

What are the implications of such attentional dysfunctions to the pathophysiology of migraine, and especially to sensory symptoms? The association between attentional difficulties and interictal hypersensitivity in migraine has been validated by a recent questionnaire study from our lab (Lévêque et al., 2020). Several explanations might account for the observed relationship between attention difficulties and sensory hypersensitivity in migraine. Lévêque and colleagues (Lévêque et al., 2020) proposed three hypotheses to explain this relationship. (1) Sensory hypersensitivity would be caused, at least partially, by attentional difficulties linked to migraine: increased bottom-up attention in migraine could lead to sensory overload, as inputs from the environment trigger an orienting response regardless of their actual relevance. (2) Attentional difficulties may be caused by an increased sensitivity to environmental stimuli: sensory amplification associated to migraine would exacerbate attention capture by external stimulation and therefore would produce attention difficulties in the everyday life. (3) Both hypersensitivity and attention alterations would emerge from one's predisposition to develop migraine: neurochemical imbalances at the core of the migraine pathophysiology might be the source of both dysfunctions. Future studies should aim at exploring the causal links between attention, cognitive load and hypersensitivity in migraine, at cortical and sub-cortical levels. Finally, the knowledge that migraine is associated to disturbed attentional processes may help to shape future recommendation towards migraineurs for the management of their sensory symptoms.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding the subject matter of this article.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.05.024.

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2.4 Article 4: Top-down inhibition of irrelevant information indexed by alpha rhythms is disrupted in migraine

Top-down inhibition of irrelevant information indexed by alpha rhythms is disrupted in migraine

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ABSTRACT

There is growing evidence that migraine is associated with an abnormal attention function both during and outside migraine attacks, which would impact the cognitive processing of sensory stimulation. However, these attentional alterations are poorly characterized and their neurophysiological basis is still unclear. Nineteen migraineurs without aura and nineteen healthy participants were recruited to perform a task which used visually-cued auditory targets and distracting sounds to evaluate conjointly top-down and bottom-up attention mechanisms.Magnetoencephalography (MEG) signals were recorded. We investigated top-down attention via the analysis of alpha rhythms during the target anticipation period and bottom-up attention via the analysis of gamma rhythms induced by distracting sounds. Compared to healthy participants, migraineurs presented a significantly less prominent alpha increase in visual areas in anticipation of the auditory target. However, there was no significant group difference regarding the alpha decrease in the auditory cortices in anticipation of the target, nor regarding the distractor-induced gamma increase in the ventral attention network. These results suggest that top-down inhibitory processes are deficient in migraine but there is no clear evidence supporting a disruption of top-down facilitatory attentional processes or of bottom-up attention capture. This relative inability to suppress irrelevant sensory information may be underlying the self-reported increased distractibility and the sensory disturbances in migraine.

Keywords: Migraine, MEG, Alpha rhythms, Gamma rhythms, Attention, Distraction

1 Introduction

If headache is undoubtedly its most prominent symptom, migraine is also at its core a sensory processing disorder [21,34]. Migraine attacks are associated to an aversion to external stimulation across all sensory modalities (photophobia, phonophobia, osmophobia and allodynia) [5,25,43,51,91,98] and this hypersensitivity persists even in the attack-free period, but to a lesser extent [55,91,92] The most prominent model to explain these sensory disturbances, particularly during the interictal state, has been the migraineurs' brain habituation deficits [17,87]. Lack of habituation of EEG responses to repeated non-noxious stimulation has been one of the most reported functional abnormalities associated to the interictal state in migraine. However, in the last decade, converging pieces of evidence have suggested that dysfunctional attention processing of sensory inputs may also participate in the migraine hypersensitivity, especially during the attack-free period. Migraineurs display increased electrophysiological markers of attention orienting to incoming stimuli [20,59,62,65] and the functioning of the right temporo-parietal junction (rTPJ), an area involved in involuntary attention orienting [19], has been shown to be disrupted in migraine [52,53,59,61]. Migraineurs self-reported attention difficulties in everyday life [15,50] and these difficulties correlate with multimodal sensory sensibility between headaches [50]. A deficient attention filter may lead to an abnormal management of sensory inputs, exposing migraineurs to a state of hyper-responsiveness.

The brain relies on a balance between top-down and bottom-up attentional processes to select relevant information in an environment rich in sources of sensory stimulation. Top-down (TD) attention is voluntary and goal-oriented: it promotes the processing of task-relevant information through facilitatory mechanisms and suppresses the processing of irrelevant information through inhibitory mechanisms [11,12,33,40]. Bottom-up (BU) attention is involuntary and stimulus-driven: its role is to maintain responsiveness to unexpected but meaningful events through automatic attention shifts that override goal-directed processes [18,29,66]. It is still unclear which attentional mechanisms are actually altered in migraine. Investigating brain rhythms could shed light on the matter as they are a particularly useful tool to investigate both top-down and bottom-up attention, particularly alpha and gamma rhythms. Alpha rhythms (7-15 Hz) are considered to reflect functional inhibition of the cortical areas from which they are generated [41,45] and have been proposed to reflect the neural substrate of top-down facilitatory and inhibitory mechanisms [26,31]. On the other hand, gamma rhythms (>30 Hz) reflect the activation

of the cortical areas from which they are generated [8] and have been consistently associated with feedforward pathways directing information from primary sensory areas to associative areas [9,44]. They are proposed to be the manifestation of bottom-up attention processes [28,31].

In the present article, we recorded magnetoencephalography (MEG) signals during an attention task evaluating conjointly top-down and bottom-up attention in order to better understand the physiological underpinnings of the attention difficulties associated to migraine. We expect that: (1) altered top-down attentional processes would translate into deficient modulation of alpha power during target anticipation in relevant and irrelevant sensory areas; (2) exacerbated bottom-up attentional processes would translate into enhanced distractor-induced gamma activity.

2 Material and methods

The present study makes use of the same dataset than Masson et al. (2020) [59]. The task, procedure and preprocessing of MEG data remain identical. Data from 10 control participants are also part of the study presented in Elshafei et al. (2019) [28].

2.1 Participants

25 migraine patients (17 female, 8 male) suffering from migraine without aura were included in this study. Inclusion criteria were age between 18 and 60 years and have a diagnosis of migraine with a reported migraine frequency between 2 to 5 days per month. Exclusion criteria for patients comprised migraine with aura, chronic migraine, and migraine preventive medication. Every patient was examined by a neurologist (GD, Hospices Civils de Lyon). As we were interested in studying attention during the interictal state, if the patient had a migraine attack during the 72 hours before the testing session, the session was postponed to an ulterior date. If the patient had a migraine attack during the 72 hours after the session, collected data were not used in the analyses, as it is common practice in neuroimaging studies of migraine [21]. Data from 19 patients (13 female, 6 male) were analyzed: data from 5 patients were discarded because a migraine attack happened in the 72 hours following the recording session and data from 1 patient because the patient failed to perform the task correctly. Migraine participants filled the HIT-6 and the MIDAS scales to assess the severity of the disease [46,85].

19 control participants free of migraine and matched to the patients for sex, age, laterality, education level, and musical practice[1] were included in this study. Exclusion criteria for all subjects included a medical history of psychiatric or neurological disorder except migraine, ongoing

1 Pitch discrimination is required in the task described below, and is an ability increasing with musical practice.

background medical treatment other than contraceptive medication, pregnancy, and hearing disability. All subjects gave written informed consent and received a monetary compensation for their participation. Migraine, especially in chronic forms of the disease, is often associated with increased anxiety and depression [22,47,94]. Participants filled the Hospital Anxiety and Depression scale [99] in order to verify that anxiety and/or depression were not confounding variables. All demographic statistics can be found in Table 1.

2.2 Task and procedure (Figure 1)

75 % of the trials consisted in a visual cue (200 ms duration) followed after a 1000 ms delay by an auditory target (100 ms duration with 5 ms rise and fall times). The cue was centrally presented on a screen (gray background) and could be a green arrow pointing to the left, to the right, or to both sides. Left and right cues (*informative*) informed the participant in which ear the target sound will be played, while "both sides" cues (*uninformative*) did not inform of the side of target presentation. ~~The informational value of the cue has not been investigated in the present study.~~ The target sounds were monaural pure sounds presented at 25 dB SL. The low-pitched target sound had a fundamental frequency of 512 Hz, the high-pitched target was 1 semi-tone higher than the low-pitched sound (574 Hz). If during training the subject was unable to discriminate the two sounds, the pitch difference could be increased up to 3 semi-tones by steps of half a semi-tone prior to starting MEG recordings.

In the other 25 % of trials, the same trial structure was used, but a binaural distracting sound (300 ms duration, 55 dB SL) was played at some point between the cue offset and the target onset. Distracting sound started between 50 ms and 650 ms after the cue offset. If the distracting sound onset was early (50 ms to 350 ms after cue onset), the trial was categorized as *DIS1*; if the distracting sound onset was late (350 ms to 650 ms after cue onset), the trial was categorized as *DIS2*. In the 75% remaining trials during which no distracting sound was played; trials were categorized as *NoDIS*. A total of 40 different ringing sounds were used as distracting sounds (clock-alarm, door-bell, phone ring, etc.). Each distracting sound was thus played 4 times during the whole experiment, but no more than once during each single block to limit habituation.

Participants were instructed to perform a discrimination task and to respond as fast as possible by pushing or pulling a joystick. The mapping between the targets (low or high) and the responses (pull or push) was counterbalanced across participants, but did not change across blocks. Participants were asked to allocate their attention to the cued side in the case of informative cues. Participants were informed that informative cues were 100 % predictive and that a distracting sound could be sometimes played. Participants had a 3.4 second response window. At any time in the

absence of the visual cue, a blue fixation cross was presented at the center of the screen. Participants were instructed to keep their eyes fixating on the cross and to minimize eye movements while performing the task.

Participants were in a seating position. All stimuli were delivered using Presentation software (Neurobehavioral Systems). Auditory stimuli were delivered through air-conducting plastic ear tubes. First, the auditory threshold was determined for the low-pitched target sound, in each ear, for each participant using the Bekesy tracking method [49]. Second, participants were trained with a short sequence of the task (task difficulty was adjusted if needed, see above). Finally, participants performed 10 blocks of 64 trials of the task (640 trials in total): the whole session lasted around 80 minutes.

2.3 Analysis of behavioral data

The Competitive Attention Test (CAT) provides robust behavioral indexes of top-down attention, bottom-up attention capture and phasic arousal in various populations: healthy young adults [10,26,28,58], the elderly [27] or healthy children [38]. In these previous studies, participants were faster in trials with informative cues compared to those with uninformative cues: the difference in reaction time (RT) between *informative* and *uninformative* trials was considered a proxy for top-down anticipatory attention. Participants were faster in trials with an early distractor than in those without distracting sound: the difference in RT between NoDIS and DIS1 trials was considered a proxy for an increase of phasic arousal. Finally, participants were slower in trials with a late distractor compared to those with an early distracting sound: the difference in RT between DIS2 and DIS1 trials was considered a proxy for bottom-up attention capture.

Analyses of behavioral data were already performed in a previous article using this dataset [59]. Only trials with a correct response were retained and median RT for each subject and condition were computed. A repeated-measures ANOVA with CUE category (2 levels: *uninformative, informative*) and DISTRACTOR condition (3 levels: *NoDIS, DIS1, DIS2*) as within-subject factors and GROUP category (2 levels: *control, migraine*) as a between-subject factor. To correct for possible violations of the sphericity assumption, Greenhouse-Geisser correction was applied to resulting p-values. Post-hoc comparisons were conducted using t-tests followed by a Bonferroni correction. Statistical analyses were conducted using the software JASP (version 0.9).

2.4 MEG recording and preprocessing

Simultaneous EEG and MEG data were recorded with a sampling rate of 600Hz during task performance. A 275-channel whole-head axial gradiometer system (CTF-275 by VSM Medtech Inc., Vancouver, Canada) was used to record electromagnetic brain activity (0.016–150Hz filter bandwidth and first-order spatial gradient noise cancellation). Head movements were continuously monitored using 3 coils placed at the nasion and the two preauricular points. EEG was recorded continuously from 7 scalp electrodes placed at frontal (Fz, FC1, FC2), central (Cz), and parietal (Pz) sites, and at the two mastoids (TP9, TP10). The reference electrode was placed on the tip of the nose, the ground electrode on the forehead. One bipolar EOG derivation was recorded from 2 electrodes placed on the supra-orbital ridge of the left eye and infra-orbital ridge of the right eye. Please note that EEG data are not presented in this article, see Masson et al. (2020) [59] for more details.

For each participant, a 3D MRI was obtained using a 3T Siemens Magnetom whole-body scanner (Erlangen, Germany), locations of the nasion and the two preauricular points were marked using fiducials markers. These images were used for reconstruction of individual head shapes to create forward models for the source reconstruction procedures.

MEG data were processed offline using the software package for electrophysiological analysis (ELAN Pack) developed at the Lyon Neuroscience Research Center [1]. Continuous MEG data were bandstop-filtered between 47 and 53 Hz, 97 and 103 Hz, and 147 and 153 Hz (zero-phase shift Butterworth filter, order 3) to remove power-line artifacts. An independent component analysis (ICA) was performed on the 0.1-40 Hz band-pass filtered MEG signal to remove eye-movements and heartbeat artifacts. Component topographies and time courses were visually inspected to determine which ones were to be removed through an ICA inverse transformation. 2 to 5 components were removed on the “bandstop-filtered” MEG signal in each participant.

Only trials for which the participant had answered correctly were retained. Trials contaminated with muscular activity or any other remaining artifacts were excluded automatically using a threshold of 2200 femtoTesla for MEG channels. Trials for which the head position differed of more than 10 mm from the median position during the 10 blocks were also excluded from the analyses. For all participants, more than 80 % of trials remained in the analyses after rejection. Finally, MEG data were band-pass filtered between 0.2 and 40 Hz (zero-phase shift Butterworth filter, order 3).

In anticipation of the baseline correction for distractor-related activity in further analyses, for each distractor onset time range, surrogate distractors were created in the *NoDIS* trials with similar distribution over time than the real distractors.

2.5 Time-frequency analyses

All further analyses were conducted using the Fieldtrip MATLAB toolbox (MATLAB 2015A version, Fieldtrip release version 20151231 [71]. This study is focusing on cue-induced alpha and distractor-induced gamma activities. Definition of time-frequency bands and time-windows of interest are based on previous works in healthy young adults by Elshafei et al. (2018, 2019) [26,28]. Based on these previous studies, we expected the following pattern of modulations of oscillatory power: (1) increase in the high-alpha frequency band (11-15 Hz) in the occipital cortices in anticipation of the target sound, reflecting top-down inhibitory processes; (2) decrease in the low-alpha frequency band (7-11 Hz), notably in the motor and auditory cortices, in anticipation of the target sound, reflecting top-down facilitatory processes; (3) increase in the gamma frequency band in the ventral attention network following the presentation of the distracting sound, reflecting the triggering of bottom-up attentional processes.

a Sensor-level activity

For each single event, the corresponding time-locked response (event-related field) was removed in order to analyze only induced activity free from any evoked activity. Oscillatory power was calculated using Morlet wavelet decomposition with a width of four cycles per wavelet (m = 7; [86]) at center frequencies between 1 and 150 Hz, in steps of 1 Hz.

For cue-related alpha activity, baseline correction was performed by computing relative change between activity of interest (low-alpha: 7 to 11 Hz; high-alpha: 11 to 15 Hz, 0 to 1.8s post-cue) and the baseline activity (-0.3 to -0.1s pre-cue, averaged over time). For distractor-related gamma-activity, baseline correction was performed by computing relative change between activity of interest (60 to 100 Hz, 0 to 0.35s post-distractor) in response to distractors vs. surrogate distractors.

Then, for each frequency band, the baseline-corrected activity of interest of the migraine group was contrasted to the control group's one using a non-parametric cluster-based permutation analysis [56], a statistical strategy that controls for multiple comparisons in time and sensor space dimensions.

b Source-level activity

First, for each event, the time-locked response was removed in order to analyze only induced activity free from any evoked activity. Then, we utilized the frequency–domain adaptive spatial technique of dynamical imaging of coherent sources (DICS, [37]) in order to reconstruct alpha and

gamma activities in the source space dimension. Cross-spectral density (CSD) matrices were calculated using the multitaper method from -0.2 to 2s relative to cue onset (lambda 5%) with a target frequency of 11 (± 4) Hz for NoDis trials, and from -0.1 to 0.35 s relative to distractor onset (lambda 5%) with a target frequency of 80 (±20) Hz for all trials. For each participant, an anatomically realistic single-shell headmodel based on the cortical surface was generated from individual head shapes [69]. A grid with 0.5 cm resolution was normalized on an MNI template, and then morphed into the brain volume of each participant. Leadfields for all grid points along with the CSD matrix were used to compute a common spatial filter that was used to estimate the spatial distribution of power for the time-frequency window of interest.

In order to estimate source-level activity for each event, we contrasted baseline activity (either pre-stimulus activity for cue-related activities or surrogate distractor-related activity for the real distractor-related activity) to the activity of interest, using non-parametric cluster-based permutations tests which control for multiple comparisons in the source space dimension [56]. The choice of time-frequency windows of interest was informed by the results from previous studies using this paradigm [26–28]. High and low alpha-band activities were investigated between 0.7 and 1.1s post-cue onset (the target sound being played at 1.2 s post-cue). Gamma-band activity was investigated between 0.1 and 0.3 s after the distracting sound onset.

Then, baseline activity was subtracted from the activity of interest and the resulting difference was contrasted between control and migraine participants using non-parametric cluster-based permutations tests. The choice of time-frequency windows of interest was informed by the results of analyses at the sensor-level.

3 Results

3.1 Behavioral results (Figure 2)

Main effects of the DISTRACTOR and CUE categories were found significant. Participants responded significantly faster in the *informative* condition than in the *uninformative* condition. Participants responded significantly faster in trials with an early distracting sound *(DIS1)* compared to trials without distracting sound *(NoDIS)*. Participants responded significantly slower in trials with a late distracting sound *(DIS2)* compared to trials with an early distracting sound *(DIS1)* or even compared to trials without distracting sound *(NoDIS)*. Neither the main effect of the GROUP category nor the interactions of GROUP with CUE or DISTRACTOR category were found significant. Full description of the behavioral effects can be found in Masson et al. (2020) [59].

3.2 Cue-elicited alpha-band activities

a Anticipation of the target sound (Figure 3)

As expected, in the control group, the anticipation of the auditory target led to two distinct activation patterns for the low-alpha (7-11 Hz) and high-alpha frequency band (11-15 Hz) at the sensor level (Figure 2).

At the sensor level, both the control and migraine group presented a decrease of low-alpha power over left central and temporal sensors in anticipation of the target sound. Cluster-based permutation analysis at the source-level indicated that this decrease in low-alpha power corresponded to a significant cluster including left motor areas in the control group ($p=0.018$) and left motor areas and the left auditory cortex in the migraine group ($p=0.029$).

Control participants presented an increase in high-alpha power over the occipital and right temporo-parietal gradiometers starting from 0.7 s post-cue onset. Cluster-based permutation analysis at the source-level indicated that this increase in high-alpha power corresponded to a significant cluster located only in the right hemisphere and which overlapped with occipital and parietal areas, the auditory cortex and the orbitofrontal cortex ($p=0.007$). In the migraine group, the increase of high-alpha power over occipital sensors was much more short-lived. Cluster-based permutation analysis at the source-level did not confirm the presence of a significant pattern of high-alpha increase ($p=0.091$).

b Group differences in alpha-band activities (Figure 4)

At the sensor-level, cluster-based permutation analysis indicated that migraineurs presented less high-alpha power in anticipation of the auditory target and during target processing. This corresponded to a significant cluster over occipital gradiometers, ranging from 0.9 to 1.6 s ($p=0.048$). Based on this result, high-alpha activity during the 0.9 to 1.6 s time-window was reconstructed, in order to localize the group effect. The cluster-based permutation analysis at the source-level indicated that the decrease in alpha power observed among migraine participants emerged from a cluster including bilateral occipital cortices and the right dorso-frontal cortex ($p=0.043$) (Figure 3).

No significant group difference was found in the low-alpha band at the sensor-level. In order to confirm this null result, low-alpha activity in anticipation of the target (0.7 to 1.1 s time-window) was reconstructed. The cluster-based permutation analysis at the source-level showed no significant difference in low-alpha power between the migraine and control groups ($p>0.31$).

3.3 Distractor-elicited gamma-band activity (Figure 5)

As expected, in the both groups, the distracting sound induced an increase in gamma power (60-100 Hz) at the sensor-level (Figure 4). This increase of gamma power was visible over a large diffuse area of the scalp but was maximal over a left and a right focal clusters of temporo-parietal gradiometers. In the control group, cluster-based permutation analysis at the source-level indicated that this increase of gamma-band power corresponded to a significant cluster including the bilateral temporo-parietal junctions, both auditory cortices and the right dorso-lateral prefrontal cortex ($p<0.001$). In the migraine group, cluster-based permutation analysis at the source-level indicated that the increase of gamma-band power corresponded to four significant clusters including the right temporo-parietal junction and the left auditory cortex ($p<0.01$ for all four clusters).

No significant group difference was found in the gamma-band at the sensor-level ($p=1$). In order to confirm this null result, a cluster-based permutation analysis at the source-level was performed a showed no significant difference in gamma power between the migraine and control groups ($p=1$).

4 Discussion

Migraine has been associated with abnormalities of the attention function through subjective reports [15,50,80], through neuropsychological tests [90,93] or through EEG and event-related potentials (ERPs) [63]. In a previous MEG/EEG study [59], our group attempted to characterize alterations of attention processing in migraine without aura using the Competitive Attention Test (CAT), a paradigm which conjointly evaluates top-down and bottom-up attention, using visually-cued target sounds and unexpected task-irrelevant distracting sounds. Despite the absence of between-group differences at the behavioral level, analyses of ERPs showed that migraineurs presented exacerbated bottom-up orienting responses to all incoming sounds, which was associated with an increased activation of the rTPJ. However, there were was also some evidence suggesting an enhanced recruitment of top-down attentional processes. In the present study, we used a similar protocol in order to investigate specifically how disruptions of brain rhythms may underlie the attentional difficulties observed interictally in migraine. We focused on alpha activity during top-down anticipatory processes (auditory target anticipation) and on gamma activity during bottom-up processing of distracting auditory stimuli.

4.1 Top-down anticipatory processes in migraine

There is growing consensus that alpha rhythms reflect active functional inhibitory processes through the modulation of neuronal excitability [41,45]. Notably, the "inhibition by gating" hypothesis asserts that alpha synchronization in regions not required for the task redirects the information towards task-relevant regions/pathways [41]. During attention tasks, attending to the location, feature or timing of a stimulus decreases alpha power in sensory areas relevant for its processing, while increases of alpha power are detected in sensory areas irrelevant for the processing of the stimulus feature. These alpha modulations have been described in the visual modality [42,57,75–77,84] and in the auditory modality [60,67,96,97]. During multimodal paradigms, alpha power has been reported to increase in brain areas processing the unattended sensory modality and to decrease in relevant areas [23,30,32]. It has been specifically observed in a previous study using the same task: the anticipation of an auditory target is associated to an increase in high-alpha power in the task-irrelevant occipital cortex concomitant to a decrease in low-band alpha power in the task-relevant auditory cortex, reflecting distinct facilitatory and inhibitory mechanisms [26]. Inhibition of the visual pathway was found functionally meaningful as behavioral performance positively correlated with the increase of alpha power in the occipital cortex [26].

In the present study, we confirmed with our control group that the anticipation of an auditory target leads to: (1) a decrease of low-alpha power in the auditory cortex, interpreted as a facilitation of auditory processing and (2) an increase of high-alpha power in the occipital cortex, interpreted as an inhibition of visual processing. Compared to healthy control participants, migraineurs presented a less pronounced and more short-lived alpha power increase in the occipital cortex in anticipation of the auditory target and during target processing. Migraineurs appear to be unable to suppress the task-irrelevant visual pathways, which suggests that migraine is associated with deficient top-down inhibitory processes. Migraineurs also presented decreased alpha power in dorsal prefrontal areas compared to control participants. The dorsal prefrontal cortex has been consistently associated with goal-oriented, top-down attentional processes [6,19], and as part of the dorsal attention network it has been proposed that it coordinates alpha power modulation in sensory cortices [14,24,39,54,67,97].

By contrast, no significant difference was observed between the two groups in terms of low-alpha decrease. One could have expected an inadequate alpha desynchronization in the auditory cortex in anticipation of an auditory target. This result suggests that top-down facilitatory processes might be preserved in migraine, as task-relevant sensory pathways appear to be functionally unaffected here. This is consistent with our previous work investigating event-related potentials in

the same group of migraineurs using the Competitive Attention Task [59]. We found that migraineurs presented an increased negative difference (Nd) in response to the target sound, a response that is considered to reflect top-down facilitatory processes [3,33,68]. This is also in line with Mickleborough et al. (2011) study which showed that migraineurs present a better-than-normal ability to modulate in a top-down fashion the processing centrally-presented visual targets but show a decreased ability to suppress unattended inputs in the periphery [64]. In general, migraine is associated with an impairment of visual noise exclusion [95].

Few studies have investigated alpha rhythms in migraine and never in paradigms involving attention to our knowledge. Unlike healthy participants, migraineurs present highly synchronized steady-state activity in the alpha band during flickering stimulation [4,88,89] and they display higher alpha power during an eyes-closed resting-state session, especially above the occipital cortices [12,56] and a decrease in alpha power in the frontal cortex [16]. Our present results seem to confirm that migraine is associated with abnormal excitability of occipital cortices [7]. Further research would also be necessary to confirm this pattern of disruption of occipital alpha in migraine with aura. Migraine with aura is sometimes considered as a distinct clinical entity from migraine without aura [78], is more associated with visual disturbances [79] and often present distinct electrophysiological abnormalities [21].

4.2 Bottom-up attentional processes in migraine

Gamma rhythms have been associated with attention mechanisms. During attention tasks, gamma rhythms display the opposite behavior of alpha rhythms as gamma power is enhanced in task-relevant cortical areas [36]. They are proposed to reflect bottom-up processes, contrary to alpha rhythms which are more closely associated with top-down mechanisms [31,82].

As expected from ElShafei et al. (2019) [28] who analyzed data from a set of participants overlapping with that of the present study, we observe that distracting sounds trigger an increase in gamma power within the ventral attention network (VAN) and auditory cortices in healthy participants. This distractor-induced gamma synchronization is interpreted as being the physiological manifestation of attention capture by distracting sounds, as the VAN is considered to underlie stimulus-driven, bottom-up attention mechanisms [18,19,81]. In the present study, contrary to our a priori hypotheses, there is no significant disruption of the distractor-induced gamma synchronization in migraine. Migraine patients do not appear to present an enhanced recruitment of the VAN in response to a salient, unexpected sound.

This is surprising as our previous work investigating event-related potentials in the same group of migraineurs has shown exacerbated markers of bottom-up attention in response to

distracting sounds and an increased recruitment of the right temporo-parietal junction, a crucial node of the VAN [59]. Previous studies using the oddball paradigm have shown that the gamma activity following novel stimuli present similar spatial and temporal characteristics than those of the P3a [2,48], an ERP closely associated with bottom-up attention capture by novel events [29,74,83]. The conflicting results may be due to the fact that the distractor-induced gamma burst (100-300 ms, during the P3a response) happens before the observed group effect on event-related potentials and fields (>350 ms, during the Reorienting Negativity). Attention capture by distracting sounds in migraine may be unchanged in migraine, while the ability to recover from distraction would be negatively impacted.

4.3 Conclusions & Clinical Perspectives

In a world filled with multiple sources of sensory stimulation, top-down attention enables us to focus on relevant aspects of the environment and ignoring those which are irrelevant, while bottom-attention allows to remain aware of unattended but potentially meaningful events. Based on the present results, migraine seems to be associated with a deficient recruitment of top-down inhibitory mechanisms as migraineurs appear to be less capable of inhibiting visual areas when they are not relevant to the task. However, there is no evidence in the present data that top-down facilitatory mechanisms are negatively impacted in migraine or that the recruitment of the ventral attention network is abnormal.

The apparent inability of migraineurs to suppress irrelevant information may be the neurophysiological underpinning of their complaints of attention difficulties and increased distractibility in their daily life [15,50,63,80]. The characterization of the attentional alterations associated with migraine might inform therapeutical strategies to improve their daily life and possibly reducing the attack frequency. Based on the present results, migraineurs would not have major problems to focus on their work but would fail to effectively block unwanted sources of noises. Clinical training specifically focusing on distraction and noise suppression may be found useful for symptoms management. Finally, deficient top-down inhibitory mechanisms may play a role in the multimodal hypersensitivity during both the headache phase and the pain-free period [50,55,91,92]. A link between attention and hypersensitivity has been proposed in some psychiatric disorders. Atypical sensory sensitivity is a core symptom of autism or attention deficit disorders (ADD) and abnormal attention orienting has been proposed to participate in the excessive sensory discomfort experienced by those individuals [13,35,72,73]. Further research is needed to establish a clearer relationship between sensory complaints and the disruption of the attention processing of sensory stimuli in migraine.

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Legends

Table 1: Demographics and headache profile of the control and migraine groups. Two control participants did not filled the Hospital Anxiety and Depression (HAD) scale. Mean and standard deviation are provided. Group differences are tested using a non-parametric Mann-Whitney U test. NA: not applicable.

	Migraine	Control	p-value
Sample size	19	19	-
Age (years)	32.7 (8.7)	31.2 (7.8)	0.53
Sex (number of female participants)	13 (68%)	13 (68%)	-
Education level (years)	15.8 (3.1)	15.8 (2.2)	0.99
Musical practice (years)	2.8 (3.3)	2.8 (3.5)	0.74
Laterality (number of right-handed)	19	19	-
Anxiety score	5.7 (3.5)	4.6 (2.5)	0.42
Depression score	2.6 (2.6)	1.8 (2.0)	0.31
Migraine duration (years)	16.8 (7.4)	NA	-
HIT-6 score	64.2 (7.1)	NA	-
MIDAS score	12.8 (12.1)	NA	-

Figure 1: Protocol. The task was to discriminate between a low- and a high-pitched sound, presented monaurally. A visual cue initiated the trial, and was either informative (50%, top row) or non-informative (50%, bottom row) about the target ear. 25% of the trials included a distracting sound (bottom row). (a) Example of an informative trial with no distracting sound: a one-sided visual cue (200 ms duration) indicates in which ear (left or right) the target sound (100 ms duration) will be played after a fixed 1000 ms delay. (b) Example of an uninformative trial with a distracting sound: a two-sided visual cue (200 ms duration) does not provide any indication in which ear (left or right) the target sound will be played. The target sound can be a high- or low-pitched sound indifferently of the cue informational value. In 25% of all trials (with informative or uninformative cues), a loud binaural distracting sound (300 ms duration), such as a clock ring, is played during the cue-target interval at a random delay after the cue offset: the DIS1 condition corresponds to early distracting sounds (starting 50–350 ms after cue offset), the DIS2 condition corresponds to late distracting sounds (starting 350–650 ms after cue offset).

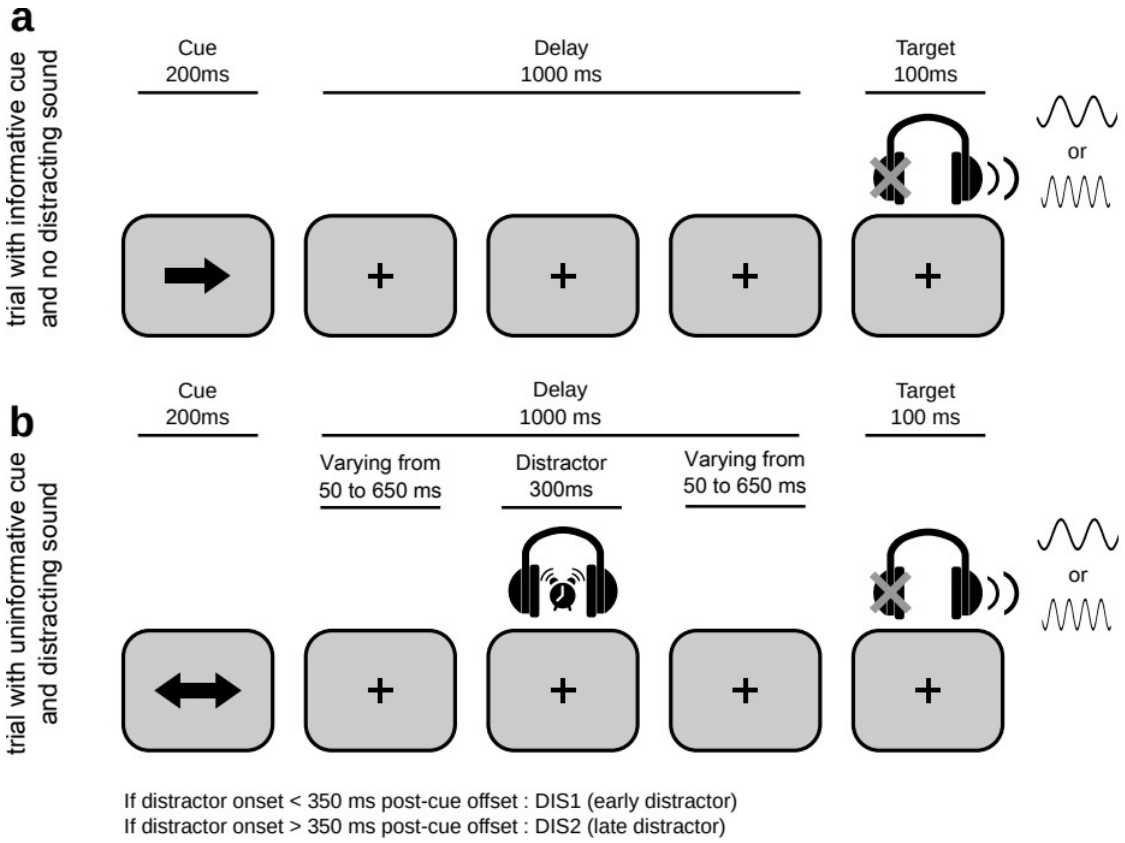


Figure 2: Behavioral results. Reaction time (RT) as a function of the CUE and GROUP category on the left panel, RT as a function of the DISTRACTOR and GROUP category on the right panel. Participants present a significant effect of the cue informational value (*uninformative* > *informative*), a significant effect of phasic arousal (*NoDIS* > *DIS1*) and a significant effect of attention capture (*DIS2* > *DIS1*). A repeated-measures ANOVA showed no significant interaction of the GROUP with the CUE or with the DISTRACTOR category. Adapted from Masson et al. (2020) [59].

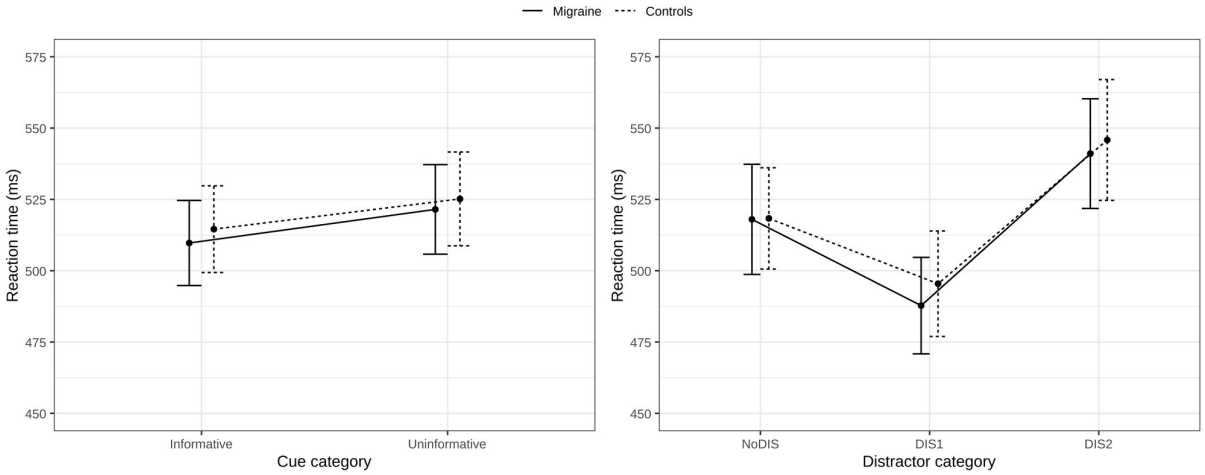


Figure 3: Cue-related low- and high-alpha activity. For each group, the low-alpha (7-11 Hz) activity is presented on the left panel, the high-alpha (11-15 Hz) is presented on the right panel. (top) Scalp topographies of the baseline-corrected low- or high-alpha power during target anticipation (time-window of interest: 0.7 to 1.1s post-cue onset; baseline window: -0.6 to -0.2 pre-cue onset). (middle) Time-frequency visualization of baseline-corrected alpha power measured at the gradiometers highlighted by black circles in the topographic maps. (bottom) Distributions of t values, masked at $p < 0.05$, from cluster-based permutation tests (one-tailed tests, cluster formation threshold at $p < 0.05$) contrasting low- or high-alpha activity during target anticipation against baseline activity at the source level.

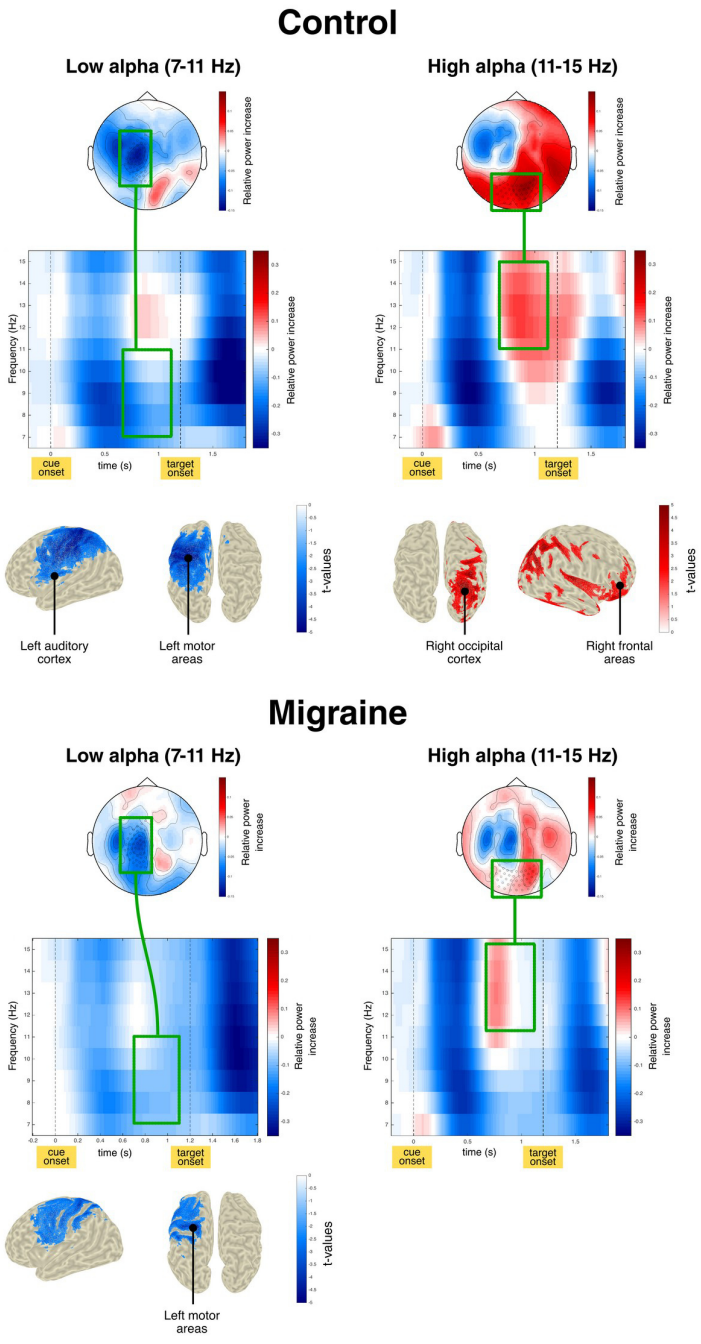


Figure 4: Group differences in cue-related high-alpha activity. (A) Scalp topography of *t* values from cluster-based permutations contrasting baseline-corrected high-alpha (11-15 Hz) activity between the control group and the migraine group at the sensor-level (time-window of interest: 0.9 to 1.6 s post-cue onset; baseline window: -0.6 to -0.2 pre-cue onset). (B) Time-courses of baseline-corrected high-alpha power at occipital gradiometers (highlighted with green circles in the topographic map) for the control and migraine groups. (C) Distributions of *t* values, masked at $p < 0.05$, from cluster-based permutation tests (two-tailed test, cluster formation threshold at $p < 0.025$) contrasting baseline-corrected high-alpha activity during the time-window of interest between the control group and the migraine group at the source-level.

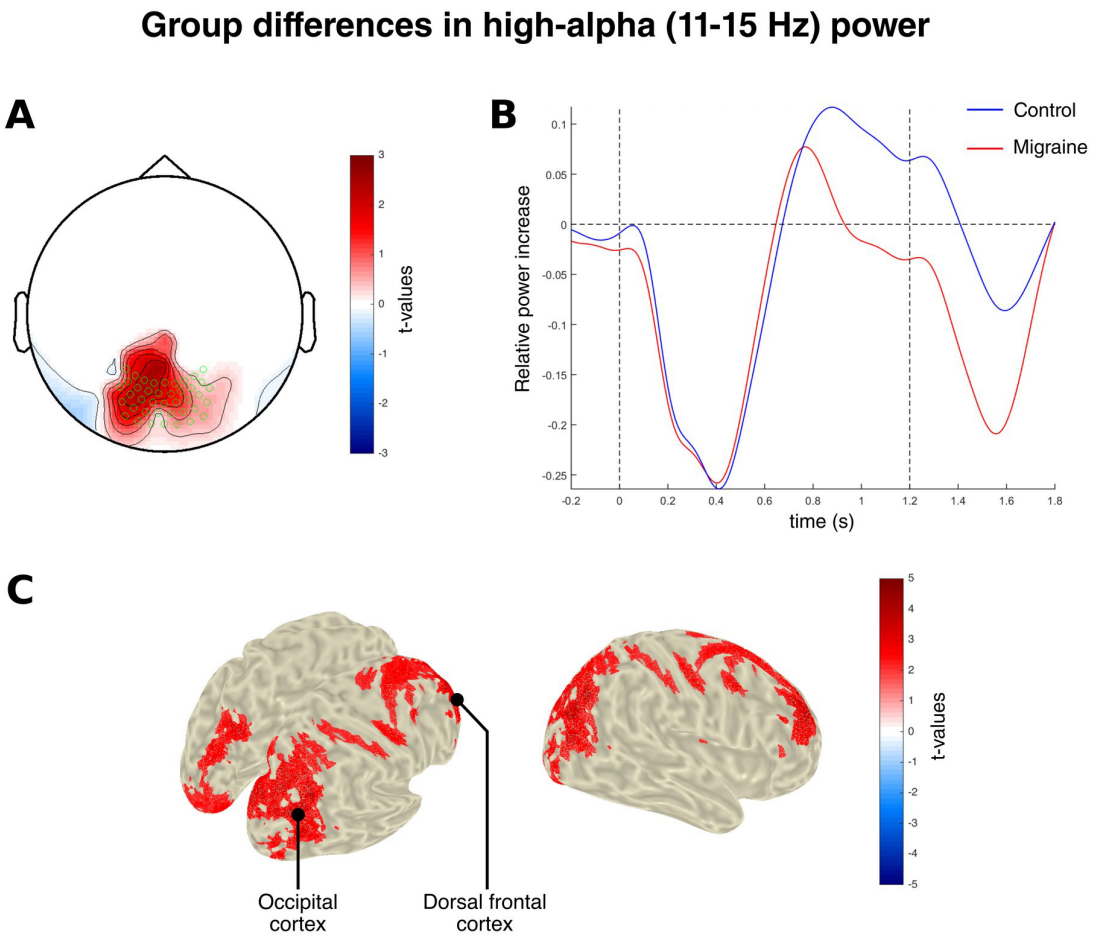
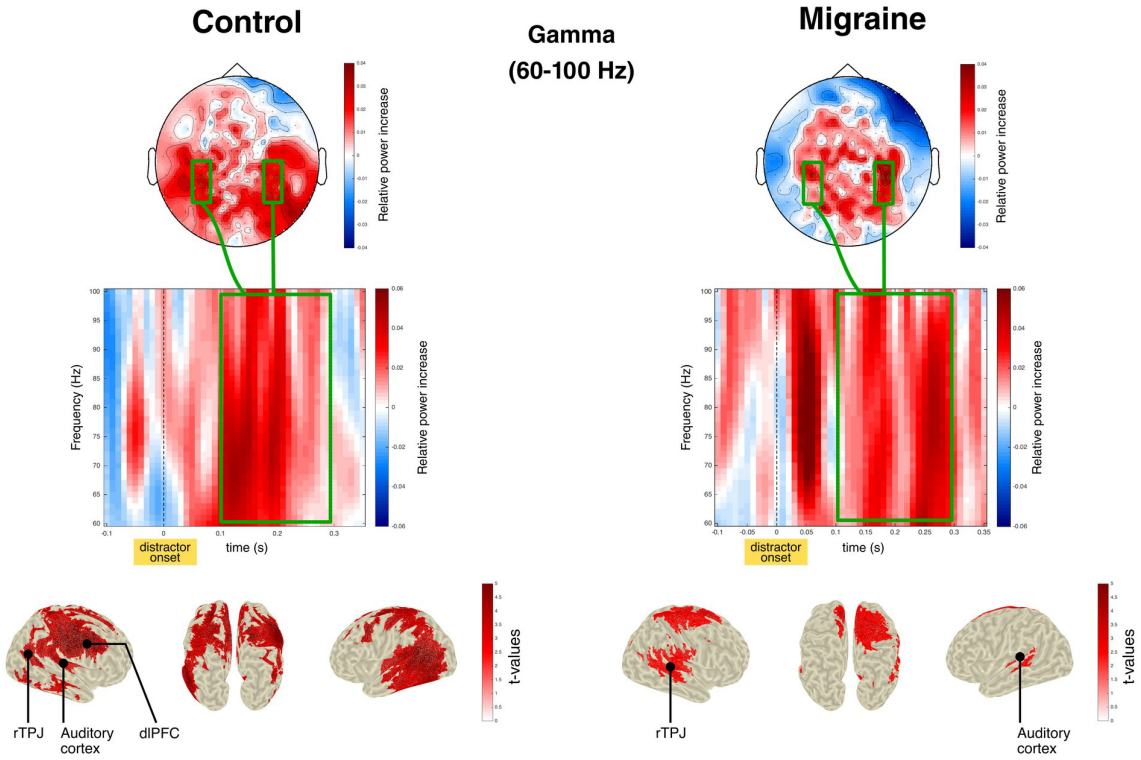


Figure 5: Distractor-related gamma activity. (top) Scalp topographies of the baseline-corrected gamma power (frequency of interest: 60-100 Hz; time-window of interest: 0.1 to 0.3 post-distractor onset). (middle) Time-frequency visualization of baseline-corrected gamma power measured at the temporo-parietal gradiometers highlighted with green circles in the topographic map. (bottom) Distributions of *t* values, masked at $p < 0.05$, from cluster-based permutation tests (one-tailed tests, cluster formation threshold at $p < 0.005$ for the control group, $p < 0.01$ for the migraine group) contrasting contrasting real and surrogate distractor gamma activity during the time-window of interest at the source level.



2.5 Final remarks

One of our primary goals was to link the attentional difficulties in migraine to the sensory symptoms associated with the disease. All our migraine participants in the MEG/EEG study has filled the questionnaire presented in the Article 2. We have attempted to correlate across participants a score of interictal hypersensitivity to the markers of attention which we found altered in our migraine group: the amplitude of the orienting component of the N1, of the RON or of the Nd, and the pre-target high-alpha power measured at occipital gradiometers. No correlation was found significant, even when taking into account demographic covariates (age, sex, severity of the disease). This is not surprising as EEG markers are notoriously very variable across individuals and the rather low sample size may have been insufficient to detect any association with a small or moderate effect size. However, these results are particularly disappointing as they prevent us to draw a clear association between the alterations of attentional mechanisms and the disruption of sensory processing.

3 Brain anatomical alterations in migraine

3.1 General introduction

The objective of this last study was to explore if there were structural substrates of the attention alterations in migraine. T1-weighted anatomical MRI and DTI sequences were acquired in the same participants which were involved in the MEG/EEG study. In the article 5, we used automatic morphometry techniques, namely voxel-based morphometry, surface-based morphometry and tract-based spatial statistics to detect a structural signature of the migraine brain. This is far from being the first attempt in the literature to investigate migraine anatomy using MRI images and morphometry techniques. Therefore in the article 5, we also performed a systematic review of the literature combined to a coordinate-based meta-analysis to determine if there are robust and consistent patterns of structural abnormalies associated with migraine.

3.2 Article 5: "Is migraine associated to brain anatomical alterations? New data and and coordinate-based meta-analysis"

Is migraine associated to brain anatomical alterations? New data and coordinate-based meta-analysis.

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Abstract: A growing number of studies investigate brain anatomy in migraine using voxel- (VBM) and surface-based morphometry (SBM), as well as diffusion tensor imaging (DTI). The purpose of this article is to identify consistent patterns of anatomical alterations associated with migraine. First, 19 migraineurs without aura and 19 healthy participants were included in a brain imaging study. T1-weighted MRIs and DTI sequences were acquired and analyzed using VBM, SBM and tract-based spatial statistics. No significant alterations of gray matter (GM) volume, cortical thickness, cortical gyrification, sulcus depth and white-matter tract integrity could be observed. However, migraineurs displayed decreased white matter (WM) volume in the left superior longitudinal fasciculus. Second, a systematic review of the literature employing VBM, SBM and DTI was conducted to investigate brain anatomy in migraine. Meta-analysis was performed using Seed-based d Mapping via permutation of subject images (SDM-PSI) on GM volume, WM volume and cortical thickness data. Alterations of GM volume, WM volume, cortical thickness or white-matter tract integrity were reported in 72%, 50%, 56% and 33% of published studies respectively. Spatial distribution and direction of the disclosed effects were highly inconsistent across studies. The SDM-PSI analysis revealed neither significant decrease nor significant increase of GM volume, WM volume or cortical thickness in migraine. Overall there is to this day no strong evidence of specific brain anatomical alterations reliably associated to migraine. Possible explanations of this conflicting literature are discussed.

Trial registration number: NCT02791997, registrated February 6th, 2015.

Keywords: migraine, voxel-based morphometry, surface-based morphometry, diffusion tensor imaging, tract-based spatial statistics, coordinate-based meta-analysis

Declarations:

Conflict of interest: The authors declare that there is no conflict of interest regarding this article.

Ethics approval: The ethical approval of this work was obtained through the Hospices Civils de Lyon, approved by the local ethical committee (Comité de Protection des Personnes SUD EST III). Therefore, this work has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate: Written informed consent has been obtained from all participants in the present study.

Consent to publish: Participants have signed written consent regarding publishing results derived from analyses of their data.

Availability of data and material: The data that support the findings of this study are not publically available as participants did not consent to data sharing.

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1. Introduction

Migraine is the most common neurological disorder in the adult population with a prevalence comprised between 8% and 17% (Henry et al. 2002). Migraine attacks are characterized by acute, moderate to severe, recurrent headaches lasting between four to 72 hours, accompanied with nausea and/or hypersensitivity to visual (photophobia), auditory (phonophobia), olfactory (osmophobia) and/or tactile (allodynia) environmental stimulations (Headache Classification Committee of the International Headache Society (IHS) 2013). Several migraine subtypes (not necessarily exclusive) have been defined based on migraine attack frequency (episodic and chronic migraine), presence of aura preceding the attack (migraine with and without aura), or even secondary symptoms such as vertigo/head dizziness (vestibular migraine).

Neuroimaging methods have widely improved since the last two decades, especially through the popularization of automated whole-brain morphometric techniques such as voxel- (VBM) and surface-based morphometry (SBM) to assess gray- and white-matter volume from anatomical MRI images and tract-based spatial statistics (TBSS) to assess white matter microstructure from diffusion tensor imaging (DTI) data. These techniques enable to perform an unbiased investigation of structural changes in the brain associated with a condition, often without the need of precise a priori hypotheses. Morphometric analyses can reveal the "anatomical signature" of a disorder and therefore provide insights on the symptomatology of a disease. VBM is able to detect gray matter atrophy associated with Alzheimer's disease (Frisoni et al. 2002; Karas et al. 2003). In various neuropsychological disorders such as excessive impulsivity (Matsuo et al. 2009), obsessive compulsive disorder (Valente et al. 2005), mild cognitive impairment (Chételat et al. 2002), attention-deficit and hyperactivity disorder (Makris et al. 2007), or dyslexia (Silani et al. 2005), gray matter abnormalities detected by VBM colocalizes with the brain network that was evidenced to be functionally altered in the disorder. As for DTI, it is a powerful tool to investigate the integrity of white matter fascicles and therefore to pinpoint potential abnormalities in brain connectivity in neurological disorders (Lim and Helpern 2002).

Identifying brain abnormalities associated with migraine is expected to provide new insights into the pathophysiology of the disease. The core symptoms of migraine may either alter brain structure through plastic mechanisms, or on the contrary originate from pre-existing brain abnormalities. It has been hypothesized that recurrent headaches over years may affect pain-related areas including somatosensory cortices or even lead to brain damage (May 2009). One can also expect that strategies used by migraine to cope with the symptoms (such as trigger avoidance or pain management) may have a lasting impact on brain structure. Indeed, structural alterations of the brain also reflect the effects of long-term plasticity as evidenced by the structural changes of gray matter volume in task-relevant brain regions following exercise and learning (Draganski et al. 2004; Boyke et al. 2008) or long-term practice of an instrument (Bermudez and Zatorre 2005; Bermudez et al. 2009). To respond to these questions, a rich and still growing literature have investigated brain anatomy in migraine using automatic morphometry techniques. Brain structural alterations in migraine have been reported by a great number of studies (May 2009; Bashir et al. 2013; Hu et al. 2015; Dai et al. 2015). However, results are often conflicting and no consensus has yet emerged

identifying a structural signature of the disease. Previous meta-analyses on the subject have attempted to compile results from the literature and their conclusions are also inconsistent: some detected decreased gray matter volume in pain-related areas (Dai et al. 2015; Jia and Yu 2017), some in the frontal and cingulate cortices (Hu et al. 2015; Jia and Yu 2017) but the most recent one failed to detect any alteration of gray matter in migraine (Sheng et al. 2020).

The purpose of this article is to find out if there is convincing evidence of structural brain alterations associated to migraine. In order to respond to this question, we first provide new data aiming to identify gray (GM) and white matter (WM) abnormalities in patients with migraine during the interictal period using several hypothesis-free whole-brain morphometry analyses: VBM, SBM and TBSS. Second, a systematical review of the literature was performed on whole-brain studies of GM and WM abnormalities in migraine in order to try to make sense of the conflicting results. To this end a coordinate-based meta-analysis (CBMA) of the literature was run using Seed-based d mapping via permutation of subject images (SDM-PSI), a novel meta-analysis technique which enables to detect robust and consistent structural alterations based on reported foci from different experiments (Radua et al. 2010; Albajes-Eizagirre et al. 2019b).

2. New data

2.1. Methods

2.1.1. Participants

Twenty-five subjects were identified and diagnosed as migraineurs without aura by a neurologist specialized in cephalgia (GD, Hospices Civils de Lyon). Patients between 18 to 60 years old and reporting a migraine frequency between two to five attacks per month were included in this study. Exclusion criteria comprised migraine with aura, chronic migraine, a medical history of psychiatric or neurological disorders, ongoing background medical treatment other than contraceptive medication, and pregnancy. Patients who suffered from a migraine attack 72 hours prior to the scheduled MRI examination, were rescheduled at a later time, whereas those who suffered from a migraine attack within 72 hours post-MRI (n=6) were discarded from further analyses. Data from 19 migraineurs were thus retained for analyses (13 females, 6 males, mean age ± SD: 32.7 ± 8.7 years, all right-handed). Migraine patients filled the Headache Impact Test (HIT-6), a short questionnaire aiming to evaluate headache impact on everyday life (Kosinski et al. 2003) and the Migraine Disability Assessment Questionnaire (MIDAS) (Stewart et al. 1999) (Table 1).

Nineteen control subjects with no medical history of psychological or neurological disorders were identified from a cohort of sixty-three healthy participants for whom MRI scan were available and acquired with a procedure strictly identical to the migraine group. The MatchIt R package (Ho et al. 2011) was used to select subjects matched for age, sex and total intracranial volume (TIV), as those three covariates are known to have distinct contribution to GM volume (Pell et al. 2008). Propensity score matching was conducted using the nearest neighbor method (Caliendo and Kopeinig 2008) in order to minimize bias due to

confounding factors. Additional demographic details are presented in Table 1. All persons gave their informed consent prior to their inclusion in the study.

2.1.2. MRI acquisition

MRI examinations for all participants were performed on a Magnetom Prisma Siemens 3T MRI scanner equipped with a 64-channel head/neck coil. A T1-weighted sagittal magnetization-prepared-rapid acquisition with gradient echo (MPRAGE) image (repetition time (TR) = 3500 ms, echo time (TE) = 2.25 ms, inversion time (TI) = 1000 ms, field of view (FOV) = 250×250 mm, matrix size = 288×288, spatial resolution: 0.9×0.9×0.9 mm), and a diffusion tensor imaging (DTI) sequence with 64 gradient directions and 38 continuous slices (b = 0 and 1000 s/mm^2, TR = 10000 ms, TE = 72 ms, FOV = 240×240 mm, matrix size = 132×132, spatial resolution: 1.8×1.8×1.8 mm) were acquired.

2.1.3. Voxel-based and surface-based morphometry

The VBM and SBM analysis were conducted using the Computational Anatomy Toolbox (CAT12, dbm.neuro.uni-jena.de/cat/), an extension toolbox of Statistical Parametric Mapping software (SPM12, www.fil.ion.ucl.ac.uk/spm/software/spm12/). Default settings as detailed in the CAT12 manual (http://dbm.neuro.uni-jena.de/cat12/CAT12-Manual.pdf) were applied.

For the VBM analysis, GM, WM and cerebrospinal fluid (CSF) tissue segmentation was first performed. The resulting GM and WM masks were then aligned to the SPM12 tissue probability maps (DARTEL template in the MNI space), co-registered using DARTEL (Ashburner 2007) and smoothed with a Full-Width at Half-Maximum (FWHM) kernel of 10 mm (Ashburner 2015). TIV was finally estimated for each participant.

For the SBM analysis, the automated workflow from the CAT12 toolbox which measures cortical thickness and reconstructs the central surface was used. Based on the central surface data, we estimated the gyrification index and sulcus depth (Luders et al. 2006). Cortical thickness, gyrification index, and sulcus depth data were smoothed using a Gaussian filter with a FWHM kernel of 15 mm (default parameter).

2.1.4. Statistical analyses (VBM and SBM)

Statistical designs were prepared using SPM12. A two-sample t-test was performed at each voxel to evaluate differences between migraineurs and control participants in regional GM and WM volumes, cortical thickness, gyrification index and sulcus depth data. For volumetric data, TIV, age and sex were considered as nuisance parameters and consequently entered in the design matrix as covariates as recommended in (Pell et al. 2008; Ashburner 2015). For surface data, only age and sex were entered as covariates. An implicit mask and a threshold masking (value=0.1) were applied to the images to remove voxels of the background from the analyses. Two contrasts were investigated: control > migraine, and migraine > control. Statistical inferences were made using non-parametric permutations and a Threshold-Free Cluster Enhancement (TFCE) correction was applied to the t-stats map produced (TFCE toolbox by Christian Gaser, http://dbm.neuro.uni-jena.de/tfce) to increase sensitivity (5000 permutations) (Smith and Nichols 2009)

along with a family-wise error (FWE) correction to address multiple testing. Clusters were considered significant with $p<0.05$.

2.1.5. DTI analysis

DTI analysis was conducted using tools from the FMRIB software library (FSL v5.0, fsl.fmrib.ox.ac.uk/fsl/fslwiki) and the Nipype pipelines (Gorgolewski et al. 2011). DTI images were first corrected for any susceptibility induced distortions (Smith et al. 2004), eddy currents, and head movements (Andersson and Sotiropoulos 2016). Fractional anisotropy (FA), mean diffusivity (MD), axial (AD) and radial diffusivity (RD) maps were calculated by fitting a tensor model at each voxel of the diffusion data. Tract-based spatial statistics (TBSS) was then performed on all participants' FA images. TBSS analysis consisted first on non-linearly co-registering all FA images to the FMRIB58-FA standard-space template. A mean FA image was then created along with a skeleton of the major WM fiber tracts. Next, all participants FA images were projected onto this skeleton which will be fed into the voxelwise statistical analysis. This process was similarly applied to the MD, AD, and RD maps.

2.1.6. Statistical analyses (DTI)

The voxel-level non-parametric permutation test (randomise function in FSL) was used to investigate the following contrasts on FA, MD, AD and RD maps: control > migraine and migraine > control. A TFCE correction was applied to the produced t-stats images to increase sensitivity (5000 permutations) along with a FWE correction to address multiple testing. Surviving clusters are reported with $p<0.05$.

2.1.7. Power analysis

We ran a sensitivity power analysis using the G*Power software (Faul et al. 2007), using a power of 0.8 and an α error of 0.05 for our group comparisons. The required effect size given our sample size equals 0.82, suggesting an adequate sensitivity to large effects (Cohen 1977). Please note that it is challenging to perform power calculations for statistical analyses that involve high-dimensional data (Durnez et al. 2016), here power analysis was calculated as if we performed a simple one-tailed t-test.

2.2. Results

2.2.1. VBM results

Neither significant decreases nor significant increases of GM volume in migraine were detected. Compared to controls, WM volume was significantly decreased in migraine (corrected $p=0.042$, $\eta^2 = 0.78$) in the left hemisphere which intersected the superior longitudinal fasciculus and the superior corona radiata (MNI coordinates of cluster peaks: [-30,-30,39], [-33,-26,26] and [-20,-38,39]), close to the superior temporal areas and the postcentral gyrus (Fig. 1). The reported effect size of this test is close to the required effect size of 0.82 as calculated by the G*Power software. No significant increases of WM volume in migraine were detected.

2.2.2. SBM results

No significant differences in cortical thickness, gyrification index, and sulcus depth were detected between the control and migraine participants.

2.2.3. DTI results

No significant differences in FA, MD, AD, or RD were detected between the control and migraine participants.

2.3. Discussion

With the present dataset, no brain anatomical differences could be detected in migraine regarding GM volume as assessed with VBM, cortical surface (thickness, gyrification and sulcus depth) as assessed with SBM, and in the integrity of WM as assessed with TBSS.

However, WM volume appeared to be decreased in migraine in the left superior longitudinal fasciculus (SLF). Only three studies (from the same research team) have yet reported WM volume decreases in migraine but none of them pinpointed such an alteration in the left superior longitudinal fasciculus (Schmitz et al. 2008; Arkink et al. 2017; Palm-Meinders et al. 2017) Moreover, no DTI study including the present one has reported altered WM integrity in this particular tract.

The SLF is an association tract which connects occipital and temporal areas to the frontal lobe. This pathway is involved in various cognitive processes (Schmahmann et al. 2008), however the left SLF has been consistently linked to language processing (e.g. Frye et al. 2010; Maldonado et al. 2011; Nagae et al. 2012; Madhavan et al. 2014) as it connects Broca's and Wernicke's area (Catani and Mesulam 2008). To our knowledge, migraine is not associated to major language defects, however some neuropsychological studies have reported that migraineurs performed worse than healthy participants in verbal memory and verbal skills tasks (for a systematic review, see Vuralli et al. 2018). The SLF might also be involved in the control of the vestibular function (Spena et al. 2006): an alteration of its integrity could underlie the vestibular symptoms observed in migraine as migraineurs are much more prone to vertigo and dizziness episodes than the general population (Vuković et al. 2007; Cha et al. 2009).

Overall we found little evidence for brain anatomical alterations in migraine, we now consider these negative results in light of a systematic review and a meta-analysis of the relevant literature.

3. Meta-analysis

3.1. Material and methods

3.1.1. Data sources and study selection

Systematic searches were performed on January 2019 in PubMed database without any publishing time restriction. For VBM studies, we used the combination of keywords migraine AND ((voxel based morphometry) OR VBM); for SBM studies, we used the combination of keywords migraine AND ((surface based morphometry) OR (cortical thickness) OR (gyrification)); for DTI studies, we used the combination of

keywords migraine AND ((diffusion tensor imaging) OR DTI). Additional studies were also searched from reference lists of the included articles. Inclusion criteria were: (1) the article was an experimental article; (2) it was published in an English-speaking peer-reviewed journal, (3) it included a VBM (gray and/or white matter), SBM, or DTI comparison of adult patients with migraine vs. healthy controls. If patient group overlapped with another study, the study with the larger sample size was retained. A paper was excluded if the patient group was not afflicted with migraine as defined by the International Headache Society (Headache Classification Committee of the International Headache Society (IHS) 2013) (presence of cluster headache, medication-overuse headache, tension headache, etc.). Furthermore, studies performing whole-brain analysis and reporting results coordinates in a standard stereotactic space (MNI or Talairach) were separated from studies performing ROI analysis or that failed to include stereotactic coordinates of the results. For DTI studies, we did not exclude articles which did not report stereotactic coordinates of the results as it did not appear to be a common practice. For each paper, demographics and headache profile of the sample and analysis methods were extracted.

3.1.2. SDM-PSI meta-analysis

Regarding VBM or SBM studies, if a sufficient number of studies (>10 studies) was obtained during the systematic review of the literature, results of those studies were combined with Seed-based d Mapping with Permutation of Subject Images (SDM-PSI) using the SDM-PSI software (version 6,21, sdmproject.com) to identify brain structures that were consistently affected in migraine. The full SDM-PSI procedure is described in the tutorial available on their website (Albajes-Eizagirre et al. 2019a). First, when a study reported a significant difference between the control and migraine group, coordinates of the peaks of significant clusters and the associated t-value were extracted. If the original study reported *z-s*cores or p-values instead of *t-values*, they were converted to t-values using the online tool provided by the SDM project website (sdmproject.com). Negative studies were included in the meta-analysis. Preprocessing was performed according to standard SDM-PSI parameters, using a 20 mm full width half maximum (FWHM) anisotropic Gaussian kernel and 2mm voxel size. As advocated by SDM-PSI guidelines, significant results were thresholded using a family-wise error (FWE) correction based on threshold-free cluster threshold enhancement (TFCE) with corrected p-value threshold of 0.05 and a minimal cluster extent of 10 voxels. However, this FWE correction can be an overly conservative strategy in some situations and lead to false negative results (Albajes-Eizagirre et al. 2019b). Therefore, significant results were also thresholded with a very lenient voxel uncorrected p-value threshold of 0.025 and a minimal cluster extent of 10 voxels as an exploratory strategy.

3.2. Results

3.2.1. VBM – Gray matter

The search strategy resulted in 61 relevant documents among which only 23 were retained (Table 2, Figure 2). Some articles investigated more than one subtype of migraine: results are then considered separately for

the meta-analysis elevating the number of "actual" studies to 32. They involved a total of 1172 healthy participants and 1071 migraineurs.

Out of 32 studies, 23 (72%) found differences in GM volume in migraine. 18 (56%) observed a decrease and 13 (41%) an increase of GM volume in the brain, including 8 studies (25%) reporting both GM volume increases and decreases in migraine. The meta-analysis indicated no consistent GM volume increase or decrease in the migraine group, even with a lenient statistical threshold (uncorrected $p<0.025$).

3.2.2. VBM – White matter

Out of the 27 articles retained for the meta-analysis of GM volume, only 8 analyzed WM volume. 2 of these eight investigated two subtypes of migraine elevating the number of "actual" studies to 10 (Table 2, Figure 3). They involved a total of 249 healthy participants and 269 migraineurs.

Out of ten studies, five (50%) found increases in WM volume in migraine, including one study (10%) reporting both WM volume increases and decreases in migraine. The meta-analysis indicated no consistent WM volume increase or decrease in the migraine group, even with a lenient statistical threshold (uncorrected $p<0.025$).

3.2.3. SBM – Cortical thickness

The search strategy resulted in 42 relevant documents among which only 12 were retained (Table 3, Fig. 2). Some articles investigated two subtypes of migraine: results are then considered separately for the meta-analysis elevating the number of "actual" studies to 16 (Table 3). They involved a total of 848 healthy participants and 776 migraineurs.

Out of 16 studies, 9 studies (56%) found differences in cortical thickness in migraine. 6 studies (38%) observed decreases of cortical thickness, 4 studies (25%) observed increases of cortical thickness and 1 study (6%) reported both increases and decreases of cortical thickness in migraine. The meta-analysis indicated no consistent cortical thickness increase or decrease in the migraine group, even with a lenient statistical threshold (uncorrected $p<0.025$).

Others surface metrics

Only two studies (including the present one) have investigated cortical gyrification. Zhang and colleagues found an increased gyrification index in left postcentral gyrus, superior parietal lobule and right lateral occipital cortex, and decreased gyrification index in the left rostral middle frontal gyrus in migraine (Zhang et al. 2017), while our study did not observe any group difference. Only two studies (including the present one) have investigated sulcus depth and none of them detected a significant difference between migraine and control groups (Zhang et al. 2017).

3.2.4. DTI

The search strategy resulted in 57 relevant documents among which only 7 were retained.Some articles investigated two subtypes of migraine: results are then considered separately for the meta-analysis elevating the number of "actual" studies to twelve (Table 4). They involved a total of 252 healthy participants and 352 migraineurs.

No SDM-PSI analysis was conducted regarding DTI studies as no stereotactic coordinates of significant results were reported in the articles. In the following, we will consider *decreased* FA or AD and *increased* MD or RD as a sign of altered WM integrity. Out of twelve studies, four (33%) found differences in WM integrity. Decreased WM integrity in migraine was detected in three studies (25%), which involved 86 healthy participants and 91 migraineurs, in different fiber tracts depending on the studies. Only one study (8%) reported increased WM integrity in migraine. Further information is available in Table 4.

3.3. Discussion

All studies considered here investigated brain structures during the interictal period, for obvious practical considerations and also because some results suggest that the migraine headaches cause transient changes of the brain structure (Coppola et al. 2015), which may not reflect long-term alterations of the migraine brain. It is noteworthy that migraine symptoms are not exclusive to the ictal period. If sensory disturbances clearly climax during the attacks, alterations of sensory processing extend beyond the ictal state (Main et al. 1997; Vingen et al. 1998; Granovsky et al. 2018; Lévêque et al. 2020). Migraine may be associated to minor cognitive dysfunctions interictally (Zeitlin and Oddy 1984; Hooker and Raskin 1986; Mongini et al. 2005; Vuralli et al. 2018) and to vertigo and dizziness episodes (Vuković et al. 2007; Cha et al. 2009).

SDM-PSI analysis is a powerful tool to investigate the spatial convergence of reported structural alterations in morphometry studies. It is an improvement compared to previous coordinate-based meta-analysis (CBMA) methods such as the popular Activation Likelihood Estimation (ALE) (Eickhoff et al. 2012), notably because it allows to take into account studies with null results and the peaks' effect size in positive studies, and uses the jack-knife analysis to limit the contribution of a small subset of studies. The systematic review of the literature resulted in a sufficient number of studies for a SDM-PSI analysis for GM volume, WM volume, and cortical thickness. For either of these metrics, no significant difference between the control and the migraine groups was detected, even with a lenient statistical threshold. Regarding WM volume, the relatively low number of studies makes any conclusion uncertain. It appears that there is a tendency of WM loss on migraine as half of the studies reported WM volume decrease while only one reported WM volume increase. However, reported loci of WM volume decrease are relatively scattered across the brain. The situation is even more obscure concerning cortical thickness, since a similar number of studies reported cortical thickness increase and decrease which affected cortical areas dispersed across the cortical surface.

Finally, regarding DTI, a minority of studies reported alteration of white matter tracts in migraine. When they did, reported anatomical alterations were generally widespread but did not necessarily intersected across

studies. In studies only investigating regions of interest (not presenting whole-brain analyses), alterations of white matter integrity in migraine were reported in regions as diverse as the thalamus (Coppola et al. 2014), the brainstem (Kara et al. 2013; Marciszewski et al. 2018), the corpus callosum (Li et al. 2011; Yuan et al. 2012), visual processing networks (Granziera et al. 2006; Rocca et al. 2008) or fronto-insular tracts (Gomez-Beldarrain et al. 2016; Liu et al. 2018).

In conclusion, for these three metrics of brain anatomical integrity, there is no emerging pattern of anatomical alteration in migraine.

4. General discussion

The question which underlies this whole study was quite simple: *are there chronic anatomical alterations of the brain associated to migraine?* In spite of a rich and growing literature, we are still far from a consensus on whether migraineurs present such alterations and which brain areas are potentially affected. Previous studies reported highly heterogeneous results, either in terms of the presence of a group effect or in terms of the direction and the localization of a potential effect. Can we make sense of this conflicting literature?

4.1. Heterogeneity of protocols, heterogeneity of results?

As illustrated in the tables 2 to 4, there exists quite a heterogeneity in the protocols chosen in previous studies in the literature.

First, numerous studies have favored investigating one subtype of migraine (migraine with/without aura, episodic/chronic migraine, vestibular migraine), in an attempt to reduce the variability in the migraine group. Previous results suggest that migraineurs with aura may differ anatomically from migraineurs without aura in terms of GM volume (Messina et al. 2017), of cortical thickness (Magon et al. 2018), and white matter integrity (Szabó et al. 2017; Shibata et al. 2018), highlighting the importance of considering the two groups separately. Vestibular migraine differed from other types of migraine in terms of GM volume (Messina et al. 2017). Finally, GM damage appears to be increased in chronic compared to episodic migraine (Neeb et al. 2017; Chen et al. 2018) and it correlates with attack frequency (Valfrè et al. 2007; Kim et al. 2008; Schmitz et al. 2008; Neeb et al. 2017; Messina et al. 2018). In conclusion, based on the literature, it is probable that each subtype of migraine presents a specific anatomical signature. More studies are needed for this hypothesis to be tested in a meta-analysis.

Second, all the studies considered here are not necessarily homogenous in terms of demographic characteristics. The mean age of the migraine sample ranges from under 30 to over 70 years old while there are suspicions that anatomical alterations evolve with age (Schmitz et al. 2008; Liu et al. 2013; Chong et al. 2014; Neeb et al. 2017; Messina et al. 2018). Gender seems to interact with the pathology (Dai et al. 2015), yet some studies chose to only include women and other (including the present study) opted for a sex-ratio closer to the migraine sex-ratio in the general population. Other variables such as comorbidities, education level, or medication overuse may interact with the pathology and affect the patterns of anatomical alterations.

Finally, if voxel-based and surface-based morphometry analyses are based on standardized, streamlined workflows, slight deviations in the parameters can affect results in a major way. As illustrated in the tables 2 to 4, there are discrepancies on the statistical thresholds applied in such analyses: some studies have opted for uncorrected p-values, which is often an overly lax statistical strategy, or for a cluster-level control of FWE (implemented by default in SPM12 statistics) which is unlikely to be appropriate for VBM as it assumes stationary smoothness (Ridgway et al. 2008). Inappropriate or lax statistical strategies may have led to a disproportionate rate of false positives, accounting for some of the heterogeneity in previous results. However, if we presume that there is a major anatomical alteration in migraine (i.e. with a large effect size), it should have been detected consistently, irrespective of the statistical strategy and therefore it should have been revealed through this meta-analysis.

4.2. A lack of statistical power?

Small sample sizes can be appropriate for exploratory studies as trivial effects are very unlikely to reach significance which ensures that only large-sized effects with actual scientific importance will be detected (Friston 2012). However, low statistical power reduces the reproducibility of the results and increase the probability of false positives (Button et al. 2013). Moreover, if subtle effects are to be expected, scrupulous matching of the control participants is crucial in order to avoid the detection of spurious effects (May 2009).

Statistical power is usually relatively satisfactory in the studies considered in this meta-analysis. Most studies presented a sample size superior to 20 participants (in each group), especially in SBM and DTI studies. Some of them presented a sample size superior to 60 participants, ensuring the detection of even small effects and a limited probability of a false positive (Friston 2012). Interestingly, out of the three VBM studies with a large sample size (>60), only one of them detected an effect on GM volume. Out of the three SBM studies with a large sample size (>60), two of them detected an effect on cortical thickness, but not in the same direction. Such observations do not support the hypothesis of the presence of brain anatomical alterations in migraine.

4.3. The issue of publication bias

Publication bias is a widespread concern which is known to distort the results of meta-analyses as positive results are more likely to be published than negative results (Thornton and Lee 2000). This risk is consubstantial to any attempt of performing a meta-analysis. There exist tools to evaluate publication bias in coordinate-based meta-analyses based of the reported effect sizes of the significant loci (Acar et al. 2018). However, their role is to assess the robustness of convergent results, a prerequisite which is not fullfilled in the present situation. Beyond the fact that the reported structural alterations associated to migraine in the literature are widely inconsistent, there are other serious signs that the publication bias might be particularly exacerbated in the present situation.

First, anatomical images (especially T1-weighted MRI images) are routinely acquired in numerous studies, notably in functional studies using fMRI. It is very likely that many scientific teams have usable

datasets available for morphometry analyses. Second, voxel- and surface-based morphometry are fairly simple to use and widely available techniques, as streamlined workflows exist in two common free analysis toolboxes (SPM and FSL). They do not necessitate much of computing power nor are they too time-consuming. It is reasonable to assume that numerous researchers in the field of migraine have attempted to analyze their anatomical data but that a large part of these analyses have never got published due to unconvincing results. Regarding VBM and SBM studies, even in the available literature, between one third and half of the articles did not report any significant difference between the control and migraine participants. It is probable that this proportion of negative results would be much higher if unpublished analyses were to be considered. Such proportions do not reassure on the actual presence of anatomical alterations in migraine.

This reasoning is not as appropriate for DTI studies as diffusion sequences are not routinely acquired in functional studies and as DTI analysis workflows are less common and streamlined than their VBM counterparts.

5. Conclusions and future directions

Previous studies reporting anatomical alterations in migraine do not converge neither on the direction nor on the spatial localization of the effect. Negative results are quite prevalent, especially in the context of a potentially strong publication bias. Based on current knowledge, there is to this day no strong evidence for the presence of systematic brain anatomical abnormalities associated to migraine. However, this study alone is not sufficient to rule out the existence of subtle anatomical alterations in migraine nor the existence of alterations specific to some migraine subtypes. Also, the number of studies on WM integrity and cortical surface in migraine is still quite low leading to weak conclusions. Further research is needed to produce a better picture.

What could be the next steps in researching brain anatomy alterations in migraine?

Small-sized, exploratory studies do not appear to be sufficient to shed light on possible anatomical alterations in migraine, especially regarding GM alterations. If a large-size effect existed, it should have been consistently reported by these studies. However, it remains scientifically crucial to keep on reporting morphometry analyses results, even if the statistical power is low, in order to provide information for future meta-analyses.

One of the major future developments could be longitudinal studies at different timescales. Migraine has been postulated to be a progressive disease with brain damage accumulating over the years, even if this proposition is controversial (May 2009). To our knowledge, at least two studies have attempted to study long-term effects of migraine (after a one-year or a four-year follow-up evaluation) with promising results (Liu et al. 2013; Messina et al. 2018). Further research is needed to confirm those results. It would be particularly interesting to investigate through longitudinal studies if spontaneous migraine remission with

age is associated to a receding of anatomical alterations. On a different timescale, it has been suggested that anatomical alterations evolve along the migraine cycle (Coppola et al. 2015). All but one study in this article reported structural images during the interictal period. Deeper understanding of the dynamics of brain plasticity during the migraine cycle through short-term longitudinal studies would be of great interest.

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Fig. 1 New Data. Voxels with a significant decrease of white matter volume in migraine participants (n=19) compared to healthy controls (n=19). From left to right, sagittal, coronal and axial views, MNI coordinates of the views are reported on the figure.

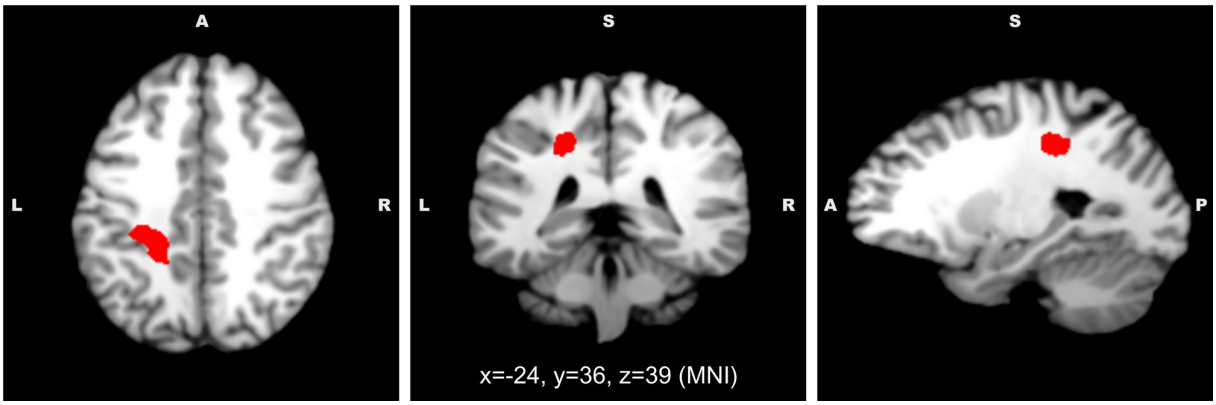

Fig. 2 Search strategy used for the inclusion of the studies considered in the present meta-analysis.

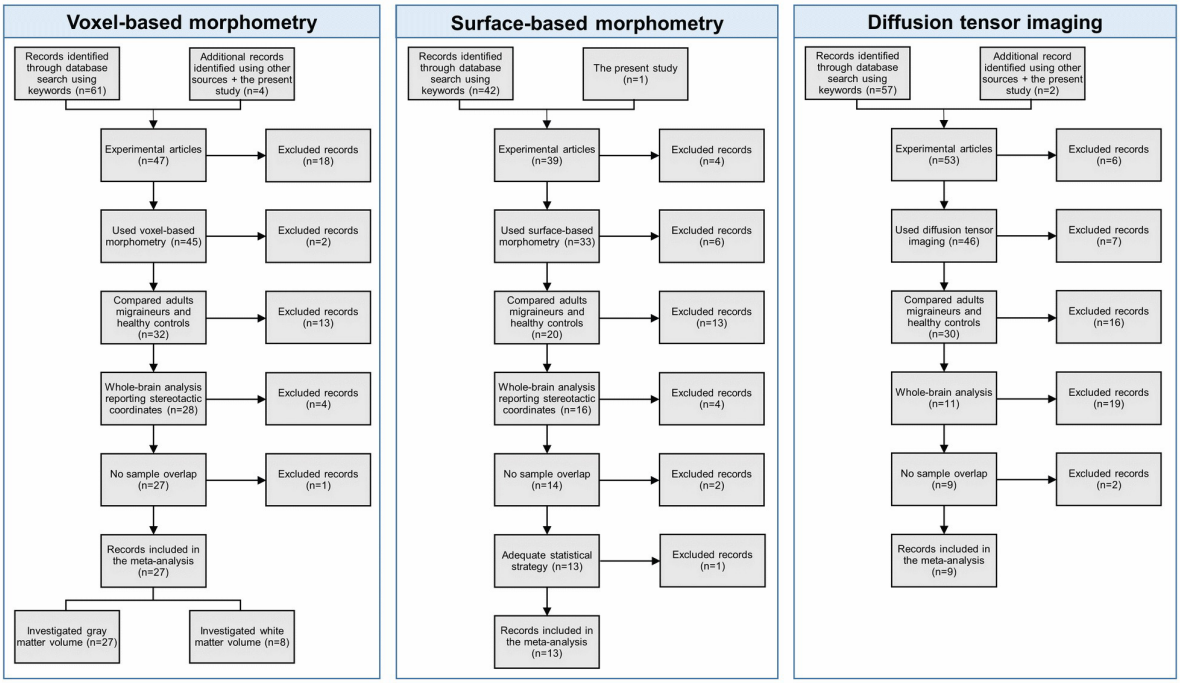

Fig. 3 Here are reported on a standard T1-weighted image all loci from the literature in which a significant difference in grey matter volume, white matter volume and cortical thickness in migraine has been detected (respectively n=32, n=10 and n=16 studies). Foci are blurred using a Gaussian filter with a Full-Width Height Maximum value computed based on the sample size of the study. The green gradient corresponds to an increase in migraine, the red gradient corresponds to a decrease in migraine. Please note that some studies have reported only the peak of significant clusters while others also reported also local maxima inside the significant cluster: a relatively high concentration of foci may not necessarily reflect convergence between studies.

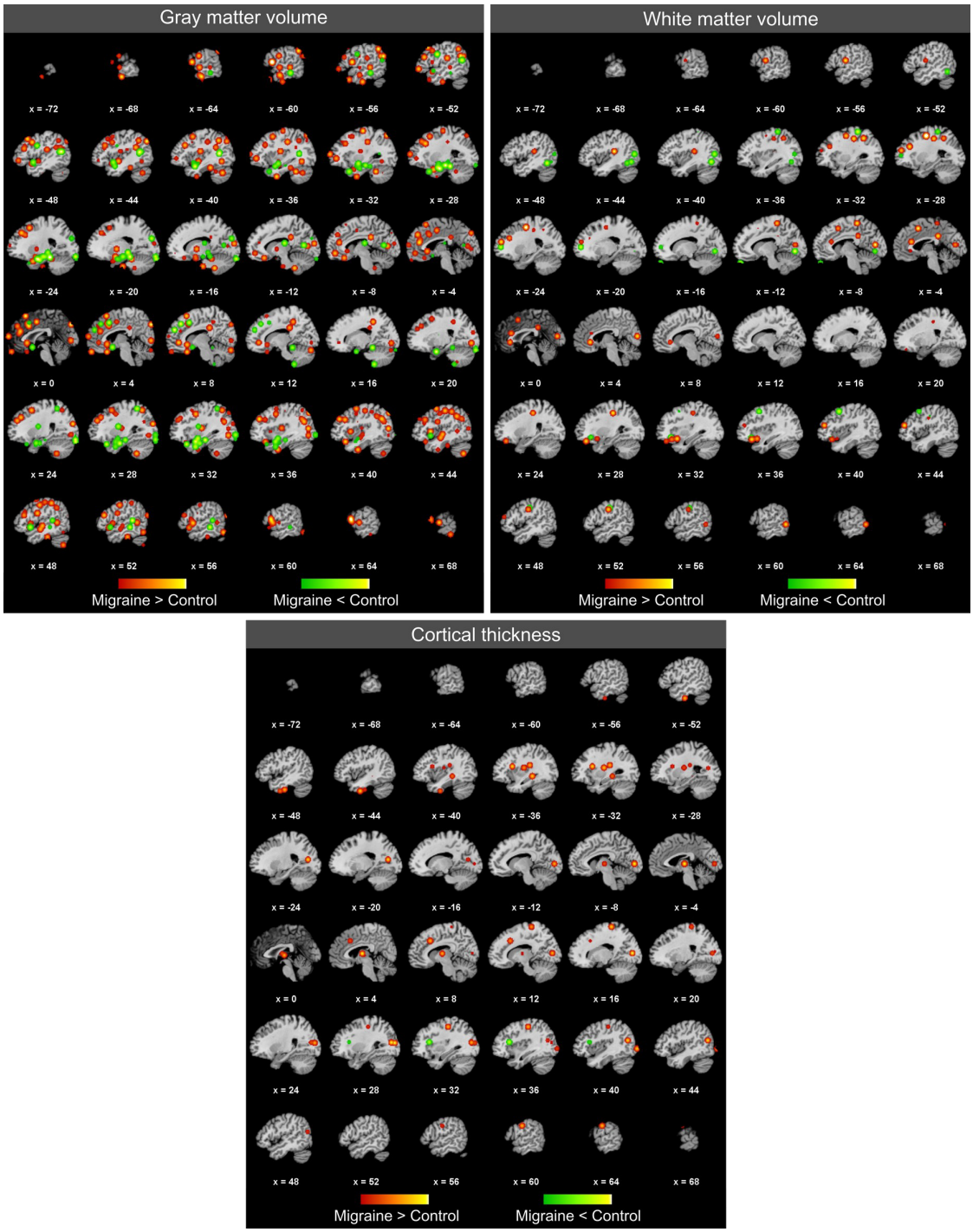

Table 1 New Data. Demographics and headache profile of the control and migraine groups. HIT-6 scores are comprised between 36 (negligible impact of migraine on daily life) and 78. MIDAS scores between 0 and 5 correspond to little to no disability due to migraine, while scores higher than 21 correspond to a severe disability. Mean and standard deviation are provided when relevant. Group differences are tested using non-parametric Mann-Whitney U tests. NA: not applicable.

	Control	Migraine	p-value
Sample size	19	19	-
Age (years)	33.6 (11.5)	32.7 (8.7)	0,93
Sex (number of female participants)	13 (68%)	13 (68%)	-
Total intracranial volume (mm3)	1543.1 (102.6)	1546.9 (173.8)	0,73
Laterality (number of right-handed)	19	19	-
Attacks per month	NA	3.3 (1.1)	-
Migraine duration (years)	NA	16.8 (7.4)	-
HIT-6 score	NA	64.2 (7.1)	-
MIDAS score	NA	12.8 (12.1)	-

Table 2 Summary of the voxel-based morphometry (VBM) studies included in the meta-analysis. N.T. = not tested, MwA = migraine with aura, MwoA = migraine without aura, FWE = family-wise error, FDR = false detection rate, TFCE = threshold-free cluster enhancement, vox = voxels, FWHM = full-width height maximum.

Table 3 Summary of the surface-based morphometry (SBM) studies included in the meta-analysis. N.T. = not tested, MwA = migraine with aura, MwoA = migraine without aura, FWE = family-wise error, FDR = false detection rate, TFCE = threshold-free cluster enhancement, vox = voxels, FWHM = full-width height maximum.

Table 4 Summary of the diffusion tensor imaging studies (DTI) included in the meta-analysis. N.T. = not tested, MwA = migraine with aura, MwoA = migraine without aura, TBSS = tract-based spatial statistics.

Article	Subtype of Migraine	Aura	Sample size		Female		Age		Frequency (attacks per month)	Scanner (T)	FWHM	Threshold	Software	Significant diff GM		Significant diff WM	
			Control	Migraine	Control	Migraine	Control	Migraine						Decrease	Increase	Decrease	Increase
Arkink 2017	unknown	MwoA	48	19	30	18	47.0	47.0	unknown	1.5	8	P<0.05 (FWE corrected) + p<0.001 (vox> 100)	SPM8	Yes	No	Yes	No
		MwA	48	14	30	13	47.0	47.0	unknown					Yes	Yes	Yes	No
Celle 2018	Episodic	MwA or MwoA	39	25	30	16	75.4	75.0	7.4	1.5	8	P<0.05 (FWE corrected. cluster-level)	SPM8	No	No	No	No
Chen 2018	Episodic or chronic	unknown	43	56	28	37	36.2	37.5	13.8	3	8	P<0.05 (FWE corrected cluster-level with p<0.005 for cluster formation. vox > 271)	SPM8	Yes	Yes	N.T.	N.T.
Coppola 2017	Chronic	unknown	20	20	13	14	28.5	31.3	23.0	3	8	P<0.001 uncorrected	SPM12 / CAT12	Yes	No	N.T.	N.T.
Coppola 2015	Episodic	MwoA	15	14	11	11	28.6	31.6	3.4	3	12	P<0.001 uncorrected	SPM8	Yes	No	N.T.	N.T.
Hougaard 2016	Episodic	MwA	60	60	42	42	33.3	33.3	1.0	3	6.9	P<0.05 (TFCE)	FSL-VBM	No	No	N.T.	N.T.
Hubbard 2014	Episodic or chronic	unknown	18	17	13	14	41.7	38.9	unknown	unknown	8	P<0.05 (FWE corrected. cluster-level with p<0.005 for cluster formation, vox >100)	FSL-VBM	No	Yes	N.T.	N.T.
Husøy 2019	unknown	unknown	309	80	124	60	57.4	58.7	unknown	1.5	8	P<0.05 (FWE corrected. cluster-level)	SPM12	No	No	N.T.	N.T.
Kim 2008	Episodic	MwA or MwoA	33	20	29	17	33.7	33.8	2.7	1.5	10	P<0.001 vox >200 + small volume correction p<0.005	SPM2	Yes	No	N.T.	N.T.
Lai 2016	Chronic	unknown	33	33	27	27	39.7	39.7	19.5	1.5	8	P<0.05 (FWE corrected. cluster-level with p<0.005 vox >266)	SPM8	Yes	No	N.T.	N.T.
Liu 2017	Episodic	MwoA	80	50	80	50	22.6	22.8	6.3	3	4	P<0.05 (FWE corrected. cluster-level with T=2)	FSL-VBM	No	Yes	N.T.	N.T.
Liu 2015	Episodic	MwoA	111	135	111	135	21.3	21.7	6.4	3	4	P<0.05 (FWE corrected. cluster-level with T=2)	FSL-VBM	Yes	Yes	N.T.	N.T.
Matharu 2003	unknown	MwoA	17	17	16	16	34.0	34.0	unknown	2	unknown	Ps<0.05 (FWE corrected). Ps<0.005 uncorrected for dorsal pons and hypothalamus	SPM99	No	No	No	No
		MwA	11	11	10	10	31.0	31.0	unknown					No	No	No	No
Messina 2017	Vestibular and episodic	unknown	20	19	13	12	36.9	40.0	6.0	3	8	P<0.001 uncorrected. vox>10	SPM12	No	Yes	N.T.	N.T.
	Non-vestibular and episodic	MwA	20	19	13	12	36.9	35.1	2.0					Yes	Yes	N.T.	N.T.
		MwoA	20	19	13	13	36.9	35.5	5.0					Yes	Yes	N.T.	N.T.
Messina 2018	Episodic	MwA or MwoA	46	73	29	50	32.9	35.1	3.5	3	8	P<0.001 uncorrected. vox>10	SPM12	Yes	Yes	N.T.	N.T.
Neeb 2017	Chronic	MwoA	21	21	15	15	49.4	49.04	17.4	3	10	P<0.001 uncorrected	SPM8	No	Yes	N.T.	N.T.
	Episodic		21	21	15	15	49.4	49.36	5.3					Yes	Yes	N.T.	N.T.
Obermann 2014	Vestibular and episodic	unknown	17	17	14	14	42.2	42.7	3.8	1.5	10	P<0.001 uncorrected	SPM8	Yes	No	N.T.	N.T.
Palm-Meinders 2017	Episodic	MwA or MwoA	35	84	25	57	54.6	57.8	0.8	1.5	8	P<0.001 uncorrected. vox > 20	SPM8	Yes	Yes	Yes	No
Rocca 2006	Episodic	MwA or MwoA	15	16	13	15	38.6	42.7	1.7	3	12	P<0.001 uncorrected	SPM2	Yes	No	N.T.	N.T.
Russo 2012	Episodic	MwoA	14	14	7	7	28.6	30.6	6.0	3	8	P<0.001 uncorrected. vox > 100	SPM8	No	No	N.T.	N.T.
Schmidt-Wilcke 2008	Episodic or chronic	unknown	32	31	32	31	32.3	32.4	unknown	1.5	12	P<0.05 FWE corrected + small volume correction on subcortical areas and cingulate cortex	SPM2	Yes	No	No	No
Schmitz 2008	Episodic	MwA or MwoA	28	28	28	28	42.5	43.5	3.5	3	10	P < 0.001	SPM2	Yes	No	Yes	Yes
Tedeschi 2016	Episodic	MwA or MwoA	20	40	12	24	29.2	30.1	3.7	3	unknown	P<0.001 uncorrected. vox>100	SPM8	No	No	No	No
Tessitore 2013	Episodic	MwoA	20	20	10	10	28.9	28.2	6.0	3	8	P<0.001 uncorrected. vox>100	SPM8	No	No	N.T.	N.T.
Valfre 2007	Episodic or chronic	MwA or MwoA	27	27	21	20	34.9	34.9	11.8	3	12	P<0.05 with small volume correction	SPM2	Yes	No	N.T.	N.T.
Zhang 2017	Episodic	MwoA	32	32	24	24	38.8	38.3	3.4	3	8	P<0.05 (FDR corrected with P<0.005 threshold)	SPM12 / CAT12	No	Yes	N.T.	N.T.
Present study	Episodic	MwoA	19	19	13	13	31.2	32.7	3.3	3	10	P<0.05 TFCE + FWE corrected	SPM12 / CAT12	No	No	Yes	No

	Subtype of Migraine	Aura	Sample size		Female		Age		Frequency (attacks per month)	Scanner (T)	Threshold	Software	Cortical thickness		Cortical gyrification		Sulcus depth	
			Control	Migraine	Control	Migraine	Control	Migraine					Decrease	Increase	Decrease	Increase	Decrease	Increase
Datta 2011	Episodic	MwoA	28	28	24	24	33.0	35.0	3.4	3	P<0.05 (permutations + FDR corrected)	Freesurfer	No	No	N.T.	N.T.	N.T.	N.T.
		MwA	28	28	24	24	33.0	35.0	4.1				No	No	N.T.	N.T.	N.T.	N.T.
Gaist 2018	Episodic or chronic	MwA	137	166	137	166	48.0	48.0	unknown	3	P<0.05 (Monte-Carlo)	Freesurfer	No	Yes	N.T.	N.T.	N.T.	N.T.
Hougaard 2016	Episodic	MwA	60	60	42	42	33.3	33.3	1.0	3	P<0.05 (Cluster-based permutations)	FSL-VBM	No	No	N.T.	N.T.	N.T.	N.T.
Hubbard 2014	Episodic or chronic	unknown	18	17	13	14	41.7	38.9	unknown	unknown	P<0.005 (Cluster forming threshold p<0.005, vox > 100, random-field-theory-based corrected)	FSL-VBM	Yes	No	N.T.	N.T.	N.T.	N.T.
Husøy 2019	Episodic or chronic	unknown	309	80	124	60	57.4	58.7	unknown	1.5	P<0.05 (FDR)	Freesurfer	No	No	N.T.	N.T.	N.T.	N.T.
Kim 2014	Episodic	MwoA	34	56	56	34	34.2	35.7	2.5	3	P<0.05 (Monte-Carlo)	Freesurfer	No	Yes	N.T.	N.T.	N.T.	N.T.
Maleki 2015	Episodic or chronic	unknown	46	46	46	46	34.1	34.7	unknown	3	P<0.05 (Monte-Carlo)	Freesurfer	No	Yes	N.T.	N.T.	N.T.	N.T.
Messina 2013	Episodic or chronic	MwoA	18	31	13	22	37.2	38.6	unknown	3	P<0.01 uncorrected vox > 100 / p<0.05 FDR	Freesurfer	Yes	No	N.T.	N.T.	N.T.	N.T.
	Episodic or chronic	MwA		32	13	20	37.2	35.2	unknown				Yes	No	N.T.	N.T.	N.T.	N.T.
Petrusic 2018	Episodic	MwA	30	48	23	36	39.6	39.3	0.7	1.5	P<0.05 (Monte-Carlo)	FSL 5 – Freesurfer	No	No	N.T.	N.T.	No	No
Zhang 2017	Episodic	MwoA	32	32	24	24	38.8	38.3	3.4	3	P<0.05 (Cluster forming threshold p<0.005 + FDR corrected)	SPM12 / CAT12	Yes	Yes	Yes	Yes	N.T.	N.T.
Woldeamanuel 2019	Chronic	MwA or MwoA	30	30	24	24	40.0	40.0	27.0	3	P<0.001 + FDR corrected or cluster corrected	Freesurfer	No	No	N.T.	N.T.	N.T.	N.T.
Magon 2018	Episodic	MwA	115	38	81	109	29.1	30.8	3.3	3	P<0.05 (FDR corrected)	Freesurfer	Yes	No	N.T.	N.T.	N.T.	N.T.
		MwoA		93									Yes	No				
Present study	Episodic	MwoA	19	19	13	13	31.2	32.7	3.3	3	P<0.05 TFCE + FWE corrected	SPM12 / CAT12	No	No	No	No	No	No

Article	Type of Migraine	Aura	Sample size		Female		Age		Frequency (attacks per month)	Scanner (T)	Software	White matter integrity	Localization
			Control	Migraine	Control	Migraine	Control	Migraine					
Chong 2015	Episodic or chronic	unknown	18	23	12	15	37.7	38.5	7.9	3	TRACULA	Decreased	Left and right anterior thalamic radiations, the left corticospinal tract, and the right inferior longitudinal fasciculus tract
Neeb 2015	Episodic	MwoA	21	21	15	15	49.4	49.4	5.3	3	TBSS FSL	-	
	Chronic		21	21	15	15	49.4	49.0	17.4			-	
Schmitz 2008	Episodic	MwA or MwoA	28	28	28	28	42.5	43.5	3.5	3	In house software	Decreased	Frontal lobes, the brainstem, and the cerebellum
Shibata 2018	Episodic	MwoA	46	68	37	59	38.4	40.8	5.0	1.5	TBSS FSL	-	
		MwA	46	17	37	14	38.4	40.1	3.3			-	
Szabo 2017	Episodic	MwoA	28	25	25	22	31.7	35.7	1.1	1.5	TBSS FSL	-	
		MwA	28	18	25	15	31.7	32.1	1.2			Increased	Bilaterally in the parieto-occipital white matter, the corpus callosum, and the cingular white matter
Tedeschi 2016	Episodic	MwA or MwoA	20	40	12	24	29.2	30.1	3.7	3	TBSS FSL	-	
Yu 2013	Episodic	MwoA	40	40	16	29	33.2	35.9	4.9	3	TBSS FSL	Decreased	Widespread alterations: corpus callosum, internal capsule, cerebral pedoncule, corona radiata, cingulum bundle, corticospinal tract, thalamus radiation, superior longitudinal fasciculus.
Zhang 2017	Episodic	MwoA	32	32	24	24	38.8	38.3	3.4	3	FSL + SPM12	-	
Present study	Episodic	MwoA	19	19	13	13	31.2	32.7	3.3	3	TBSS FSL	-	

Part V

General discussion

The discussion sections presented in each article of the "Experimental works" part have already pointed out the major implications of each study. The aim of the present section is to link results together and presenting how they fit in a more general framework. Additionally, in each section, I will propose future lines of research that could be useful to further our understanding.

1 What happens when we hear a novel sound?

Alfred North Whitehead wrote in 1929 in his "*Process and Reality*": "The safest general characterization of the European philosophical tradition is that it consists of a series of footnotes to Plato.". The same could be said (provocatively) of the research field of attention. It consists of "a series of footnotes" to research pioneers from the 1960's and 1970's – namely Solokov, Kahneman, Näätänen, or Posner, whose frameworks still shape and influence the way we think about the attention function. As I will discuss below, even if our results contradict some assumptions in recent studies about distraction, they are not radical from a historical point of view and fit quite well with early descriptions and theories of attention orienting.

1.1 Distractors are not always distracting

At the turn of the millennium, the "distraction-oddball paradigm" was becoming a popular tool of choice in researching auditory distraction, due to the influential work of Escera et al. (1998) and Schröger and Wolff (1998b) (for a full discussion, see p.94). As a reminder, this distraction paradigm consists in playing an oddball sound shortly before the target stimulus: deviant and/or novel sounds are expected to trigger involuntary attention switching, leading to prolonged reaction time to the successive target stimulus. It was inspired by previous studies showing "delayed RTs to target stimuli caused by preceding irrelevant sound changes or novels sounds". In the introduction of the article, Escera was well aware that involuntary attention switches should be understood in the framework of the orienting response (OR). However, the fact that the OR comprises an arousal component in addition with the attention orienting component is not further discussed and the behavioral impact of novel sounds is solely attributed to bottom-up attention. In the beginning of the 2010's, paradoxical results began to emerge with studies showing non-distracting novel sounds (Li, Parmentier, and Zhang 2013; Ljungberg et al. 2012; Parmentier, Elsley, and Ljungberg 2010; Parmentier 2014) or even facilitating novel sounds which reduced reaction time instead of prolonging it (SanMiguel, Linden, and Escera 2010; Wetzel, Widmann, and Schröger 2012). Several voices

suggested that distractors may trigger beneficial arousal effects on top of the orienting cost, and that the ending behavioral result ultimately depended on task demands (SanMiguel, Linden, and Escera 2010; SanMiguel et al. 2010; Wetzel, Widmann, and Schröger 2012; Wetzel, Schröger, and Widmann 2013; Max et al. 2015; Schomaker and Meeter 2014; Schomaker and Meeter 2015). Distracting sounds were no longer only distracting.

The strength of the Competitive Attention Test (CAT) was that it managed to elicit both facilitation and distraction by novel sounds within the same task, only by varying the delay interval between the distractor and the target (Bidet-Caulet et al. 2015). However, there were still some open issues regarding how to interpret the results and new data were needed to respond to them, motivating the "Article 1".

First, the nature of the facilitation effect was still not elucidated. Bidet-Caulet et al. (2015) postulated that the facilitation effect was due to a phasic increase of arousal, which boosted target processing and made the participant more ready to respond. However, two other alternative hypotheses were raised by the literature and other researchers. Distracting sounds during the CAT might trigger a earlier attention shift towards the auditory modality, which would facilitate the processing of the auditory target. We demonstrated that the facilitation was modality-aspecific and was still present for visual targets. Distracting sounds may somewhat act as temporal cues by reminding the subject that a target will arrive "soon". This effect was limited in the original CAT paradigm by the fact that there is already a cue in all trials and that the distractor-target interval was variable forbidding any precise temporal prediction. The facilitation effect was still present during the alternative version of the CAT despite much longer (and still variable) distractor-target intervals which limited even more any temporal prediction. The only remaining hypothesis was the arousal-related facilitation.

Second, our work gave more precise insights into the dynamics of phasic arousal. In Bidet-Caulet et al. (2015), it was already apparent that attention capture and phasic arousal effects by distracting sounds shared a different dynamic: attention capture was short-lived and was prominent for distractors close to the target, phasic arousal was a more enduring effect which became visible once the attention capture effect has faded out (Figure 25). However, our work showed that the effect of phasic arousal was quite stable over time, as it was not significantly reduced after 1750 ms. This is in line with other measures of phasic arousal, such as pupil dilation response or skin conductance responses, which last several seconds before returning to baseline.

1.2 Rediscovering the P3a

The "distraction-oddball" paradigm caused a shift in how the P3a was perceived. The P3a has been associated with the orienting response and attention processing of novelty/deviance for a long time. However, it was after the popularization of the "distraction-oddball" paradigm that the P3a was considered an effective index of bottom-up attention capture, but also that it might be a biphasic component with an early fronto-central phase and a late fronto-parietal phase. The understanding that distractors trigger both attention capture and facilitation by arousal challenged the assumption that the P3a was solely an index of distraction. For this point, it was reasonable to imagine that the phasic arousal effect was also reflected at some point in the distractor-elicited ERPs. Our work shows that the amplitude of the early phase of the P3a correlates with the arousing properties of distracting sounds, but not that of the late phase. These results suggest that the early phase of the P3a is a specific index of the phasic arousal response triggered by novel sounds. They also reinforce the suspicion that the early and late phases of the P3a are functionally distinct entities, with the early-P3a representing the genuine P3a and the late-P3a often believed to represent the genuine index of attention capture (Barry and Rushby 2006; Escera et al. 2000; Roye, Jacobsen, and Schröger 2007). The two subcomponents do not share the same scalp topography, suggesting the involvement of different brain networks. The early-P3a/P3a is considered to be generated in the anterior cingulate cortex and various frontal areas, interestingly areas in common with the cingulo-opercular network responsible for maintaining alertness (Coste and Kleinschmidt 2016). To our knowledge, no study has attempted source reconstruction of the late-P3a per se: however, its scalp topography is very reminiscent of that of activities in the fronto-parietal attention networks (see Figure 4).

These conclusions may be of importance for a better understanding of past results. For example, Gumenyuk et al. (2005) observed that ADHD children are more distracted by novel sounds while their early-P3a is reduced and their late-P3a is enhanced. These paradoxical results that the authors struggled to interpret are better understood if the early-P3a is not considered as a marker of distraction, but of phasic arousal – especially in a disorder more and more associated with dysfunctional arousal regulation (Hegerl and Hensch 2014; Strauß et al. 2018). In the future, it might be valuable to have a reliable index of phasic arousal for both fundamental and clinical studies. However, further research is also needed to confirm and refine the association between the fronto-central P3a and phasic arousal. One of the shortcomings of our work is our failure to correlate the behavioral facilitation effect to the arousing properties of the distracting sounds and the P3a amplitude. Future studies should also explore how the P3a relates to autonomic measures of arousal, namely pupil dilation response, skin conductance response or heart rate variability.

1.3 Perspectives for the Competitive Attention Test

A more understated achievement of this thesis work is the replication of previous results obtained using the CAT, supplying additional evidence that the initial reported effects are robust (Bidet-Caulet et al. 2015). We replicated several times the behavioral effects – facilitation & distraction by distractors, benefits of the informational value of the cue – with independent samples and different versions of the task with various tweaks in the experimental design. We replicated results from ElShafei et al. (2018) with an independent sample of healthy participants by observing distinct sub-bands in the alpha rhythms in anticipation of the cue. These replications help to solidify the CAT as a reliable experimental paradigm to investigate the attention and arousal functions in healthy and clinical populations.

We took advantage of this paradigm and the clarifications the first study has provided to study the attention function in migraine.

2 Attention and migraine

Migraine is characterized by a sensory hypersensitivity at its peak during the headache, but which lingers between headaches. Since the 1980's, the framework that has prevailed to explain sensory disturbances in migraine was that they stemmed from a lack of habituation to repeated sensory stimulation. In a pair of articles, Demarquay et al. (2011b) and Morlet et al. (2014) showed that habituation to repeated auditory stimulation was actually preserved in migraine but on the other hand, they reported abnormal markers of attention capture among migraineurs, including the P3a. If habituation deficits could not account for sensory disturbances in migraine (at least in the auditory modality), another framework was needed. The migraine project described in this thesis was created with the intention to better characterize attentional alterations in migraine, with the hope that it would help to shed light on the hypersensitivity in migraine.

The previous work regarding the functional role of the P3a was useful for the interpretation of future results using the CAT with migraineurs as abnormal P3a responses were reported in migraine not only in Morlet et al. (2014), but also in other previous studies (Koo et al. 2013; Wang, Schoenen, and Timsit-Berthier 1995; Wang and Schoenen 1998).

2.1 A comprehensive view on attention dysfunction in migraine

As I discussed in the introduction (see p.88), there is already a quite substantial literature suggesting that the attention in general is moderately impaired in migraine (Vuralli, Ayata, and Bolay 2018). However, most of the neurophysiological tests used in this literature did

not specifically target attention, and the reported group effects may stem from a general cognitive dysfunction. It remained unclear which attention function was specifically impaired in migraine. And most of all, it was not known if the daily life of migraineurs was actually impacted by potential attentional alterations: to our knowledge, only a couple of studies reported that migraineurs were complaining of difficulties to concentrate before, during and after a headache (Giffin et al. 2003; Giffin et al. 2016).

Along this thesis work, we have investigated attention with various but complementary methods. First, through a questionnaire study, we confirmed that migraineurs indeed self-perceive attention difficulties in their daily life, outside of the headache period. Then we recorded EEG and MEG signals while migraine and control participants performed the CAT to understand which attention mechanism is dysfunctional in migraine. In the Table 1, you will find a summary of all the results obtained during this study. Disappointingly, there were no group difference in behavior: behavioral indexes of top-down attention, bottom-up attention and phasic arousal were unchanged in the migraine group. However, the analysis of M/EEG data showed that different attention function were affected. Markers of bottom-up attention were increased in migraine, namely the orienting component of the N1 to unattended distractors and attended targets, the RON and the activation of the right temporo-parietal junction (rTPJ). Regarding top-down attention mechanisms, the situation was a bit more complex. On the one hand, migraineurs showed enhanced recruitment of facilitatory mechanisms as reflected by the increased Nd. On the other hand, they displayed weaker alpha synchronization in the occipital cortices in anticipation of the target sound, suggesting deficient inhibitory processes. Migraine was not associated with any change in arousal effects compared to control participants. In summary, migraineurs appear to be more distractible than healthy individuals as they have difficulties suppressing irrelevant sensory information from the environment. However, based on these data, we hypothesize that migraineurs may have developed a compensatory strategy by recruiting more top-down facilitatory processes to counteract these shortcomings. In doing so, they reequilibrate the top-down/bottom-up balance and maintain adequate performance in tasks requiring to resist distraction such as the CAT.

It would be interesting to test this theory in future studies. If migraineurs have to engage more top-down processes to maintain task-efficiency, it would certainly be costlier in terms of cognitive resources. One could expect that the strategy would no longer hold in a more demanding task during which there are no spare cognitive resources left to actively counterbalance the deficiency in top-down inhibition and the exacerbated bottom-up attention.

Finally, we investigated the anatomy of the migraine brain using morphometry techniques with the hope of detecting a structural signature of the attention difficulties associated

in migraine. One could have expected anomalies in gray matter volume in the fronto-parietal attention networks, or an altered structural connectivity between the frontal, parietal and sensory cortices. No significant difference in gray matter volume, cortical thickness and shape, and in the integrity of white matter tracts was detected between migraineurs and healthy participants. This was confirmed by a systematic review and a coordinate-based meta-analysis of the literature about migraine anatomy. If numerous studies reported structural abnormalities associated with migraine, results were too inconsistent to reveal any robust structural signature of the disease. Given the present results, further investigations on the macrostructure of the migraine brain will probably not be a fruitful research endeavor and is not likely to inform much about the migraine pathophysiology.

2.2 Attention dysfunction and sensory symptoms

The end goal of this migraine project was to provide an alternative theory to the hypersensitivity symptoms in migraine, especially those associated with the pain-free period during which the headache pathophysiology can no longer account for the sensory disturbances. We hypothesize that deficient attentional filtering and/or exacerbated orienting responses to all incoming sounds could lead to the state of hyper-responsiveness associated with migraine. Some of our results support this theory. In the questionnaire study, interictal sensory sensitivity correlated with attention difficulties. Results from the M/EEG study suggest a likely underlying mechanism: the exacerbated bottom-up attention and the deficient top-down inhibitory processes would hinder the ability of migraineurs to ignore and suppress irrelevant events in their environment. This hypothesis is not so exotic and far-fetched as it has been also formulated in other neurological disorders. Atypical attention orienting has been proposed to participate in the excessive sensory discomfort experienced by autistic individuals (Gomot et al. 2002; Orekhova and Stroganova 2014). ADHD individuals often display atypical sensory sensitivity, which may be a core symptom of the disease (Bijlenga et al. 2017; Mangeot et al. 2001; Panagiotidi, Overton, and Stafford 2018; Parush et al. 1997).

However, it is important to tread carefully as there are major caveats to this conclusion. First, "correlation does not equal causation": as discussed in the Article 2, other explanations may account for the correlation between attention difficulties and interictal sensory sensitivity. The causality may be reversed: attention difficulties could also stem from hypersensitivity as sensory amplification caused by migraine would lead to exacerbated attention responses. Or attentional difficulties and enhanced sensory responsiveness could both originate from a common third cause, namely the individual predisposition to develop migraine. Second, participants from the M/EEG study all filled the questionnaire and all our attempts

		Top-Down Attention		Bottom-Up Attention	Arousal
		Facilitation	Inhibition		
Behavior	Cue effect	→			
	Attention capture effect			→	
	Facilitation effect				→
ERPs	Orienting component of the N1			↗ (to both distractor and target)	
	P3a/Early-P3				→
	Late-P3			→	
	RON			↗ (*)	
	Nd	↗			
	CNV (cue effect)	→			
Activations	rTPJ during the RON			↗ (*)	
	Gamma activity in the VAN			→	
Alpha rhythms	Pre-target occipital high alpha		↘		
	Pre-target temporal low alpha	→			

Table 1: Summary of all the behavioral and electrophysiological indexes investigated in migraine during this thesis work using the CAT. Arrows indicate if the index is increased, identical or decreased in the migraine group. Red color suggests a detrimental effect on attention filtering, green color a beneficial effect on attentional filtering. (*) The association of RON effects with only bottom-up attention is debatable.

to correlate the altered indexes of attention function (orienting component of the N1, RON, pre-target alpha, etc.) with the hypersensitivity scores did not produce any significant result. Therefore, further research is absolutely needed to provide more evidence in favor of a causal relationship between attention difficulties and the dysfunctional sensory processing in migraine.

Part VI

Conclusions

This thesis work has provided new insights on the attention function in migraine by integrating complementary techniques from questionnaires and behavior, to event-related responses, neural oscillations and anatomical analyses. Our results have led to the proposition of a new framework to understand the sensory symptoms associated with the interictal state of migraine. Our experimental protocol has proven to be efficient in the dissociation of the different facets of attention and to produce valuable behavioral and electrophysiological indexes of each attentional mechanism. Beyond our particular paradigm, this work has helped to define a marker of phasic arousal elicited by salient events, which may become a useful tool in basic and clinical research to more adequately investigate distraction and the orienting response. Finally, we have also shown that morphometric analyses are not a panacea for understanding the pathophysiology of a clinical disorder and do not necessarily lead to robust and reliable findings. In conclusion, we hope that this work may serve as a blueprint for the investigation of the attention function in other populations. Current projects within our research team are exploring distractibility using this experimental design during the development, in aging and in frontally-damaged individuals.

Part VII

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