A two-system theory of sensory-evoked brain responses

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Summary

Sudden and unexpected environmental stimuli likely signal events demanding immediate behavioural responses. These stimuli also trigger some of the largest and most widespread electrocortical responses in the awake mammalian brain. Many researchers implicitly interpret these sensory-evoked brain responses as mainly reflecting modality-specific sensory processing mediated by high-fidelity ‘lemniscal’ thalamocortical pathways to primary sensory cortices. Here we contend that this interpretation is unjustified. We provide evidence that virtually all electrocortical responses elicited by the sudden sensory stimuli used in systems and cognitive neuroscience are strongly contributed to by non-modality-specific processes mediated by diffuse ‘extralemniscal’ thalamocortical projections, reflected in the scalp vertex potential (VP). We conclude by suggesting a mechanism through which transient extralemniscal responses affect ongoing brain activity and promote swift reactions to sudden environmental changes.

Key words: EEG, fMRI, Saliency, Surprise, Thalamus, Cognitive Neuroscience, Sensory Systems, Urgent behaviour.

1 Brain responsiveness to surprising environmental stimuli

To survive in a dynamic world an organism must infer its state, a process that implies making predictions about sensory inputs (Friston 2009). Surprising environmental events reflect the violation of these predictions and often require behavioural reactions. Perhaps the simplest example of such an event is a sudden and isolated change of sensory energy, which breaks the expectation that the environment will remain stable in the short-term (Näätänen and Picton 1987; Somervail et al. 2021, 2022). Although sudden environmental changes may well reflect irrelevant situations, they can indicate a situation urgently demanding an immediate behavioural response.

These surprising changes of sensory energy elicit large and widespread cortical responses in several species, measurable using invasive and non-invasive electrophysiology (Figure 1; see **Section 3** for a detailed phenomenological description of these responses), as well as blood-flow based neuroimaging (Velasco et al. 1980, 1985; Velasco and Velasco 1986; Velasco, Velasco, and Velasco 1989; Velasco, Velasco, and Velasco III 1989; Mouraux and Iannetti 2009; Wang et al. 2010; Iannetti and Mouraux 2011; Valentini et al. 2011; Legrain et al. 2011; Torta et al. 2012; Liang et al. 2013; Hu et al. 2015; Novembre et al. 2018, 2023; Somervail et al. 2021, 2022). The fact that these responses are phenomenologically similar across different species suggests their importance for survival (Hu et al. 2015; Hu and Iannetti 2019; Somervail et al. 2021; Novembre et al. 2023).

The main issue we address in this Perspective is that the responses elicited by sudden stimuli are often used to study modality-specific processing in sensory cortical regions, with the implicit assumption that they are mediated by the canonical sensory pathways that project from specific thalamic relay nuclei to their corresponding primary sensory cortex (e.g. in Chen et al. 1979; Jones 1992; Hegerl et al. 1994; Martin and Boothroyd 2000, 1999; Iannetti et al. 2005; Spackman et al. 2006; Baumann et al. 2008; Ben-David et al. 2011; Carpenter and Shahin 2013; Baltzell and Billings 2014; Han and Dimitrijevic 2015; Paloyelis et al. 2016; Wagner et al. 2016; Squintani et al. 2018; Valeriani et al. 2021). However, several lines of evidence from humans and other animals clearly contradict this narrative. Indeed, there is a large and surprisingly neglected body of evidence indicating that the largest component of these responses, the vertex potential (VP[1]), reflects the activity of a diffuse ‘extralemniscal’ thalamocortical sensory system, which operates in parallel to the canonical ‘lemniscal’ sensory pathways. In this Perspective, we critically assess this evidence and provide a novel hypothesis about the function of these surprise-related responses[2].

2 The lemniscal and extralemniscal systems

Lemniscal system is a name for the canonical auditory and somatosensory pathways that transmit environmental information from the peripheral sensory organs to the granular layer of the corresponding primary sensory cortex via thalamic relay nuclei (i.e. the medial geniculate nucleus [MGN] and the ventroposterior nuclei [VPL and VPM]; Figure 2a). Although defined anatomically in these modalities, we extend the term to refer also to the visual pathways from the retina to visual cortex via the lateral geniculate nucleus.

Lemniscal pathways are modality-specific, and carry high-fidelity sensory information that allows detailed perception of the environment. For example, cells in the MGN (the thalamic relay nucleus for the auditory lemniscal pathways) display a clear tonotopy, building a population code that represents the spectral content of a sound (Kandel et al. 2013a). Similarly, the somatosensory lemniscal system comprises cells with precise somatotopic and frequency specificity (e.g. responding to flutter of a certain frequency in a limited skin area; Mountcastle 2005; Kandel et al. 2013b). Given their ability to faithfully encode a continuous sensory input, lemniscal responses are highly resistant to habituation when stimuli are repeated at short latency (Albe-Fessard and Besson 1973; Li et al. 2024). Understandably, these pathways have been a major research focus due to their importance in explaining perception.

The name *extralemniscal system* refers to a set of sensory pathways parallel to the modality-specific lemniscal pathways. It was coined by French et al in 1953 (French et al. 1953), who described earlier results showing “secondary” somatosensory cortical responses which were not confined to somatosensory cortex and had longer latencies

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[1] The VP should not be confused with the ‘vertex sharp wave’ observed during non-REM sleep (Kooi et al. 1964).

[2] For the sake of clarity, we highlight that here we only refer to electrocortical activities elicited by unexpected and *isolated* stimuli, and not to other EEG phenomena such as the mismatch negativity or P300, which are only detected in response to streams of stimuli repeated at high frequency.

than the lemniscal “primary” responses (Derbyshire et al. 1936). Since then, a wealth of invasive recordings in rodents and cats showed similar heteromodal responses with long latencies in “non-specific” intralaminar and midline thalamic nuclei[3] that project widely to supragranular layers of the cerebral cortex (possibly via calbindin-positive matrix cells, see **Section 5**) bypassing the primary sensory relay nuclei (Figure 2b; Albe-Fessard and Besson 1973).

In stark contrast to the lemniscal system, the extralemniscal system is supramodal, i.e. it can be engaged by stimuli of several sensory modalities (Albe-Fessard and Besson 1973), provided that they are sufficiently fast-rising and surprising (Albe-Fessard and Kruger 1962; Peschanski et al. 1981). Extralemniscal responses habituate dramatically when stimuli are repeated at predictable inter-stimulus interval shorter than approximately 2 seconds (Albe-Fessard and Kruger 1962; Massion et al. 1965; Albe-Fessard and Besson 1973; Peschanski et al. 1981; Bordi and LeDoux 1994). Aside from this sensitivity to sudden changes, the extralemniscal responses in thalamus are relatively insensitive to other stimulus features, lacking the precise tonotopic or topographic specificity of their lemniscal counterparts (Albe-Fessard and Besson 1973).

Despite this rich history of investigations, the extralemniscal system is nowadays neglected and largely absent from major neuroscience textbooks (Kandel et al. 2013c). This is remarkable, given that it represents a major sensory outflow of the thalamus, and likely subserves a large part of the brain cortical responses measured in cognitive neuroscience.

3 Cortical responses to sudden stimuli: phenomenology and modality-specific interpretation

The earliest descriptions of surprise-related responses in the human brain date back to the 30s (Davis et al. 1939). Davis et al. showed that isolated and abrupt sensory stimuli of different modalities elicit highly-similar large electrocortical transients maximal at the vertex (Figure 1). This transient and biphasic response consists of a

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[3] Note that some authors use the term “non-lemniscal system” to describe multisensory cells in parts of thalamic relay nuclei that project to secondary sensory cortices (Hu 2003). Here we use the term “extralemniscal” only to refer to the wider-reaching outflow from intralaminar and midline nuclei.

first negative wave (N) followed by a slightly longer-lasting positive wave (P) (Davis et al. 1939). Twenty years later, Bancaud and Gastaut provided the first description of their scalp distribution. Having observed that the maximal amplitude of the response was measured at the vertex electrode (Cz), with a gradual fall-off symmetrical on both hemispheres, they coined the term vertex potential that is still currently used (Bancaud et al. 1953; Gastaut 1953). In more recent years, this central and symmetrical topography was repeatedly confirmed with high-density EEG technology (Walter 1964; Davis and Zerlin 1966; Snyder and Hillyard 1976; Mouraux and Iannetti 2009; Wang et al. 2010; Legrain et al. 2011; Valentini et al. 2011; Torta et al. 2012; Novembre et al. 2018; Somervail et al. 2021, 2022; Fong et al. 2023). Furthermore, it became clear that the VP occurs concomitantly to other, modality-specific components reflecting activity in the pertinent primary sensory cortex (Figure 3; Valentini et al. 2012; Hu et al. 2014).

In scalp electrophysiology the VP is typically observed after averaging a number of single-trial responses in the time domain. When performing a time-frequency analysis of the amplitude of electrocortical oscillations in single trials (Mouraux and Iannetti 2008), it becomes clear that the stimuli eliciting a VP also induce several widespread non-phase-locked responses, such as a transient increase of gamma power and a longer-lasting decrease of alpha power (Mouraux et al. 2003; Hu and Iannetti 2019).

Responses similar to the VP have also been observed with invasive recordings from cortical and subcortical structures of rodents (Simpson and Knight 1993a, 1993b; Hu et al. 2015; Hu and Iannetti 2019; Somervail et al. 2021), cats (Albe-Fessard and Rougeul 1958), monkeys (Novembre et al. 2023) and humans (Velasco et al. 1985; Velasco and Velasco 1986; Velasco, Velasco, and Velasco III 1989). Some of these investigations also confirmed the invariance of this response with respect to stimulus modality or stimulus location (Albe-Fessard and Rougeul 1958; Velasco et al. 1984, 1985; Velasco and Velasco 1986; Velasco, Velasco, and Velasco III 1989; Hu et al. 2015; Hu and Iannetti 2019).

When brain activity is sampled with fMRI, the same stimuli that evoke a VP also elicit a large and bilateral BOLD response widespread in both cortical and subcortical structures as well as the primary sensory cortex pertinent to the modality of the applied stimulus (Downar et al. 2000; Mouraux et al. 2011; Vigotsky et al. 2023).

The use of EEG and fMRI responses elicited by isolated and sudden stimuli to study the cortical processing of a single sensory modality is a common practice in cognitive neuroscience. Accordingly, these responses, despite being strongly contributed to by non-modality specific sensory pathways, are still referred to using labels that hint, or even strongly imply, that the underlying neural activity reflects modality-specific cortical processing, exclusively or primarily mediated by the canonical lemniscal pathways (Chen et al. 1979; Jones 1992; Hegerl et al. 1994; Martin and Boothroyd 2000, 1999; Iannetti et al. 2005; Spackman et al. 2006; Baumann et al. 2008; Ben-David et al. 2011; Carpenter and Shahin 2013; Baltzell and Billings 2014; Han and Dimitrijevic 2015; Paloyelis et al. 2016; Wagner et al. 2016; Squintani et al. 2018; Valeriani et al. 2021). More importantly than the labels used, the interpretation of the recorded responses is often limited to the modality of the applied stimulus or the function investigated.

The pain field offers glaring examples of this incorrect reasoning. The idea that the EEG or fMRI responses elicited by sudden and unexpected nociceptive stimuli causing pain reflect the activity of a “pain matrix” or a “pain signature” has been hegemonic for a long time (for a detailed discussion see Hu and Iannetti 2016; Mouraux and Iannetti 2018). Despite an ongoing debate about the specificity of these responses, statements like “The **pain matrix** is thought to play a key role in elaborating two important aspects of the **nociceptive experience**: the sensory-discriminative aspect and the affective-motivational aspect” (Borelli et al. 2023), or “**pain matrix**; a network of brain regions that is activated in response to nociceptive stimuli and **contributes to pain perception**.” (Dreismickenbecker et al. 2023; bold added by us) remain pervasive. Similarly, the electrocortical responses elicited by noxious laser stimulation are interpreted by many (including ourselves in our initial publications) as reflecting nociceptive processing and pain perception (Iannetti et al. 2005; Paloyelis et al. 2016; Hird et al. 2018; Squintani et al. 2018; Valeriani et al. 2021; Zhang et al. 2021). Other examples come from auditory neuroscience research, where the responses elicited by sudden auditory stimuli are often interpreted as a measure of neural activity in auditory cortex, and used to infer neural mechanisms subserving hearing (Shahin et al. 2003; Sharma et al. 2006; Baumann et al. 2008; Ben-David et al. 2011; Ruhnau et al. 2011; Carpenter and Shahin 2013; Baltzell and Billings 2014; Wagner et al. 2016; Kostanian et al. 2022). Just to offer one example, Wagner et al (2016) state that “Neural ensembles within auditory cortex respond to acoustic features within the spoken word. These cortical responses are reflected within the P1-N1-P2 and T-complex waveforms of the auditory evoked potentials (AEP).” The issue is that, while technically true, statements like this downplay the possibility that the P1-N1-P2 response is largely contributed to by non-modality specific activity outside of auditory cortex.

These modality-specific interpretations are often justified by source analysis studies that found neural generators in sensory regions pertinent to the modality of the eliciting stimulus (e.g. in Scherg et al. 1989; Hegerl et al. 1994; Picton et al. 1999; Mulert et al. 2002; Pratt et al. 2010; Han and Dimitrijevic 2015). However, source analysis of EEG has a very high degree of uncertainty due to the extremely large solution space, and is highly prone to confirmation bias given that source analysis algorithms often require prior assumptions about the number and initial locations of equivalent dipoles (Grech et al. 2008). This problem is compounded when the analysis is applied to a widespread EEG response reflecting the concomitant activity of many neural sources (Grech et al. 2008), as is the case for the responses elicited by sudden and isolated stimuli (see Näätänen and Picton 1987; Simpson and Knight 1993a, 1993b; Mouraux and Iannetti 2009, as well as **Section 4**, below).

It is not far-fetched to say that most sensory evoked potential studies do not mention the possibility that the response under examination at least partly reflects non-modality-specific brain activity. This important neglect, together with the widespread use of modality-specific labels and interpretations of surprise responses that are in fact largely supramodal, obstructs understanding of both physiological and pathological studies, and thereby could misinform future clinical decisions (e.g. Yang et al. 2023). This issue is a special case of the more general problem of dissecting local vs global neural activity when interpreting the nature of cortical processing. For example, when aiming to explore task-related neural dynamics, spontaneous, non-task related movements result in global cortical activity, and represent potentially serious confounds in cognitive neurophysiology (Tremblay et al. 2023).

4 Cortical responses to sudden stimuli are largely contributed to by non-specific extralemniscal activity

The core message of this paper is that the cortical responses elicited by the large majority of sensory stimuli used in cognitive neuroscience are composed of distinct components reflecting the relative contribution of the lemniscal and extralemniscal pathways.

As we will discuss later, the relative contribution of these two systems is highly variable, mostly depending on several bottom-up stimulus properties but also on the context in which stimuli are delivered. Importantly, in the case of sudden and transient stimuli delivered at inter-stimulus intervals longer than some seconds, which is extremely common in cognitive and sensory neuroscience research, the contribution of the extralemniscal system dominates. Indeed, as detailed in the previous section, while fMRI BOLD activity elicited by sudden isolated stimuli of several modalities does reveal a local activation of the primary sensory cortex pertinent to the modality of the eliciting stimulus, it also reveals a much larger, global cortical activation common across different stimulus modalities (Figure 3b; Mouraux et al. 2011). These local and global activities likely reflect the engagement of lemniscal and extralemniscal thalamocortical projections, respectively. Indeed, dynamic causal modelling of this set of BOLD responses demonstrates that the widespread cortical activation is mediated by extralemniscal thalamocortical pathways that bypass the primary sensory cortices, whereas the local cortical activation is mediated by lemniscal thalamocortical pathways projecting directly to the primary sensory areas (Liang et al. 2013).

In the case of scalp electrophysiology, the cortical origins of sensory-evoked potentials are less clear. Still, its high temporal resolution provides a helpful tool to pin down the relative contributions of lemniscal and extralemniscal pathway activity. Below we review the evidence that the neural activity consequent to the engagement of the extralemniscal system dominates the EEG response when it is elicited by sudden and isolated stimuli.

Phenomenological similarity of the EEG response across modalities

The first compelling piece of evidence is the qualitative similarity of the cortical responses elicited by sudden stimuli belonging to different modalities, with respect to both the polarity of their components and their scalp distribution (Bancaud et al. 1953;

Chapman et al. 1981; Velasco et al. 1985; Velasco and Velasco 1986; Mouraux and Iannetti 2009). A defining property of the extralemniscal system is its supramodality, as shown by the similarity of response morphology in non-specific thalamus across sensory modalities (Albe-Fessard and Besson 1973; Velasco and Velasco 1986). Thus, the repeated observation that the scalp response is highly spatially similar across sensory modalities suggests that it largely reflects extralemniscal activity, with minimal contribution of modality-specific lemniscal pathways.

Beyond initial qualitative comparisons of scalp topographies (Bancaud et al. 1953), more recent studies have used quantitative methods to dissect the constituent components of the response. These methods range from simple EEG re-referencing to isolate local from global components (Iannetti et al. 2005; Hu et al. 2010) to more sophisticated techniques such as adaptive spatial filtering (Bufacchi et al. 2021), microstate analysis (Hu et al. 2014) and probabilistic independent component analysis (Mouraux and Iannetti 2009; Liang et al. 2010). All these approaches have revealed that the EEG response to sudden and isolated stimuli is dominated by a large and global supramodal subcomponent (the VP), while more local and modality-specific subcomponents offer a smaller contribution (Mouraux and Iannetti 2009; Liang et al. 2010; Hu et al. 2014) (Figure 3). For example, the response to sudden somatosensory stimuli consists of the N1 and P4 components, which contribute to the earliest and latest part of the response and reflect neural activity in the corresponding primary sensory cortex contralateral to the stimulated body part, while the vertex N and P components, which dominate the middle part of the response, reflect activity arising from more diffuse, bilateral cortical generators (Figure 3c) (Liang et al. 2010; Valentini et al. 2012; Hu et al. 2014). Furthermore, the trial-by-trial latencies of the modality-specific N1 and P4 components correlate with each other, but not with the vertex N and P waves (and vice versa; Hu, Valentini, et al. 2014), providing further evidence that the N1 and P4 components (on the one side) and the vertex N-P complex (on the other side) reflect distinct, parallel systems.

Animal literature is also informative in this respect. For example, invasive recordings in cats reveal similar responses across sensory modalities in several widespread cortical areas, nicely dovetailing what is observed in human scalp electrophysiology (Amassian 1954; Albe-Fessard and Rougeul 1958). Importantly, in this animal literature those widespread supramodal cortical responses were never interpreted as reflecting modality-specific lemniscal processing.

Sensitivity to sudden sensory changes

Human EEG studies have clearly shown that the amplitude of the VP is highly sensitive to stimulus rise-time (Figure 4c; Onishi and Davis 1968; Kodera and Hink 1979) and the amount of stimulus intensity change (Figure; 4d; Somervail et al. 2021): when fast-changing and intense stimuli are used, whether increases or decreases of intensity (Figure 4a-b), the resulting EEG responses are largely composed of the VP component. This sensitivity to sudden changes parallels another defining property of the extralemniscal system: the fact that it is only optimally engaged by fast-rising and intense stimuli, whereas the lemniscal system also faithfully encodes the temporal properties of slow-rising and tonic stimuli, e.g. by slowly applied pressure, light touch or hair bending (Albe-Fessard and Kruger 1962; Albe-Fessard and Besson 1973; Peschanski et al. 1981).

Habituation to repeated stimulation

A third piece of evidence indicating that extralemniscal neural activity dominates the EEG response to sudden stimuli is the fact that the bulk of the response habituates when the stimulus is repeated at short and predictable intervals (Figure 4e-g) (Ritter et al. 1968; Chapman et al. 1981; Woods et al. 1984; Treede et al. 2003; Iannetti et al. 2008; Wang et al. 2010; Herrmann et al. 2015). This observation indicates that the response does not primarily reflect the activation of the lemniscal system, which reliably responds to stimuli repeated as fast as 10 Hz[4], but rather the extralemniscal system, which is optimally engaged by isolated stimuli (Albe-Fessard and Kruger 1962; Massion et al. 1965; Albe-Fessard and Besson 1973; Peschanski et al. 1981; Bordi and LeDoux 1994).

The difference in habituation of the lemniscal and extralemniscal responses to repeated stimulation provides elegant evidence for the two main messages of this work: that sensory-evoked brain responses reflect a mixture of lemniscal and extralemniscal activities, and that when sudden stimuli are presented in isolation the

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[4] Consider, for example, that to obtain a clean readout of lemniscal somatosensory processing when measuring the N20-wave elicited by electrical stimulation of the median nerve, high frequencies of stimulation (up to 10 Hz) are recommended (Nuwer et al. 1994).

extralemniscal activity can dwarf the lemniscal activity. For instance, Chapman et al showed that increasing the frequency of stimulation dramatically dampens the large supramodal VP component of the response evoked by either auditory or somatosensory stimuli, while leaving earlier and later modality-specific components largely unaffected (Figure 4e; Chapman et al. 1981).

Lesion studies

Perhaps the strongest causal evidence that the cortical responses elicited by sudden stimuli largely reflect the activation of the extralemniscal system comes from lesion studies in animal models. Indeed, both ablation and pharmacological inactivation of modality-specific lemniscal thalamic nuclei or primary sensory cortical areas leave the vertex response largely unaffected (Albe-Fessard and Rougeul 1958; Buser and Borenstein 1959; Simpson and Knight 1993a, 1993b). Even when larger cortical territories surrounding the primary cortices are removed, a full-fledged VP is observed (Albe-Fessard and Rougeul 1958; Buser and Borenstein 1959). Similarly, the VP elicited by auditory stimuli is mostly unaffected by ischemic damage to auditory cortex in human patients (Woods et al. 1984, 1987). Notably, even when the lemniscal response in primary cortices is enhanced by strychnine, again the non-specific diffuse response is unaffected (Buser and Borenstein 1959). Altogether, this large and sadly neglected[5] body of empirical evidence shows a clear independence of the cortical responses evoked by the engagement of extralemniscal vs lemniscal pathways.

Sensitivity to anaesthesia

Lemniscal activity in both modality-specific thalamic nuclei and primary sensory cortices is remarkably preserved during anaesthesia. In contrast, the extralemniscal system is particularly sensitive to anaesthesia: responses in non-specific thalamic nuclei and their widespread cortical projections are selectively abolished by most general anaesthetics, with the notable exclusion of chloralose (Albe-Fessard and Besson 1973). Similarly, general anaesthetics completely abolish the widespread VP component, while leaving the early-latency primary sensory cortical components intact (Albe-Fessard and Rougeul 1958; Simpson and Knight 1993b). Similar results have been found in humans, with VPs being attenuated by general anaesthetics such as

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[5] Just to give an example, the extremely detailed and informative experiments of Buser & Borenstein (1959) have been cited, at the time of publication of the present work, only 39 times.

propofol (Simpson et al. 2002), midazolam (Zaslansky et al. 1996), alcohol (Dreismickenbecker et al. 2023) and nitrous oxide (Jessop et al. 1991).

Together with the ablations of the primary auditory cortex described in the previous paragraph, the results of Simpson & Knight in particular show an exquisite double-dissociation of the contribution of the lemniscal and extralemniscal systems to the epidural response: barbiturate anaesthesia selectively abolishes the vertex-response with no effect on the early (auditory cortical) components, while selective ablation of the auditory cortex abolishes these early components, while leaving the vertex-response unaffected.

Thalamic stimulation

Additional causal evidence comes from direct intrathalamic stimulation: the same isolated electrical stimulation in both cats and monkeys elicits dramatically different cortical responses depending on the thalamic nuclei that are targeted (Jasper 1949). The stimulation of somatosensory-specific lateral thalamus evokes small-amplitude cortical responses likely to pass unnoticed given their being circumscribed to the contralateral primary somatosensory cortex. In striking contrast, stimulation delivered only a few millimetres more medially, in the intralaminar nuclei, evokes large-amplitude responses widespread across the cortex (Jasper 1949). Clearly, this result provides further evidence that the widespread, symmetrical distribution of the VP cannot be explained by the lemniscal pathways.

5 Are thalamic matrix cells the substrate of non-specific cortical responses? It's complicated.

The classical concept of the extralemniscal system was based on anatomical and electrophysiological observations about "non-specific" thalamic nuclei such as the intralaminar and midline nuclei (French et al. 1953; Albe-Fessard and Besson 1973; Jones 1998). However, early electrophysiological recordings were blind to specific cell types and recent work has revealed a substantial diversity in thalamocortical cells: for example, cells located in these intralaminar and midline nuclei have been shown to have distinct afferent and efferent connectivity patterns, even when located within the same nucleus (Clascá et al. 2012; Halassa and Sherman 2019). Thus, the concept of functionally-homogenous "non-specific" thalamic nuclei, initially supported by electrophysiological evidence (Albe-Fessard and Besson 1973, Jasper 1949), has gone out of fashion (Bentivoglio et al. 1991; Groenewegen and Berendse 1994; Van Der Werf et al. 2002). This clearly highlights the importance of a cellular understanding of thalamocortical systems.

Considering the distinction between *matrix* and *core* cells proposed by Jones is particularly relevant for this discourse (Jones 1998, 2001, 2002). Parvalbumin-positive *core* cells dominate in specific sensory and motor relay nuclei (although they can also be found in intralaminar nuclei) and only project to limited cortical areas, synapsing at middle layers (Jones 1998, 2001, 2002). In contrast, calbindin-positive *matrix cells* are found throughout the thalamus and project widely across the cortex, synapsing at superficial layers. Similar to non-specific nuclei, matrix cells have broad receptive fields resulting in low-fidelity representations of sensory stimuli, e.g. low tonotopic specificity in audition and low somatotopic specificity in somatosensation (Albe-Fessard and Besson 1973; Jones 1998, 2001). Jones argues that the non-specific integrative functions ascribed to the intralaminar and midline nuclei are in fact subserved by matrix cells (Jones 1998, 2001), which generalises the concept of "non-specific thalamus" beyond the intralaminar and midline nuclei. Due to these similarities, we have previously related supramodal responses to matrix cells (Iannetti and Mouraux 2010). However, there remain several issues with this account.

First, although matrix cells are found throughout the thalamus, local field potential recordings from various thalamic structures containing matrix cells do not show VP-like responses. For example, there are matrix cells which respond to stimuli of multiple modalities in the vicinity of the somatosensory-specific ventroposterior nucleus (VPL) and of the auditory-specific medial geniculate nucleus (MGN) (Jones 1998; Hu 2003), but electrophysiological recordings from these areas do not show VP-like responses (Velasco et al. 1985). Indeed, these matrix cells only project to the cortical area surrounding the primary sensory cortex corresponding to the thalamic relay nucleus core which they surround (Jones 1998), making it unclear how they could account for the practically identical widespread scalp topographies elicited by sudden stimuli of different sensory modalities.

Second, the non-specific centromedian nucleus (CM) is almost entirely devoid of matrix cells (Jones 1998; Müller et al. 2020), although it also shows several physiological properties that make it a compelling candidate substrate for the VP. Indeed, (1) recordings from the CM reveal a rapid habituation to repeated identical stimuli, (2) CM inactivation suppresses supramodal cortical responses, and (3) CM stimulation produces a widespread VP-like scalp response (Albe-Fessard and Rougeul 1958; Albe-Fessard and Kruger 1962; Bignall 1967; Peschanski et al. 1981; Velasco et al. 1985; Matsumoto et al. 2001).

Third, mapping of the cortical regions whose BOLD signal correlates with matrix activity suggests that the matrix projections are somewhat asymmetric along the midline (Müller et al. 2020), in clear contrast to the symmetrical VP topography (Mouraux and Iannetti 2009; Liang et al. 2010).

Due to these issues, we remain sceptical that matrix cells are the substrate of the non-specific cortical response elicited by sudden environmental stimuli. Not surprisingly, the matrix-core dichotomy has been suggested to be simplistic, and calbindin-positive cells are not the only thalamocortical cells with diffuse projections to cortex (Halassa and Sherman 2019). Calbindin-positive cells may also be functionally heterogenous, given the fact that their projections are still constrained by the thalamic nucleus of their origin (Jones 1998). In addition, a population of core cells located in the intralaminar and midline thalamic nuclei, each with a limited cortical target but projecting, at population level, to a range of cortical areas could also explain a widespread EEG response such as the VP. Future work could tackle the important question of the whether thalamic matrix cells contribute to the VP measured in scalp EEG (see

Outstanding Questions).

6 What is the functional significance of the extralemniscal component of the response to sudden sensory stimuli?

The interpretive framework we articulated in previous sections provides valuable insights into the function of the extralemniscal component of the brain response elicited by sudden sensory events. Unlike their lemniscal counterparts, which subserve domain-specific processing of sensory information, the nuclei of the extralemniscal system are involved in domain-general modulation of the global brain state (Van Der Werf et al. 2002). Accordingly, there is clear evidence that the VP waveform reflects a rapid fluctuation of excitability across wide cortical territories, consisting of a decrease followed by an increase of excitability (Figure 5). This is shown by measuring both cortical motor *output* (Engbert and Kliegl 2003; Novembre et al. 2018), and cortical responsiveness to sensory *input* (Perovic et al. 2023).

This rapid succession of reduction and enhancement of cortical excitability is reminiscent of what occurs during sleep slow waves (Massimini et al. 2003; Cash et al. 2009). Indeed, sleep slow waves, besides having a widespread, central and symmetrical scalp distribution similar to the VP recorded in wake, reflect a dramatic fluctuation of membrane potential and cortical excitability (Steriade et al. 1993; Cash et al. 2009): during the negative peak of a slow wave, cortical neurons are hyperpolarised and their firing ceases (a cortical down-state). This is followed by a state of depolarisation in which cells fire more readily (a cortical up-state) (Steriade et al. 1993; Cash et al. 2009). In sleep, this succession between up- and down-states repeatedly disrupts brain connectivity and consciousness (Massimini et al. 2005), and has been conceptualised with the admittedly simplified idea of a “reboot” of the brain (Cash et al. 2009). In wakefulness, the biphasic VP waveform may reflect a similar, albeit weaker phenomenon: a “cortical reset” which interrupts the ongoing brain activity but without a dramatic impact on conscious experience.

A parsimonious hypothesis is that this cortical reset indexed by the VP would facilitate rapid task-switching by interrupting less urgent brain processes and allowing novel and potentially life-saving sensory information to be more effectively processed. It is important to highlight that under this hypothesis, a cortical reset indexed by the VP does not create an optimal behaviour itself, but rather provides a necessary substrate: an increase of cortical responsiveness to effectively and swiftly act if needed (e.g. escaping from a predator or catching a prey). Accordingly, the VP is followed by a few-second long increase of typical proxy-measures of central arousal, such as pupil diameter and skin conductance. Crucially, the increase of these measures is predicted by the amplitude of the preceding VP (Mobascher et al. 2009; Steiner and Barry 2011).

These effects are consistent with the idea that the VP reflects the output of a diffuse extralemniscal projection. Indeed, stimulation of non-specific thalamic nuclei results in aroused behavioural states (Redinbaugh et al. 2020; Bastos et al. 2021; Tasserie et al. 2022; Zhang et al. 2024). Finally, stimulation of the CM nucleus in humans results in broadband increases in gamma frequency power and decreases in alpha frequency power similar to those observed following the VP (Martin et al. 2021).

Thus, the extralemniscal component of the cortical response to sudden sensory stimuli exerts a domain-general modulation of the brain state, which we hypothesise facilitates the interruption of ongoing lower-priority behaviours and thereby promotes swift reactions to avoid or exploit any threats or opportunities afforded by the environmental change.

This hypothesis could be empirically tested in a number of ways, by measuring whether trial-by-trial variability of VP predicts behavioural performance or certain physiological parameters reflecting ongoing brain function, such as (1) task-switching effectiveness, (2) performance of a working memory recall task, or (3) persistence of a given EEG cortical rhythm entrained with tACS brain stimulation methods (see **Section 9 – Outstanding questions**).

7 Concluding remarks

We have presented substantial evidence that (1) the brain responses elicited by sensory stimuli reflect the relative contribution of both lemniscal and extralemniscal thalamocortical pathways, and (2) when these stimuli are sudden, unexpected and presented in isolation, the extralemniscal contribution dominates. Although there remains some uncertainty about the exact cellular substrates of this extralemniscal component, the perspective we articulate here provides a crucial interpretative framework relevant to practically every EEG or fMRI study in cognitive neuroscience using sudden and isolated sensory stimuli. This framework is critical for understanding high-profile papers reporting sensory responses outside their primary sensory areas or in “incorrect” primary sensory areas, which could be parsimoniously interpreted as reflecting non-specific thalamocortical systems (e.g. Iurilli et al. 2012; Bimbard et al. 2023). Finally, we propose a novel and biologically-plausible account of the functional significance of these extralemniscal responses: that they reflect a cortical reset that facilitates the interruption of ongoing behaviours and swift reactions to unexpected environmental changes.

8 Glossary and Definitions

Extralemniscal (or non-lemniscal) system. A supramodal thalamocortical sensory system parallel to the modality-specific **Lemniscal system**. It is effectively activated by **Sudden stimuli** signalling environmental changes and does not precisely encode other stimulus features. It projects widely to several brain structures mostly via non-specific intralaminar and midline thalamic nuclei, and for this reason is also referred to as “the non-specific system”. Here we contend that the extralemniscal system is the substrate of the widespread **vertex potential**.

Lemniscal systems. A set of thalamocortical sensory pathways, parallel to the supramodal **Extralemniscal system**. Each lemniscal pathway carries high-fidelity information of one sensory modality via modality-specific thalamic relay nuclei (e.g., the somatosensory ventral posterior lateral nucleus [VPL]). Lemniscal pathways mainly project to the primary sensory cortex congruent with the encoded modality.

Modality-specificity. A term used to describe brain systems which respond specifically or preferentially to stimuli of a single sensory modality. The neural activity of the primary somatosensory cortex indexed by the somatosensory-specific N20 potential elicited by electrical stimulation of the median nerve stimulation is prototypically modality-specific.

Sudden stimuli. Sensory stimuli entailing a rapid increase or decrease of stimulus energy, typically a rise or decay time of 1–100 ms. Sudden stimuli are widely used in cognitive and sensory neuroscience as “cues” or “targets” due to their temporal precision and ability to elicit large EEG responses. The current article argues that these responses are strongly contributed to by the **Extralemniscal system**.

Supramodality. A term used to describe the property of certain brain systems to respond to stimuli of multiple sensory modalities, even when presented *in isolation.* This is different from the phenomenon of “multisensory integration” of different modalities presented concomitantly. The **vertex potential** is a typical response indicating a supramodal system. The terms “supramodal”, “multimodal” and “amodal” are synonyms.

Vertex potential. Large and biphasic brain potential maximal at the scalp vertex. It dominates the EEG response elicited by **Sudden stimuli**, regardless of their sensory modality. We contend that the vertex potential reflects the activation of the **Extralemniscal system**, and indexes a large and widespread fluctuation of cortical excitability.

9 Outstanding Questions

What are the thalamocortical cell types which subserve the vertex potential?

While there is convincing evidence that the VP is subserved by the non-specific "extralemniscal" thalamocortical projections, it is still unclear which cell types make up these projections. For example, calbindin-positive matrix cells are a candidate, although we are sceptical about this possibility (see **Section 5**). Future work combining optogenetic manipulation of different thalamic cell types with large-scale population electrocortical recordings in mice could resolve this issue.

Why is the vertex potential waveform bipolar?

The bipolarity of the VP waveform, associated with a similar change in membrane potential of cortical cells, suggests the presence of a feedback mechanism. This could be implemented in a feedback circuit at thalamic (probably through interneurons in the reticular nucleus) or cortical level (through cortical interneurons), or be consequent to the intrinsic membrane properties of the thalamocortical projections or their cortical targets.

What is the neural machinery giving rise to habituation and dishabituation of the vertex potential?

The VP habituation with stimulus repetition is interrupted when certain stimulus properties change – an effect largely independent of top-down cognitive expectations (Valentini et al. 2011). The circuitry subserving these effects, probably implemented at fairly low levels, is unknown. The similar habituation of responses in the non-specific thalamus (Amassian 1954; Albe-Fessard and Besson 1973) suggests that the habituation happens already at thalamic level, but its mechanism remains elusive.

Does the fluctuation of cortical excitability elicited by sudden events affect behaviour?

We hypothesise that the VP reflects a "cortical reset" which interrupts ongoing brain activity and leads to a more reactive state. Does this change of state affect subsequent behaviour? We would expect that a sudden stimulus eliciting a VP would facilitate task-switching, and thereby make the agent better at responding effectively when having to face a more urgent situation. In contrast, the same change of state would disrupt performance in tasks requiring the maintenance of ongoing brain activity, such as working memory recall. Future work combining VP recordings with naturalistic behavioural paradigms could test this hypothesis.

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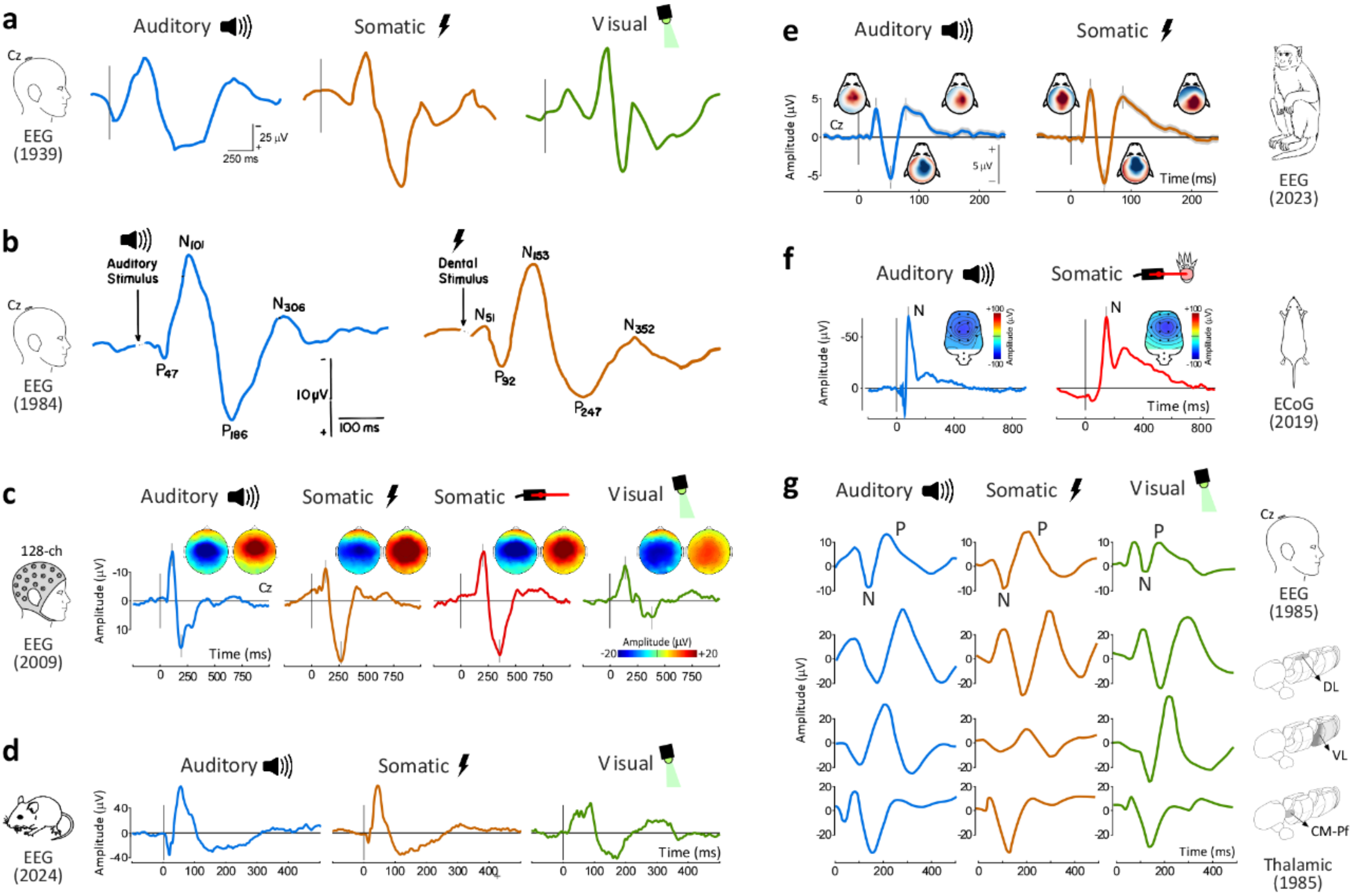

Figure 1. Sudden and unexpected stimuli elicit supramodal electrophysiological responses from the mammalian brain.

Sudden and unexpected stimuli of different sensory modalities elicit highly similar, large and widespread brain responses, dominated by a supramodal component maximal at the scalp vertex (the vertex potential; VP). **(a,b)** Early work with single-channel EEG recordings first suggested that sudden auditory, somatosensory and visual stimuli elicit highly similar electrocortical transients (Davis et al. 1939; Chapman et al. 1981). **(c)** Later work with high-density EEG demonstrated that these responses also have highly similar scalp distributions across modalities (Mouraux and Iannetti 2009). **(d,e,f)** Such supramodal responses are also recorded in rat ECoG and in mouse and monkey EEG (Hu and Iannetti 2019; Benusiglio & Asari, 2024; unpublished data). **(g)** In simultaneous scalp and invasive recordings from human patients, similarly supramodal transients can be recorded both at the scalp vertex and in non-specific thalamic nuclei (DL, dorsolateral nucleus; VL, ventrolateral nucleus; CM/Pf, centromedian and parafascicular nuclei) (Velasco et al, 1985).

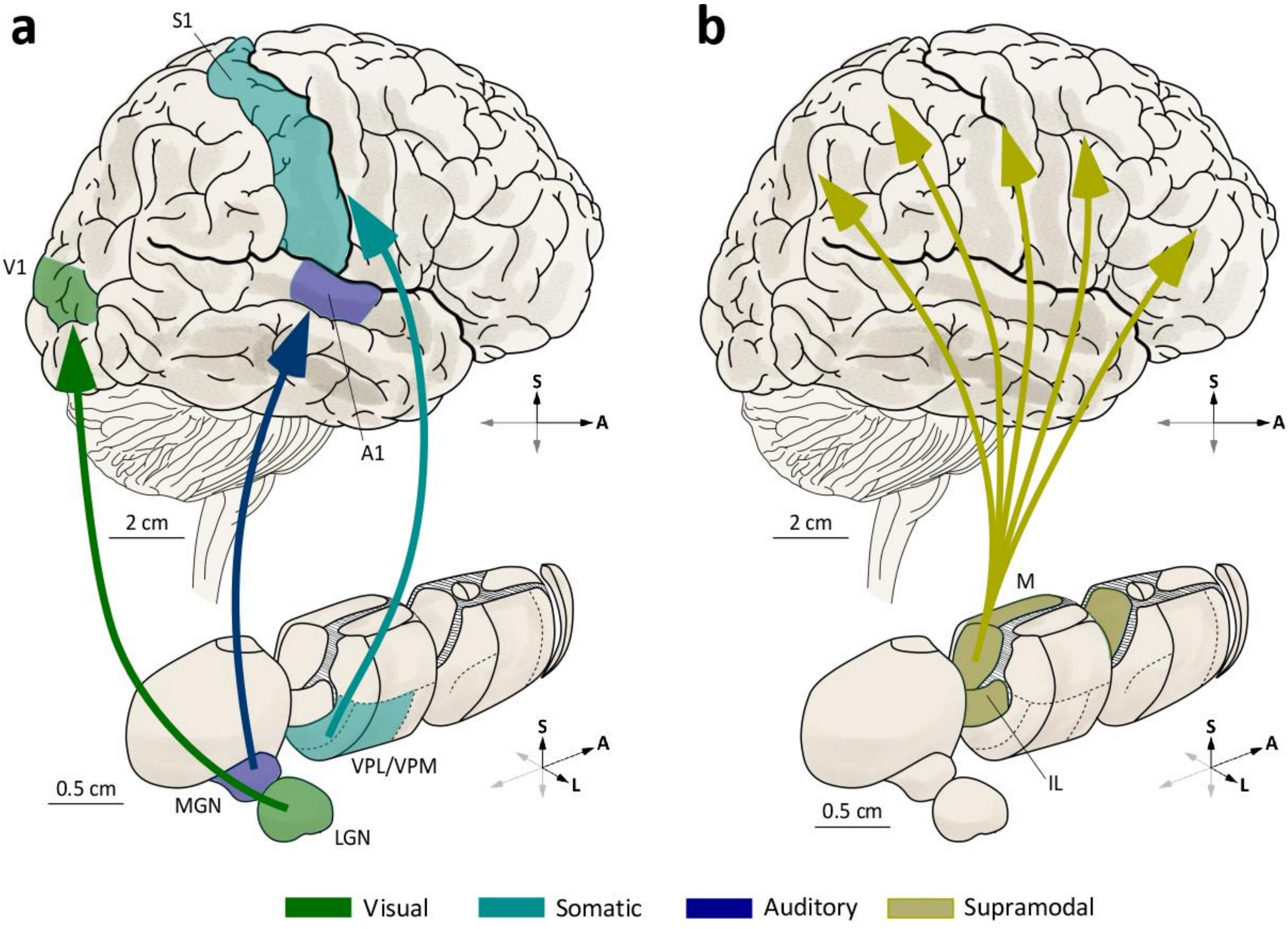

Figure 2. Thalamic origins and cortical targets of the extralemniscal and lemniscal systems. **(a)** Lemniscal (specific) pathways carry high-fidelity sensory information from modality-specific relay nuclei in the thalamus to their corresponding primary sensory cortices. For example, the somatosensory lemniscal pathways (turqouise) project from the ventro-posterior nuclei (VPL, VPM) to the primary somatosensory cortex (S1). **(b)** In contrast, extralemniscal (non-specific) pathways engaged by rapid stimulus changes (see Figure 4) and from non-specific intralaminar (IL) and midline nuclei (M) have widespread cortical projections (yellow).

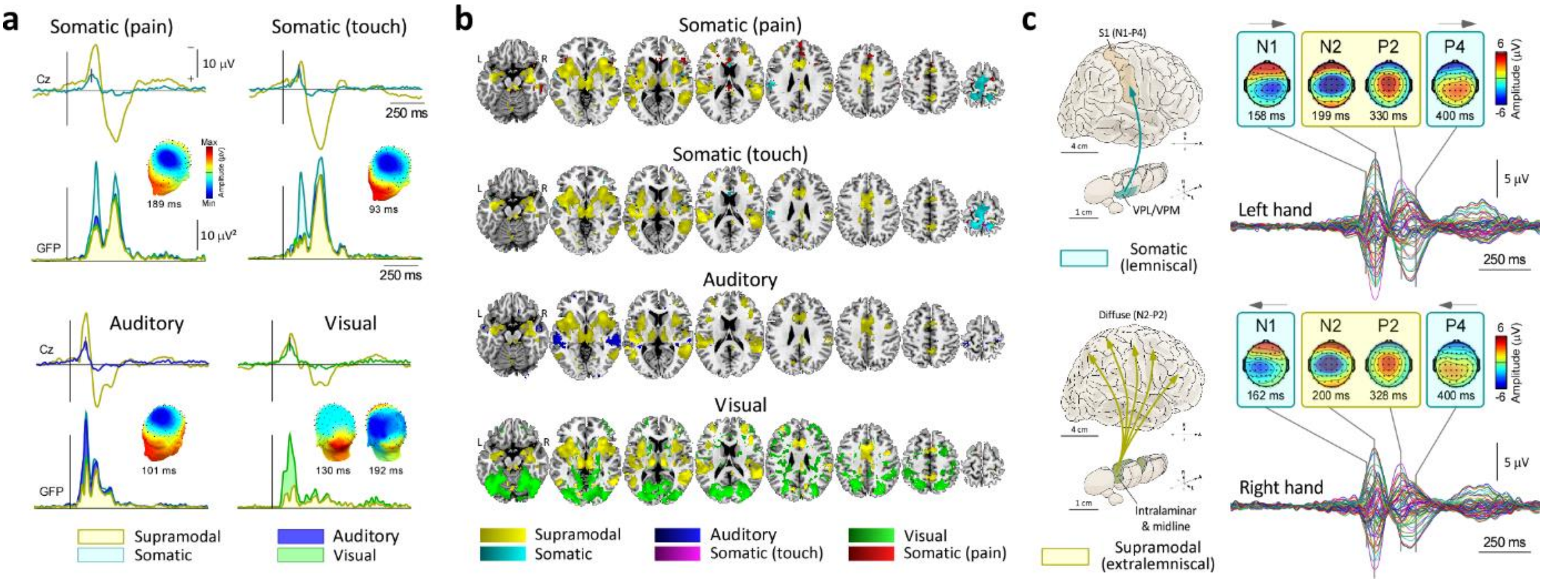

Figure 3. The transient response elicited by sudden and unexpected stimuli reflects the concomitant engagement of lemniscal and extralemniscal systems

(a) EEG responses to surprising stimuli of four sensory modalities are decomposed using probabilistic independent component analysis (pICA; Mouraux and Iannetti, 2009). The obtained independent components reflect the activity of two parallel ascending sensory systems: (1) a large and widespread supramodal component (the Vertex Potential, yellow) reflecting the extralemniscal pathways, and (2) smaller, spatially-restricted modality-specific components (non-yellow colors) reflecting lemniscal pathways. For each stimulus modality, the top waveforms show the timecourse of supramodal (yellow) and modality-specific (cyan: somatic, blue: auditory, green: visual) components at Cz, whereas the bottom waveforms show the timecourse of GFP (global field power; SD across electrodes). Scalp maps show the topographical distribution of modality-specific components. **(b)** fMRI responses to the same surprising stimuli (Mouraux et al, 2011) also reflect the distinction between lemniscal and extralemniscal systems. Most of the response is spatially overlapping across modalities and reflects the engagement of extralemniscal pathways. Conversely, smaller areas of activation, mostly non-overlapping and localized in primary sensory regions, reflect the engagement of lemniscal pathways. **(c)** EEG responses to somatic stimuli delivered to the left or right hand (data from Hu et al, 2014). The distinct and parallel activity of the two systems is noticeable even in raw EEG: we argue that the activation of the lemniscal system manifests as early N1 and late P4 peaks contralateral to the stimulated hand, reflecting the somatic input to the contralateral S1, while the extralemniscal activation manifests as the centrally-distributed vertex potential peaks (N2, P2).

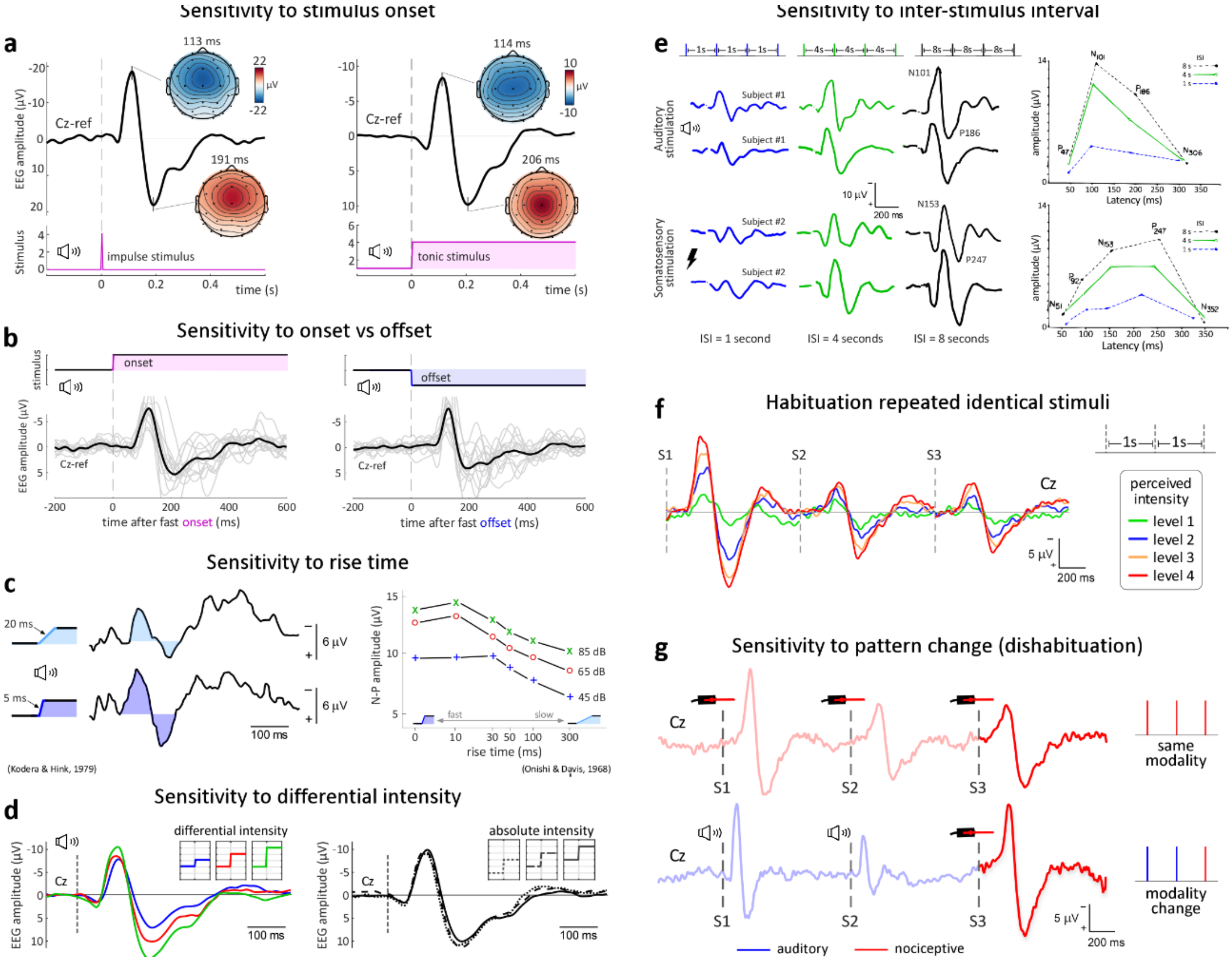

Figure 4. VP magnitude is sensitive to low-level stimulus features that determine its surprise content.

(a) The vertex potential (VP) is effectively elicited by sudden changes of sensory energy, regardless of whether after a fast onset the stimulus returns to baseline (left) or persists tonically (right) (Somervail et al, 2021). **(b)** Rapid offsets also elicit the VP response (Somervail et al, 2022). **(c)** VP magnitude is sensitive to the rise time of stimulus changes (Kodera & Hink, 1979; Onishi & Davis, 1968). **(d)** VP magnitude is also sensitive to the differential, but not absolute, stimulus intensity (Somervail et al, 2021). Altogether, panels **(a-d)** show that the VP magnitude is determined by the rate of change of stimulus energy. **(e-g)** Besides how the stimulus changes with respect to the immediately preceding *baseline*, the VP magnitude is also largely determined by the properties of the pattern of preceding *stimuli*. **(e)** Longer inter-stimulus intervals (ISIs) result in larger responses (Chapman et al, 1981). Crucially, this effect is only present for the mid latency VP peaks that we argue reflect the extralemniscal system, while it does not affect the earliest and latest peaks that likely reflect the modality-specific lemniscal system (see also Figure **3c**). This observation dovetails the tendency of the extralemniscal system to habituate to repeated stimulation, and the ability of the lemniscal system to faithfully encode stimuli delivered at higher frequencies. **(f)** The VP habituation is strongest when stimuli are delivered at a short and constant ISI (e.g. 1 s; Iannetti et al, 2008). This effect breaks the correlation between VP magnitude and perceived stimulus intensity. **(g)** A change in one of the fundamental features defining every sensory stimulus, such as its modality, will reverse the VP habituation (Valentini et al, 2011).

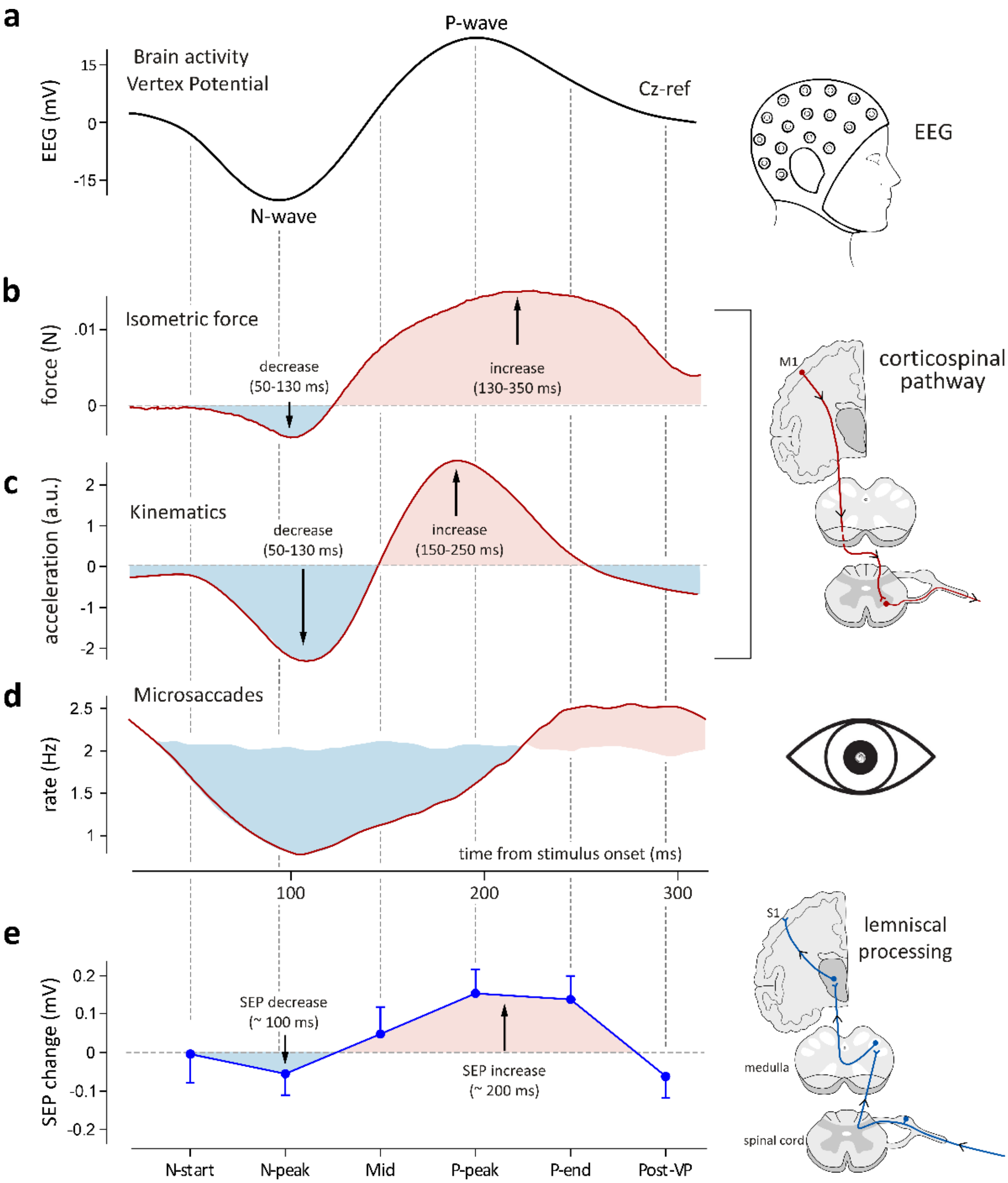

Figure 5. Coupling between VP occurrence and modulations of ongoing cortical function. The main tenet of this work is that the VP elicited by isolated and unexpected sensory stimuli (**a**, vertex potential) reflects the engagement of the extralemniscal system and its widespread thalamocortical projections. This interpretation parsimoniously explains the observation that the VP is tightly linked to a modulation of ongoing cortical function across several functional domains, often taking the form of an inhibition followed by an enhancement of ongoing cortical activity **(b-e)**. This bipolar modulation is observed when the corticospinal system is engaged in isometric force (**b;** Novembre et al, 2018) and kinematic tasks (**c**; unpublished data), in microsaccades (**d**; Engbert & Kliegl, 2003). A similar modulation is observed in the responsiveness of the primary somatosensory cortex to lemniscal input (**e**; Perovic et al, 2023).