

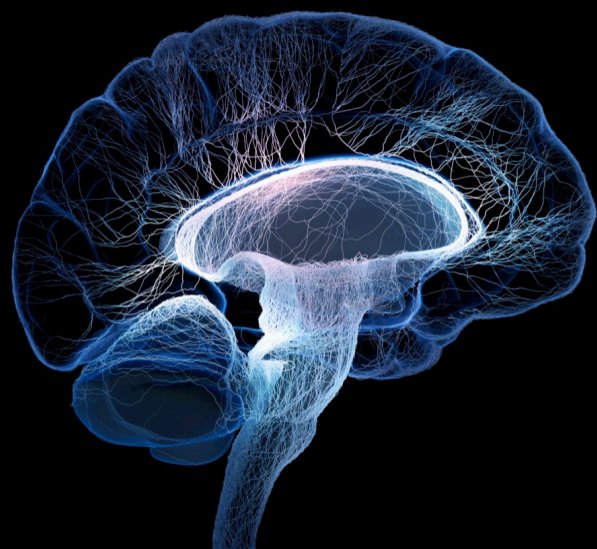
Exploring the neural mechanisms of sensory-cognitive associations: bridging sensory perception and higher cognitive functions

Edited by

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Exploring the neural mechanisms of sensory-cognitive associations: bridging sensory perception and higher cognitive functions

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Editorial: Exploring the neural mechanisms of sensory-cognitive associations: bridging sensory perception and higher cognitive functions

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KEYWORDS

sensory-cognitive integration, multi-modal, cognitive-affective regulation, computational modeling, neuroimaging

Editorial on the Research Topic

[Exploring the neural mechanisms of sensory-cognitive associations: bridging sensory perception and higher cognitive functions](#)

Introduction

The dynamic interplay between sensation and cognition lies at the core of human experience. For centuries, philosophers and scientists have sought to understand how raw sensory signals are transformed into meaningful perceptions, which in turn shape thoughts, emotions, and behaviors. Despite major advances, the neural mechanisms linking sensation and cognition remain a key challenge in modern neuroscience.

This Research Topic was designed to address this gap, bringing together studies that illuminate the neural choreography of sensory-cognitive integration from multiple perspectives. Interdisciplinary contributions address the neural and cognitive mechanisms underlying human perception, cognition, and behavior. By integrating evidence from neuroimaging, electrophysiology, computational modeling, and psychophysiological approaches, the Research Topic highlights advances bridging fundamental neuroscience with clinical and applied perspectives. Collectively, these studies argue that cognition is not merely a passive recipient of sensory input but is embedded within, and actively shapes, sensory processing from its earliest stages.

Sensory processing and multisensory integration

A central question concerns how sensory features are processed and integrated into coherent perceptions. Wang et al. demonstrated hemispheric specialization in extracting visual symmetry under noisy conditions, reflecting sophisticated neural mechanisms for pattern recognition. Their findings reveal distinct neural components associated with different stages of visual perception, contributing to the understanding of how the brain

processes symmetry. Wu et al. showed that spatial frequency dynamically modulates early audiovisual integration, highlighting rapid and reciprocal sensory interactions.

Attention and salience further determine which sensory signals are prioritized. Fujita et al. developed a computational framework linking visual salience to eye-movement behavior. Their model effectively predicts eye-movement patterns and provides insights into how neuronal abnormalities can influence visual salience, bridging computational neuroscience with behavioral data. Zhang et al. revealed that tactile imagery engages overlapping parietal networks with actual touch but exhibits distinct temporal dynamics, illustrating that tactile perception and imagery involve separate neural pathways despite both relying on somatosensory processing.

Cognitive-affective regulation and large-scale networks

The sensory-cognitive dialogue extends into self-perception and emotional regulation. Aki et al. conducted resting-state functional magnetic resonance imaging analyses to investigate the neural correlates of self-esteem. They identified robust functional connectivity between the left dorsolateral prefrontal cortex and posterior cerebellum, as well as associations with other brain regions involved in social cognition and emotional regulation, providing insights into the neural basis of self-esteem. Shibata et al. examined the functional connectivity of key brain networks in individuals with non-problematic internet use. They found alterations in the default mode, salience, and frontoparietal networks, which were associated with mood regulation, highlighting the impact of internet usage patterns on cognitive and emotional processing.

Clinical perspectives and methodological advances

Top-down modulation of sensory processing is particularly prominent in clinical and translational contexts. Golshan and Mickleborough reviewed neurophysiological mechanisms through which meditation influences brain activity in response to acute and chronic pain. Their review categorized general models explaining how meditation alters cortical responses to painful stimuli and identified key brain regions consistently implicated in pain modulation, providing a framework for understanding the neural effects of meditation on pain processing. Nicolardi et al. investigated pain perception in children and adolescents with autism using quantitative sensory testing (QST) protocols. They measured central reactivity to painful stimuli via electroencephalographic (EEG) recordings, revealing altered sensory reactivity and elucidating mechanisms of neurodivergent sensory-cognitive integration in this population.

Technological advances further enhance research capabilities. Chen et al. developed an advanced gustometer for reliably recording gustatory event-related potentials in healthy young adults. Their study aimed to improve understanding of gustatory processing and its neural correlates, providing methodological

innovations that support research on sensory perception and its neural mechanisms.

Conclusion

Collectively, these studies provide a comprehensive overview of the neural mechanisms that bridge sensory perception and higher cognitive functions. They highlight the complexity and specialization of neural pathways involved in processing sensory inputs and integrating them into cognitive and emotional responses. The diverse methodologies employed, ranging from electrophysiological recordings to neuroimaging and computational modeling, underscore the interdisciplinary approaches necessary to unravel the complexities of sensory-cognitive interactions. This Research Topic not only advances our understanding of the neural basis of perception and cognition but also lays the groundwork for future studies exploring the dynamic interplay between sensory inputs and higher-order cognitive functions.

Future research should integrate multi-modal and multi-level approaches, spanning single-neuron recordings to large-scale network analyses, and computational modeling to clinical applications. Such efforts are essential to fully elucidate how sensory information is transformed into cognition.

Author contributions

HQ: Writing – original draft, Writing – review & editing. ZZ: Writing – review & editing, Writing – original draft.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Advanced gustometer design for reliable recording of gustatory event-related potentials in healthy young adults

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Introduction: This study introduces an advanced gustometer to record Gustatory Event-Related Potentials (GERPs) in healthy young adults. We aimed to validate its functionality and reliability.

Methods: The gustometer includes a programmable controller, a human-machine interface, a modular pump system, and supporting hardware. The Neuro-Audio EEG platform recorded EEG data from 46 volunteers. Psychophysical gustatory tests assessed gustatory function. GERPs were tested using distilled water as a control and sodium chloride solutions (0.3 and 0.6%) as tastants. Tetracaine anesthetized the tongue surface to observe waveform changes and confirm GERP specificity. GERP responses were recorded at the Fz and Cz sites, focusing on the latency and amplitude of GERP P1 and P2 waves and their correlation with psychophysical test results. No stable waveforms were recorded with distilled water.

Results: All subjects displayed stable GERP waveforms following salty stimulation. These waveforms disappeared post-anesthesia, confirming GERP specificity. The recorded GERP comprised P1-N1-P2 components. The latency of P1 and P2 waves decreased with increasing salt concentration ($p < .05$). No significant differences in latency were observed between the Fz and Cz sites. Additionally, 48% of subjects showed increased P1-N1 and P2-N2 amplitudes with higher salty stimulation. The latency of P1 and P2 positively correlated with psychophysical test results.

Discussion: This novel gustometer effectively evoked reliable GERP waveforms. The study validated the consistency of GERP amplitude and latency with psychophysical tests, highlighting the gustometer's potential for clinical and research applications in gustatory system.

KEYWORDS

gustatory event-related potentials, gustometer, taste, salty stimulation, psychophysical tests

1 Introduction

Taste function not only enhances our culinary experiences and social interactions but also plays a crucial role in the detection of toxic substances. Taste dysfunction can arise from various conditions, including neurological disorders, head trauma, and infections. Estimates indicate that the prevalence of complete ageusia ranges from 0.84% to under 4% (Deems et al., 1991), while hypogeusia can affect up to 20% of individuals attending chemosensory clinics (Vennemann et al., 2008). Research by Antje Welge-Lüssen et al. suggests that approximately

5% of the general population experiences hypogeusia. However, complete ageusia is extremely rare, occurring in only one or two individuals per 1,000 (Deems et al., 1991; Welge-Lussen et al., 2011). Notably, the elderly have exhibited a significant rise in taste disorder prevalence, reaching 14–22%, which is much higher than olfactory dysfunction (Boesveldt et al., 2011). The advent of COVID-19 has underscored its role as a prominent cause of taste impairments, with studies reporting an increased prevalence of hypogeusia (12–28%) among infected individuals (Jafari et al., 2021; Imoscopi et al., 2012; Hintschich et al., 2023; Jianfeng et al., 2008). Such high prevalence, combined with its potential consequences—including poor appetite, malnutrition, depression and anxiety disorders, and compromised quality of life (Noel et al., 2017)—emphasizes the importance of gustation-monitoring and developing effective diagnostic assessments for gustatory dysfunction.

To the best of our knowledge, methods used for assessing taste disorders include: subjective methods (taste questionnaires and psychophysical methods), electrophysiological tests, blood tests, and imaging assessments (positron emission tomography, PET; functional MRI) (Nin and Tsuzuki, 2024). Although psychophysical tests are widely used for routine assessment of gustatory sensitivity in clinical practice, they may not be feasible for children, potential malingers, demented patients, or for medico-legal purposes. Moreover, the complex formation of taste, which is an aggregate outcome of retronasal olfaction (oral cavity and nasopharynx), mechanical and chemical sensitivity through the trigeminal nerve, and the gustatory system itself, often leads to confusion with olfactory function (Fark et al., 2013). To address this, electrophysiological testing, specifically gustatory event-related potentials (GERPs) tests, have been employed (Fark et al., 2013).

Since first introduced in 1971 (Funakoshi and Kawamura, 1971), GERPs have received wide attention for their ability to objectively, reliably, easily, and inexpensively assess the early cortical response to gustatory stimuli (Hu et al., 2020). GERPs have been obtained in response to sodium chloride (salty), sugar solutions (sweet) (Hu et al., 2020; Ohla et al., 2012; Ohla et al., 2010), acetic acid (sour), bitter, and umami (Hummel et al., 2010), demonstrating the activation of the gustatory pathway from the tongue receptors to the taste cortex by taste stimuli. GERP is defined by three peaks: P1, N1, and P2. The P1 peak corresponds to the beginning of the GERP. P1 and N1 peaks are described as the sensory cerebral response (Hu et al., 2020); the P1-N1 amplitude corresponds to the intensity of the cerebral activation. The P2 peak is described as the subjective interpretation of the gustative stimulus by the subject (cognitive response) (Zhu et al., 2023). The temporal features of GERPs, such as latency and amplitude, have been found to vary with the concentration and palatability of the stimuli (Payne et al., 2024).

However, unlike the widespread adoption of EEG in clinical practice, the application of GERP remains relatively limited, primarily due to the scarcity of mature commercial systems (Hu et al., 2020; Iannilli et al., 2015; Mouillot et al., 2019; Mizoguchi et al., 2002; Jacquin-Piques et al., 2015; Andersen et al., 2019). GERPs represent an aspect of action potentials, and their recording is relatively straightforward. Therefore, the development of a gustometer has become a focal point in the research of GERPs. Firstly, taste is a chemical sense that requires stimulation through a natural chemical sensing process to obtain ideal evaluation results. Secondly, tastants should be delivered on the tongue surface without producing artifacts such as thermal, tactile, or nociceptive co-activation.

Our team has been immersed in both the basic and clinical research of chemosensation, focusing on olfaction and taste (Jianfeng et al., 2008; Noel et al., 2017). The aim of the present study was two-fold. Firstly, to present our newly established gustometer, detailing the construction of the gustatory stimulator, the functionality of the device, the taste delivery mode, and the parameters for taste stimulation. Secondly, to utilize this system to investigate the GERPs for salt taste in terms of validity and reliability in a cohort of healthy young Chinese individuals. We hope to obtain fundamental data for GERP components within the healthy Chinese population and to perform comparative analyses with other centers to confirm the feasibility, reliability, and specificity of our GERPs platform.

2 Methods

2.1 Subjects

Forty-six healthy subjects (14 men and 32 women) were enrolled in this study. All these subjects had normal taste confirmed with psychophysical gustatory test (3-droplet method). The mean age was 25.4 ± 3.6 years. All of the subjects were nonsmokers. None of the subjects had oral, dental, or neurological disorders or specific medical histories. Subjects who were currently undergoing medical treatment and obese subjects were excluded.

2.2 Ethical approval

The subjects were informed about the nature and aims of the experiment, and each of them provided written consent. The study was approved by the China-Japan Friendship Hospital Ethical Committee (2022-KY-080), in accordance with the latest revision of the Declaration of Helsinki.

2.3 Procedure

2.3.1 Psychophysical gustatory test (3-droplet method)

Different concentrations of sucrose (sweet), NaCl (salty), citric acid (sour), and quinine hydrochloride (bitter) solutions were prepared. The psychophysical gustatory test was conducted using the three-droplet method, with minimum concentrations of sucrose (0.19 g/mL), NaCl (0.06 g/mL), citric acid (0.15 g/mL), and quinine hydrochloride (0.0012 g/mL) (Pingel et al., 2010). One drop of tastant was dripped onto the middle of the anterior two-thirds of the extended tongue with pipettes. The subject was asked to choose from four tastes: sour, sweet, bitter, and salty (multiple forced choice task). The score for each taste was graded from 10 to 1 with increasing concentrations and was recorded when a taste was identified twice consecutively.

2.3.2 Construction of a gustometer

The gustometer is a key component in the apparatus used for GERPs recordings, as shown in Figures 1, 2. The device consists of a main host and auxiliary parts. The main host includes a human-machine interface touchscreen, a programmable controller, a mechanical control panel, input/output interfaces, and a peristaltic

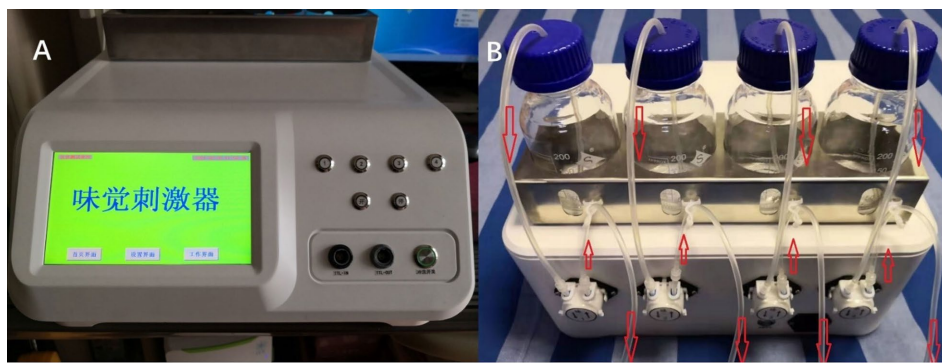


FIGURE 1
Photographs of the gustometer, showing its front (A) and back (B) views.

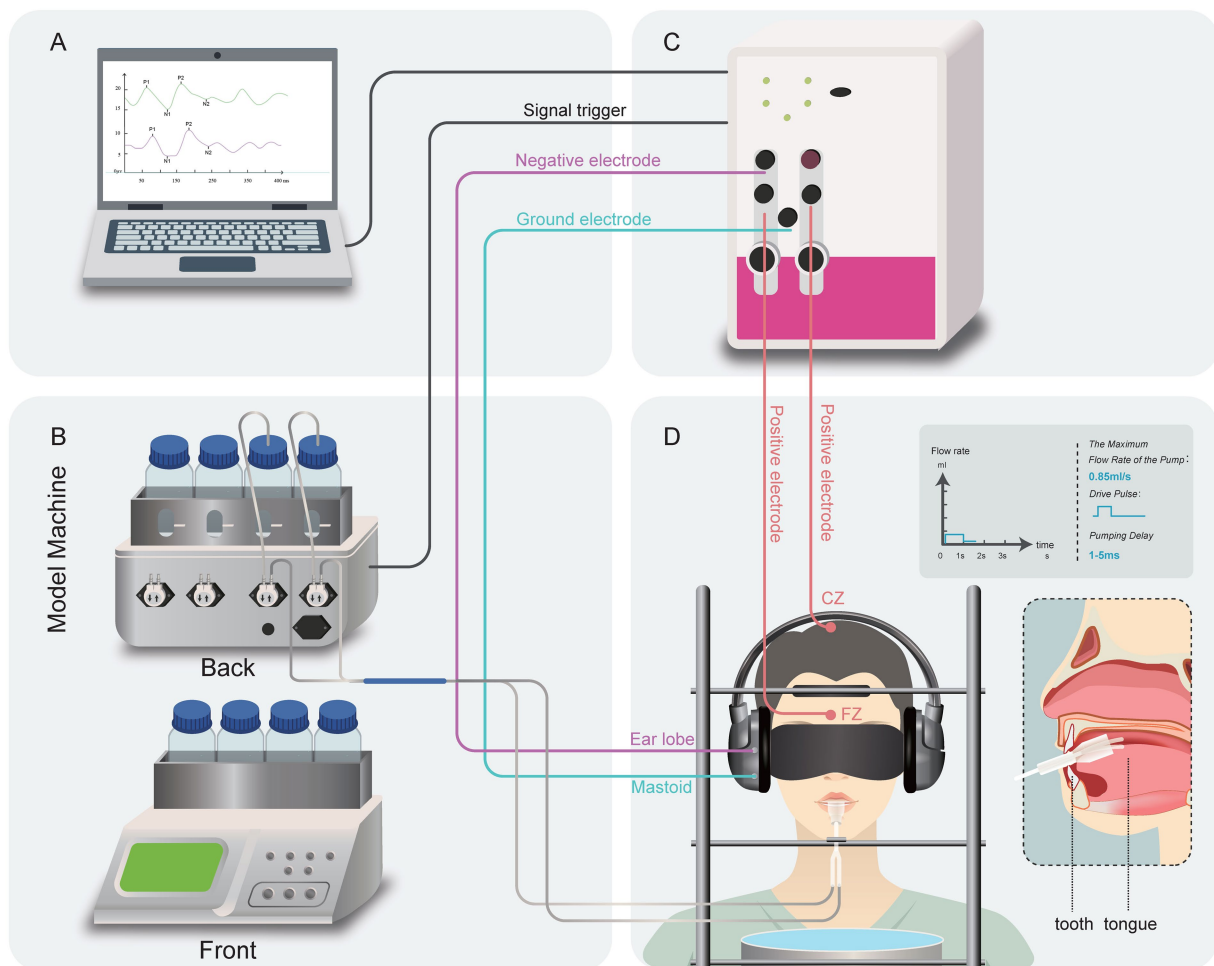


FIGURE 2
Schematic illustration of the gustometer. The front and back of the gustometer machine consists of a system of computer (A) controlled pumps (channel 1–3 for tastants, channel 4 for distilled water). The tastant solutions are contained in glass bottles (B); GERPs was recorded via Neuro-Audio EEG system (C); During testing, visual stimuli and auditory stimuli, as well as swallowing movements, were avoided. (D) The pump's drive pulse is a pulsatile flush with a delay of approximately 1–5 ms, and the maximum pump flow rate is 0.85 mL/s.

pump. The touchscreen handles system interactions, parameter settings, and command execution, while the programmable controller manages pump operation to precisely dispense the test liquid. Heating and cooling modules keep the stimuli at a temperature close to that of the tongue. The auxiliary components include a liquid bottle stand,

bottles, pump tubes, connectors, and a mouthpiece. The stimulator's external output has four channels: Channels 1–3 deliver taste solutions, and Channel 4 provides distilled water.

The stimulus parameters are configured via the human-machine interface touchscreen (Figure 3C), allowing for the selection of

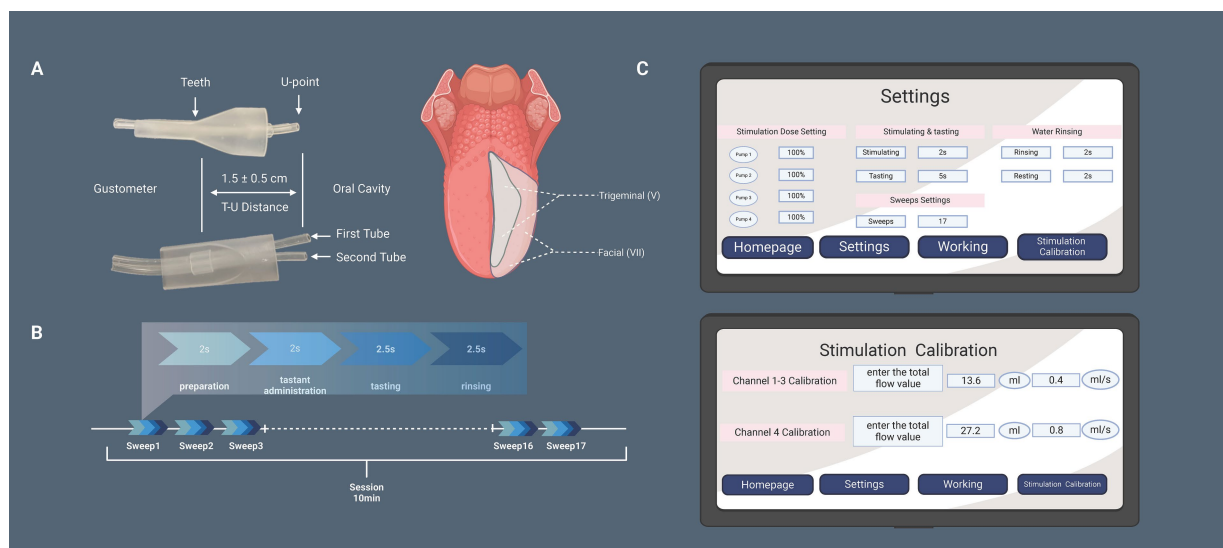


FIGURE 3

(A) The upper image shows a side view and the lower image a front view of the mouthpiece, indicating the position where it is held between the teeth. The distance between the teeth contact point and the U point is adjustable to 1.5 ± 0.5 cm, allowing for precise positioning of the internal Teflon tubing. This ensures that the taste solution stimulates the lateral anterior part of the tongue—innervated by the facial nerve—without activating the trigeminal nerve. (B) The session timeline illustrates that each stimulus consists of four phases: preparation, taste stimulus delivery, tasting, and rinsing. Each session includes a total of 17 stimuli (sweeps). (C) The gustometer's human-machine interface is displayed, showing parameter settings that allow for independent adjustments of each of the four channels. The stimulation calibration screen enables adjustments to the flow rate parameters.

tastants, number of sweeps, channel flow rate calibration, and phase duration for each step of the process (including stimulation dose setting, tastant delivery, tasting, and water rinsing) within a single sweep. Once the test begins, the main host sends synchronized commands to both the mechanical control panel and the GERP recording Neuro-Audio system through a synchronization trigger line (Figure 2), with a precision of 1 ms.

Two parallel silicone tubes were used: one from channel 4 for water (Second Tube) and the other from bottles 1–3 for a taste solution (First Tube). When you need to change the taste stimulants, switch the First Tube between bottles 1–3. It is important to activate the stimulator's flushing function before starting the actual stimulation.

For each channel, the maximum flow rate is 0.85 mL/s, with stimulation delivered as a drive pulse. The pump action delay ranges from approximately 1–5 ms, and the stimuli are square waves with a rapid rise time (Figure 2D). At the beginning of each stimulation cycle, the First Tube delivers the taste solution to the lateral side of the tongue in a pulsatile manner for 2 s, followed by a 2-s tasting period. During stimulus presentation, water supply through the second tube is temporarily suspended to maintain stimulus integrity. The rinsing phase utilizes distilled water delivered through Channel 4 at a flow rate of 0.8 mL/s for effective tongue cleansing. The flow rate of 0.4 mL/s for the taste solution was selected based on literature recommendations (Mizoguchi et al., 2002; Hummel et al., 2010).

2.3.3 The design of the mouthpiece

The ends of the two silicone tubes emanating from the main unit are encased in a plastic mouthpiece, as shown in Figure 3A, which illustrates the structure of the mouthpiece from both the front and side views. This mouthpiece can be held between the teeth, with the ends of the tubes directed toward the oral cavity (Figure 2D). The tubes were positioned at a distance of 1.5 ± 0.5 cm (T-U distance)

from the dental arch along the midline of the tongue. The T-U distance can be adjusted so that the U point is precisely located laterally to the anterior third of the tongue, avoiding stimulation of the trigeminal nerve area. Solutions were delivered to the tongue through the ends of each tube (U point).

When conducting GERP (Mastinu et al., 2024):

- 1 Subjects were asked not to eat, or drink anything but water during the time between meals and the GEP recording.
- 2 The recording device needs to be placed inside an electromagnetic and sound shielding chamber to eliminate potential electromagnetic interference and ensure the stability of the recorded waveforms, with the EEG and the gustometer placed in two separate spaces.
- 3 Participants wear noise-canceling headphones to mask switching clicks of the stimulation device and other possible sounds.
- 4 Participants should wear a blindfold to avoid light stimulation. Hence, no blink artifacts contaminated the recordings.
- 5 The subject's chin rested on a tray, with their head tilted downward, allowing the water to flow directly into a catch tray below after stimulating the tongue via the mouthpiece, thus avoiding the effects of swallowing actions (Figure 2).
- 6 They were asked to count the number of stimuli in order to focus the participants' attention.

2.3.4 Taste stimuli

The stimuli were applied to the anterior tongue via the one of the tube from the mouthpiece as shown in Figure 2. Taste stimuli (the sodium chloride (NaCl) solution) was applied in two different concentrations (weak and strong: 0.3 and 0.6%, equal to 51 and 103 mM, respectively). The distilled water was used as a blank

control. After the subjects' anterior tongues were sprayed with 1% tetracaine to anesthetize the areas innervated by the trigeminal and facial nerves on the tongue surface, the waveforms were retested. To further confirm whether tetracaine-induced surface anesthesia impaired taste perception, the subjects were asked to rate the intensity of saltiness. All 10 patients reported that the salt taste was "not detectable."

For each stimulus presentation, the process begins with the administration of a taste solution (default duration of 2 s), followed by a tasting phase (default duration of 5 s), and concludes with distilled water to rinse the tongue through channel 4 (default duration of 2 s). This constitutes a single stimulation (sweep), with a 2-s interval/rest between two sweeps (Figure 3B).

2.3.5 GERP recording and data analysis

Continuous EEG was recorded and averaged via the Neuro-Audio EEG device (Neurosoft, Ivanovo, Russia). Due to the Neuro-Audio EEG device having only 2 channels, as described by a previous study (Zhu et al., 2023), central electrode Cz and frontal electrode Fz were selected for recording (Figure 4A). The electrodes were referenced against linked earlobes, and the ground electrode was placed on the mastoid. GERPs were recorded by surface electrode with impedance <5 k Ω . A signal was sent to Neuro-Audio when a taste solution was administered (with 1 ms precision), to obtain a precise time recording of GERP. GERP analysis was performed with the same software. Each subject's data were digitally filtered using a 0.1–30 Hz bandpass filter. The sampling frequency was 512 Hz. The recorded GERP signals were averaged with 17 stimulus presentations.

GERP was defined by four peaks, as described in previous studies (Ohla et al., 2012; Ohla et al., 2010). P1, the first positive peak; N1, the first negative peak; and P2, the second positive peak. P1 latency (in ms), P2 latency (in ms), P1-N1, and P2-N2 amplitude (in μ V) of the

GERPs were registered for each recorded electrode and each tastant concentration. The P1 latency was defined as the time interval between stimulus delivery and the potential positive peak P1. The P2 latency was defined as the time interval between the stimulus delivery and the second positive peak. The amplitude of each response was calculated as the height between the first positive and the negative peaks (P1-N1 amplitude) (shown in Figure 4A) (Mouillot et al., 2019). The positive peak corresponded to the peak pointing down, whereas the negative peak corresponded to the peak pointing up.

2.4 Statistics

Continuous and categorical variables were expressed as mean $\pm$ standard or numerals (percentages), respectively. Components of gustatory ERPs from different recording sites and two concentrations were compared using *t* test. The correlation between psychophysical gustatory test scores and GERPs parameters was analyzed with simple linear regression. A *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed with Prism 10 (Version 10.1.1, GraphPad Software, Boston, Massachusetts USA).

3 Results

3.1 NaCl solution as a salty tastant elicits corresponding potentials

All subjects (*n* = 46) underwent recording and analysis at Fz and Cz sites in response to salt stimuli, and four distinct peaks were observed for all subjects. P1 is the first positive peak; N1 is

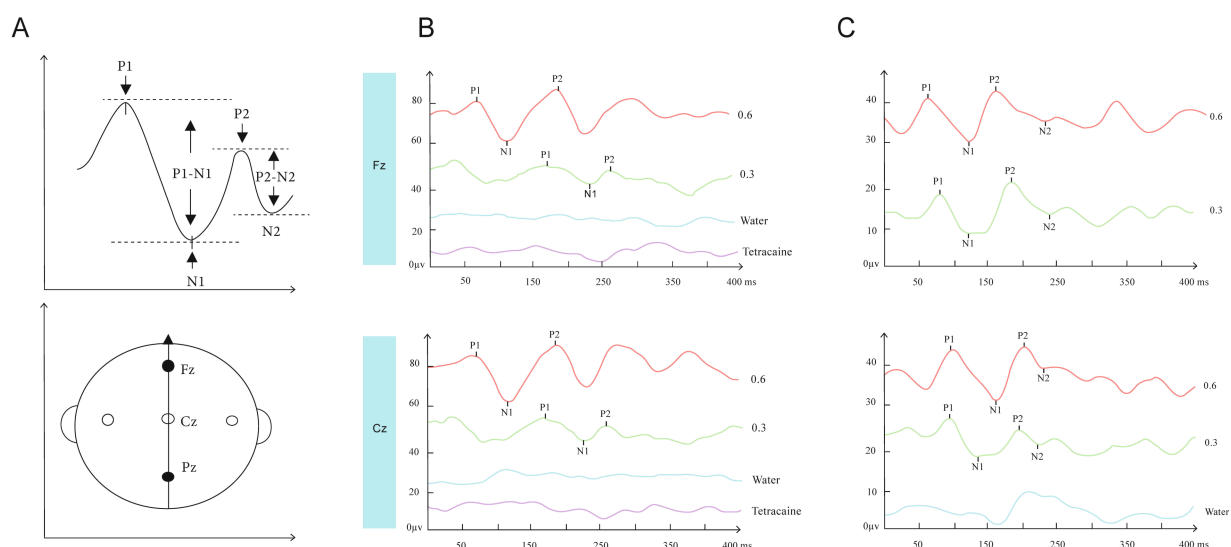


FIGURE 4

(A) schematic drawing of ERP peaks and EEG recording position. (B,C) show typical recordings from 2 subjects (No 45, 38 respectively) for all experimental conditions plus the corresponding Grand Means. GERP at recording position Fz and Cz in response to distilled water (blue), 0.3% (green) and 0.6% NaCl (red) from an individual subject. Under water stimulation, no GERPs were recorded at Fz and Cz. Compared with lower salty concentration, GERP evoked by higher salty concentration at both two recording sites had larger P1-N1 and P2-N2 amplitude (B,C) and shorter P1 and P2 latency. After the subjects' anterior tongues were sprayed with 1% tetracaine to anesthetize the areas innervated by the trigeminal and facial nerves on the tongue surface, the GERPs were tested again using the NaCl stimulus, and the aforementioned waveforms disappeared (B, purple).

the first, higher and negative peak; P2 is the second positive peak; N2 is the second negative peak (Figure 4). The latencies (ms) of P1, P2, and the amplitudes (μV) of N1-P1 and N2-P2 of GERPs were recorded. The average latencies and amplitudes of the two peaks P1 and P2 recorded at Fz and Cz at two salty concentrations are shown in Table 1. Representative recordings of GERPs on electrodes Fz and Cz from two subjects are shown in Figure 4. Significant differences between responses at the different recording sites (Fz-Cz) were observed for averaged amplitudes of P2-N2 for both salt concentrations ($0.3, p < 0.01$; $0.6 p < 0.05$). The GERPs recorded at Cz displayed higher P2-N2 amplitude than Fz, as shown in Figure 5. No significant differences were found with regard to latencies of peaks P1 and P2 between Fz and Cz positions.

3.2 No EEG waveforms recorded with distilled water and EEG by NaCl disappeared after tongue surface anesthesia

To demonstrate that the aforementioned GERPs were uniquely evoked by NaCl, this experiment also analyzed the waveforms evoked by distilled water as controls for comparison in 10 subjects (No.1–10). It was found that no significant waveforms were elicited with distilled water stimulation. Furthermore, for the same 10 subjects, after local surface anesthesia of the tongue with 1% tetracaine, the GERPs were tested again using the NaCl stimulus, and the aforementioned waveforms disappeared (Figure 4B).

3.3 Effects of stimulus concentration on latency and amplitude of GERPs

As the concentration of the salty stimulus increased, the latency of P1 and P2 at Fz and Cz significantly decreased (see Table 2, Figure 5). The paired *t*-test revealed no significant differences in the amplitudes of N1-P1 and N2-P2 at both Fz and Cz between the low and high concentrations of salty taste stimuli (Figure 5). Noticeably, some patients (48%) showed an increase in the amplitudes of P1-N1 or P2-N2 as the intensity of the saltiness stimulus increased, as depicted in Figure 4.

TABLE 1 Grand averaged latencies and amplitudes of GERPs at Cz and Fz evoked via two concentration NaCl solutions.

	0.3-Fz	0.6-Fz	0.3-Cz	0.6-Cz
P1 latency (ms)	146.2 $\pm$ 36.3	130.9 $\pm$ 40	147 $\pm$ 35.7	132.6 $\pm$ 41
N1 latency (ms)	191 $\pm$ 36.4	176.8 $\pm$ 40	190.7 $\pm$ 36.3	177.8 $\pm$ 41.4
P2 latency (ms)	242.9 $\pm$ 34.9	225.6 $\pm$ 40	241.6 $\pm$ 35.8	226.2 $\pm$ 43.3
N2 latency (ms)	290.3 $\pm$ 36.2	267.6 $\pm$ 44.7	290.3 $\pm$ 36.2	268.1 $\pm$ 47.8
P1N1 amplitude (μV)	5.3 $\pm$ 3.8	5.2 $\pm$ 4.4	5.6 $\pm$ 4.3	5.6 $\pm$ 4.8
P2N2 amplitude (μV)	4.4 $\pm$ 2.8	4.6 $\pm$ 4.5	5.3 $\pm$ 3.3	5.2 $\pm$ 4.3

3.4 Correlation between psychophysical gustatory test scores and GERPs

The psychophysical gustatory test scores of sucrose, NaCl, citric acid, and quinine hydrochloride were 8.3 ± 1.3 , 7.7 ± 1 , 8.8 ± 0.4 , and 7.6 ± 0.9 , respectively. The analysis of simple linear regression on the correlation between psychophysical gustatory function test and the parameters of GERP waveforms revealed that the psychophysical taste test scores for salt were positively correlated with the latency of P1 (Fz: $p = 0.02$, $r^2 = 0.1$; Cz: $p = 0.02$, $r^2 = 0.1$) at Fz and Cz and P2 (Cz: $p = 0.02$, $r^2 = 0.1$) at Cz in response to 0.6% NaCl stimulation, as shown in Figure 6. This study did not find a correlation between other psychophysical taste test scores, namely sweet, sour, or bitter tastes, and the parameters of gustatory event-related potential peaks.

4 Discussion

A performance-stable and reliable gustometer has been developed by our team. This study reported an independently constructed gustometer and tested it in healthy young subjects. It successfully recorded stable and specific GERPs waveforms, capturing the classic peaks of GERPs (Hu et al., 2020). The flat curves with no peaks using distilled water as a control and the no-peak waveforms obtained after anesthetizing the tongue surface are consistent with previous findings (Kobal, 1985), which further validating the specificity of the potentials obtained. The major findings of the present preliminary study were that GERP (i) there was a concentration-specific topographical distribution indicating the activation of gustatory cortex changes as stimulus concentration, (ii) GERPs recorded at the Cz had higher amplitude and shorter latency for both P1 and P2 than recording position Fz; (iii) the GERPs latencies of peaks exhibit a significant correlation with psychophysical gustatory test.

Gustometer development is key for obtaining reliable GERPs. To maximize the precision of stimulus delivery, the following issues need to be considered: the mechanical delay between trigger signal and the onset of gustatory stimulation, influenced by various variables such as the viscosity of the solution, the flow rate of the system, the length of the tubing, etc.; taste stimulus with as much of a square shape characteristic as possible; and eliminating influences of oral somatosensation, temperature, and oro-facial muscle movements. In recent decades, various taste stimulation methods have been explored to address these issues. The first GERPs to liquid stimuli were obtained almost 50 years ago. Funakoshi and Kawamura (1971) first attempted to describe cerebral taste event-related potentials via an apparatus consisting of a hinged spoon that delivered the taste solution (in a comparably large quantity) when tilted. Unfortunately, their research could not be replicated later by Schaupp (1971) or Bujas (1980). At the same time, the potential of electrical taste stimulation was explored, which applies electric pulses to lingual taste buds to elicit a unique taste percept with good stimulus control (Plattig, 1969), yet its ecological validity remains debatable. Recently, several mature gustometers have been reported by multiple centers. We have summarized and compared the origins, forms of gustatory stimulus delivery, latency of P1 and P2, amplitude of P1N1, and the appearance of these gustometers in Table 3. Agnès Jacquin-Piques from France, Burghart, Wedel from Germany, and Camilla Arndal Andersen from Denmark used an air fine spray to deliver tastants. The gustometer

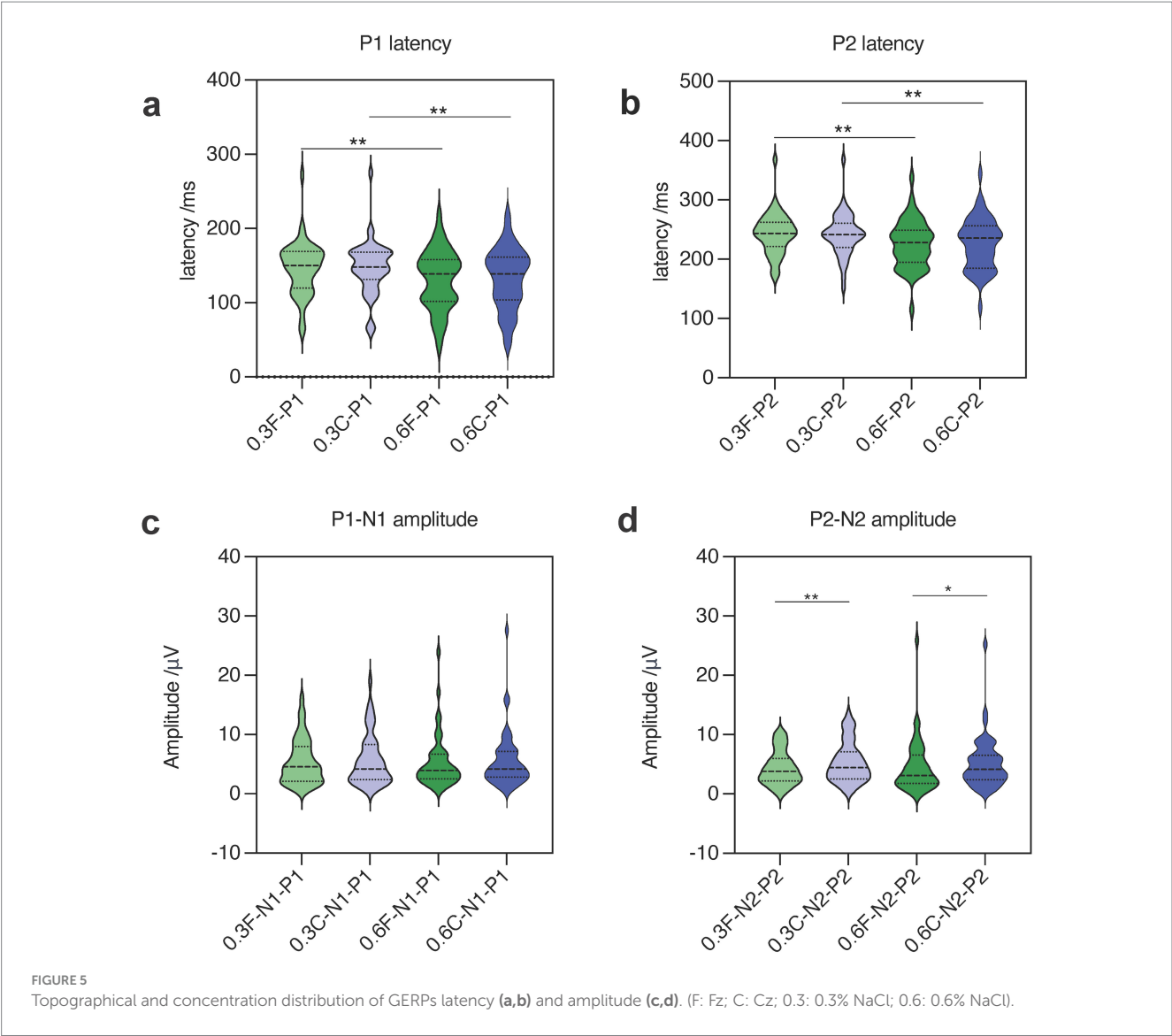


TABLE 2 Paired *t*-tests revealed comparisons of GERPs parameters (latency and amplitude) across different stimulation sites and various stimulation concentrations.

Paired <i>t</i> test	FZ-Cz				0.3–0.6			
Amplitude	0.3 N1-P1	0.3 N2-P2	0.6 N1-P1	0.6 N2-P2	Fz N1-P1	Fz N2-P2	Cz N1-P1	Cz N2-P2
<i>p</i> value	0.3	0.006	0.3	0.01	0.9	0.8	0.9	0.9
<i>t</i>	<i>t</i> = 1.1, <i>df</i> = 45	<i>t</i> = 2.9, <i>df</i> = 45	<i>t</i> = 1, <i>df</i> = 45	<i>t</i> = 2.6, <i>df</i> = 45	<i>t</i> = 0.9, <i>df</i> = 45	<i>t</i> = 0.3, <i>df</i> = 45	<i>t</i> = 0.1, <i>df</i> = 45	<i>t</i> = 0.2, <i>df</i> = 45
Latency	0.3P1	0.3P2	0.6P1	0.6P2	Fz P1	Fz P2	Cz P1	Cz P2
<i>p</i> value	0.5	0.5	0.2	0.8	0.001	0.002	0.003	0.009
<i>t</i>	<i>t</i> = 0.7, <i>df</i> = 45	<i>t</i> = 0.6, <i>df</i> = 45	<i>t</i> = 1.2, <i>df</i> = 45	<i>t</i> = 0.3, <i>df</i> = 45	<i>t</i> = 3.4, <i>df</i> = 45	<i>t</i> = 3.3, <i>df</i> = 45	<i>t</i> = 3.1, <i>df</i> = 45	<i>t</i> = 2.7, <i>df</i> = 45

developed by Emerging Tech Trans LLC and our center used pumps to deliver liquid tastants.

The gustometer developed by our team represents some improvements. It allows participants to rest their chin on a stand while wearing headphones and an eye mask. These measures are designed to minimize the effects of sound and light, prevent electromyographic activity induced by swallowing, and eliminate the influence of tactile sensations and preconceived biases. Unlike the long testing durations typically used in earlier studies, which can negatively affect participants' attention and task performance, our system incorporates a volume adjustment feature in the stimulator to regulate the amount of solution released. Through multiple trials, we identified the most comfortable stimulus volume for participants and adjusted the time interval between the salty and distilled water stimuli to generate a square-wave taste stimulus, characterized by a brief, rapid rise or fall. Reducing the sweep duration enhances synchronization of the

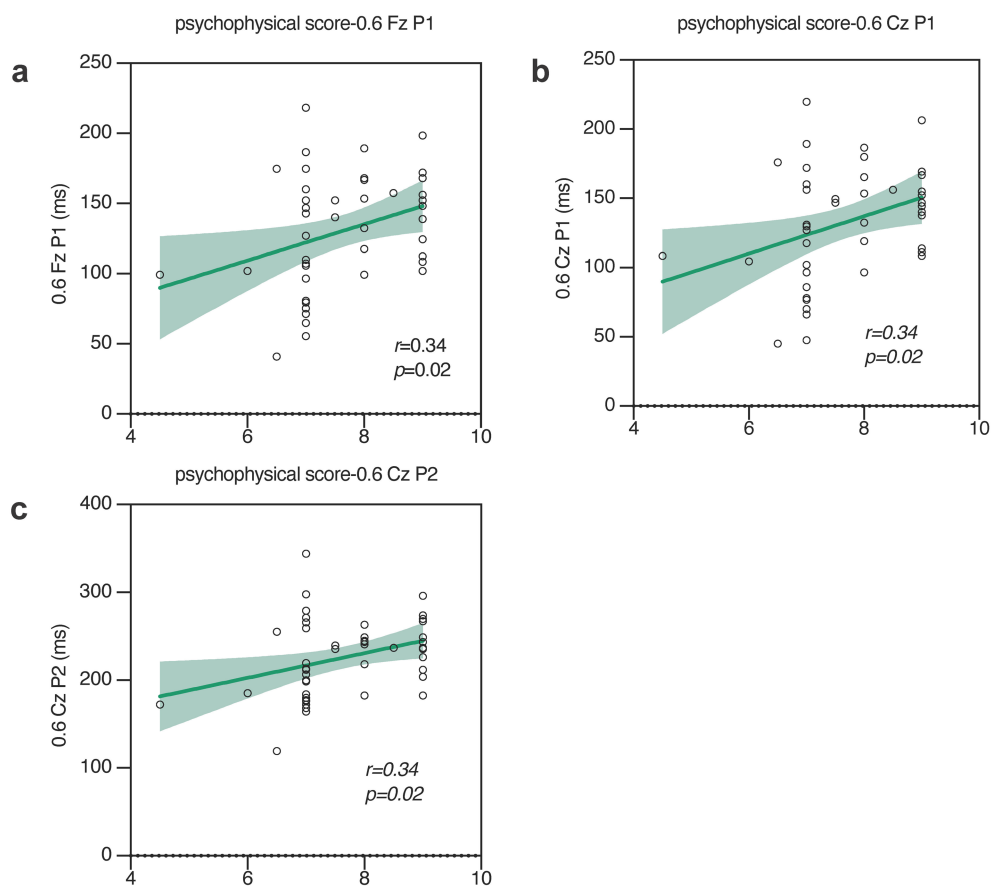


FIGURE 6

Analysis of the correlation between various GERP components and taste psychophysical tests. The latency of P1 (a,b) and P2 (c) are positively correlated with taste psychophysical tests. (F: Fz; C: Cz; 0.3: 0.3% NaCl; 0.6: 0.6% NaCl).

electroencephalographic signals, resulting in cleaner and more consistent waveforms. Furthermore, compared to gustometers in other regions, our GERPs recording system does not require swallowing, which improves participant acceptance, allows for repeated testing, and reduces overall testing time (Table 3).

In this study, all subjects exhibited significant waveforms under salty stimuli. To further confirm that the elicited waveforms were taste-specific, we used water as a control, which did not produce any waveforms. After successfully eliciting salty GERPs, we anesthetized the facial and trigeminal nerve distribution areas on the tongue surface using tetracaine, which also failed to elicit GERPs. These findings confirm that the EEG signals we recorded were indeed induced by salty taste stimuli. Previous studies have found (Hu et al., 2020; Kobal, 1985; Tzieropoulos et al., 2013) that the average latency of the P1 is 70–150 ms, and the latency of the P2 is 350–500 ms. The average latency of the P2 induced by salty taste in this study was slightly shorter than the literature. Morphologically, the presently recorded GERP were similar to those described previously (Mizoguchi et al., 2002). Apart from this, all subjects showed significantly shortened latencies and partial exhibited greater amplitudes with increasing concentrations, which is in accordance with the recordings made by Kobal and Thomas Hummel, indicating that the increase in concentration

modulated the amplitude and latency of the brain's response (Hummel et al., 2010; Kobal, 1985; Tzieropoulos et al., 2013). However, we still observed that the amplitude decreased for other subjects as the stimuli increased. This inconsistency could be due to the short rest periods between the two concentration sections, a long recording session that may have resulted in desensitization (taste fatigue), or the possibility that the differences in concentration used at present were too small to elicit the differences that had been observed earlier using different setups and different stimulus concentrations (Singh et al., 2011), or individual differences in taste preferences. Therefore, further exploration of the factors affecting GERPs and the optimal stimulus concentration is needed.

Higher psychophysical gustatory test scores for salty taste correlated with higher responses in GERPs, further confirming the consistency of sensitivity between the peripheral gustatory system and the central nervous system. Although in this study there is a statistically significant linear correlation between the psychophysical test and the P1/P2 wave latency of the objective GERP, the maximum correlation coefficient (*r*-value) is only 0.34. The literature indicates that the psychophysical results of olfactory and gustatory functions do not linearly correlate with their event-related equivalents. This is why olfactory and gustatory event-related responses are currently only

TABLE 3 A brief comparison of the various gustometer design and GERPs data across different centers.

Region	Germany	Pennsylvania, USA	China	France	Denmark and Germany
Gustometer	Burghart, Wedel (Payne et al., 2024)	Emerging Tech Trans LLC (Nin and Tsuzuki, 2024)	Patent Granted	Jacquin-Piques A (Zhu et al., 2023; Iannilli et al., 2015)	Camilla Arndal Andersen Richard Höchenberger (Mouillot et al., 2019)
Stimulus form	Air stream with constant temperature MR-compatible	Liquid Pump drive Fully MR-compatible	Liquid Pump drive MR-compatible	Compressed air (controlled through a manometer).	Air spray MR-compatible
Principles and characteristics	Eliminate the influence of liquid temperature and tactile	Delivered solutions through peristaltic pumps and Teflon tubes. Each pump has a slightly different tone, which helps inform subjects which stimulus is currently active.	Two parallel silicone tubes were used: one from channel 4 for water and the other from bottles 1–3 for a taste solution	Two silicone tubes were used: one for the control solution, one for the taste solution. Electronic device controlled valve switching.	Computer-controlled, modular pump system
Need to swallow the stimulus solutions?	No	Yes	No	Yes, but small amount.	Yes, but small amount.
P1 latency(ms) at Cz	126.67 ± 31.95	131.82 ± 46.14 (0.3 M NaCl)	151.1 ± 34.9 (0.3% NaCl)	141.1 ± 21.0 (Sweet) 150 ± 17 (Sweet) 156 ± 30 (0.5% NaCl)	-
P2 latency(ms) at Cz	431.57 ± 44.19	414.12 ± 75.86 (0.3 M NaCl)	244.6 ± 37.3 (0.3% NaCl)	-	-
P1-N1 amplitude*/μV	5.91 ± 4.31	2.53 ± 1.89 (0.3 M NaCl)	5.1 ± 4.1 (0.3% NaCl)	24.8 ± 11.6 (Sweet) 19.7 ± 8.6 (0.5%NaCl)	-
P2-N2 amplitude/μV	10.65 ± 6.9	2.85 ± 2.42 (0.3 M NaCl)	4.9 ± 3.2 (0.3% NaCl)	-	-

*The amplitude of each response was calculated from positive to negative peaks.

applicable for assessing the presence or absence of corresponding chemosensory functions (Ohla et al., 2012; Hummel et al., 2010; Lötsch and Hummel, 2006). This may be attributed to the fact that psychophysical tests themselves are influenced by various factors, such as the subject's condition and outcome judgment, which lead to variability in results.

This study has some specific limitations that need addressing. Firstly, since NeuroAudio EEG is designed for auditory electrophysiological monitoring, it is equipped with only two EEG recording channels (Figure 2), which limits our ability to control for blinking artifacts with appropriate recordings like Fp2. Nonetheless, we mitigated eye movement and blinking contamination by using an eye mask and maintaining the subjects' focus. Secondly, while the disappearance of GERPs following local anesthesia with tetracaine suggests specificity to gustatory input, it is important to acknowledge that local anesthesia only blocks peripheral nerve input and does not necessarily imply a complete absence of cortical processing. Future studies should include control ERP components, such as somatosensory or auditory ERPs, to ensure that the observed GERP disappearance is not due to a broader neural suppression effect. This approach will further validate the specificity of the recorded GERPs and strengthen the conclusions drawn from the study. Thirdly, this study validated the functionality of the gustometer by demonstrating that it reliably elicited GERPs in response to salty stimuli. While this represents an important first step, further validation across additional taste qualities is necessary to fully establish its clinical and research utility. Previous studies have reported GERPs for all five basic taste qualities, and future investigations will expand our testing to include sweet, sour, bitter, and umami stimuli. Last, several factors may contribute to variability in the recorded GERPs. Individual differences in gustatory sensitivity could have influenced response amplitudes, despite the use of psychophysical gustatory testing to confirm normal taste function. Additionally, repeated exposure to salty stimuli may have led to sensory adaptation, reducing responses over time. While inter-stimulus intervals were incorporated to minimize adaptation, future studies should consider randomized stimulus sequences to further control for this effect. The next step is to gradually advance the clinical transformation of the gustometer and GERPs device, launch corresponding commercial products, and then explore the value of GERPs in the diagnosis and treatment of taste disorder diseases.

In conclusion, the novel gustometer effectively records true and reliable GERP waveforms. This study validated the consistency of GERP amplitude and latency with psychophysical gustatory tests, highlighting the gustometer's potential for clinical and research applications in gustatory system analysis.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/7zpsy/?view_only=95382b60338e48d69e44b1b82c32d94e.

Ethics statement

The studies involving humans were approved by China-Japan Friendship Hospital Ethical Committee (2022-KY-080). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

ZC: Data curation, Formal analysis, Methodology, Software, Writing – original draft. XZ: Data curation, Methodology, Software, Writing – original draft. CL: Methodology, Project administration, Software, Writing – review & editing. JL: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing, Writing – original draft.

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Conflict of interest

CL was employed by Beijing Yuda Medical Technology Co., Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Pain perception in autism. A study of sensory reactivity in children and adolescents with autism using quantitative sensory testing and psychophysiological correlates

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Background: Hyper- or hypo-reactivity to sensory input is a diagnostic criterion for autism spectrum disorder; however, it is still not fully characterized, despite its relevance to patients' quality of life. When considering neurodevelopment, sensory reactivity in autism is often assessed through parental reports, with only a few pieces of evidence acquired using standardized protocols. Quantitative sensory testing (QST) is a standardized protocol used to quantify sensory function by assessing perceptive and pain thresholds with calibrated sensory stimuli. To date, only a few studies have used QST to investigate sensory reactivity in autism, with only one taking into account adolescents and none including children in the sample.

Methods: We aimed to study pain perception and in children diagnosed with autism using the QST protocol. Moreover, we sought to measure central reactivity to painful stimuli by recording electroencephalographic (EEG) responses to painful thermal stimuli to explore the relationship between subjective reactivity (i.e., reactions to sensory stimuli) and central processing of sensory stimuli (i.e., EEG responses). Finally, we aimed to explore the relationship between parents' reports, subjective reports, and EEG responses.

Discussion: This study will help to expand our previous knowledge concerning the sensory profile of children and adolescents with autism. Deepening our understanding of the relationship between perceptive thresholds in children with autism and the reactivity of the central nervous system, could help us understand the causal mechanism of the perceptual differences observed in autism.

Study protocol identifier: NCT06659731

KEYWORDS

pain, QST, EEG, autism, ERPs, neurodevelopment, perception

1 Introduction

Since 2013, the updated diagnostic criteria for autism, which include “hyper- or hypo-reactivity to sensory input or unusual interests in sensory aspects of the environment,” have been in place (American Psychiatric Association, 2022). In children, these two sensory profiles have been mostly studied through parental self-reports, such as the Short Sensory Profile (McIntosh et al., 1999) and the Short Sensory Profile II (Dunn, 2014). Recent studies based on these measures have reported different clusters of results, dividing children into two (Simpson et al., 2019) or five phenotypes (Scheerer et al., 2021). Simpson et al. (2019) found two clusters using the SSP-2: one cluster named *Uniformly elevated*, which reported high scores across all quadrants, and another cluster named *Raised avoiding and sensitivity*, which showed higher scores in the avoiding and sensitivity quadrants. More recently, Scheerer et al. (2021), using the SSP, identified five distinguished sensory profiles that may account for some of the behavioral heterogeneity in people with autism. Such heterogeneity was also highlighted by Proff et al. (2022) in a recent review focused on sensory processing in autism, particularly in the exteroceptive and interoceptive domains. This finding highlights that accounting for the heterogeneity of sensory processing is crucial for understanding and diagnosing autism, as well as for treatment and fostering inclusivity in our society. Pain perception is another domain of perception affected by autism. Patients may be at higher risk of self-injurious behaviors (Rattaz et al., 2013) or may have issues communicating the pain they experience (Fitzpatrick et al., 2022). Moreover, pain and its chronicity represent actual public health issues (Blyth, 2008; Cohen et al., 2021), especially for clinical populations, such as people with autism. Recently, Moore (2015) highlighted the need for a systematic investigation of pain in autism through standardized and more reproducible methodologies. Previously, it has been reported that different studies have considered various outcome measures, such as parent reports, self-reports, sensory thresholds, and objective measures. This variability has reduced consistency across different studies and results. Moreover, the absence of control groups and the use of non-standard pain measures have contributed to conflicting results, according to Moore (2015). Recently, we reviewed all the studies published after Moore (2015) review that used quantitative sensory testing (QST) to study pain in autism, and we found that only five studies investigated pain using the QST methodology. Of these few studies, only one considered adolescents, and none considered children (Nicolardi et al., 2023). This literature gap could reasonably be due to the amount of discomfort possibly associated with the administration of sensory stimuli to children and adolescents with autism, which could lead to a high number of dropouts within the sample. With a standardized protocol, such as QST, the challenge of reproducing the methodology is further increased by the necessity to test both the left and right sides and by the overall protocol duration. Indeed, the few studies that have approached this topic using QST have implemented a modified version suitable for patients’ difficulties (Symons et al., 2022; Barney et al., 2020). Even when the same methodology was used (QST), different hypotheses, outcomes, and samples were considered. Two studies (Fründt et al., 2017; Vaughan et al., 2020) reported differences in the perception of mechanical stimuli in

autism. However, other studies found lower sensitivity to thermal stimuli in people with autism (Duerden et al., 2015; Chien et al., 2020). Chien et al. (2020) also collected other measures alongside QST, reporting a decrease in sensory fiber density in a sub-sample, which could explain the sensory features in this specific sample. The most recent study concerning QST to assess sensory perception in autism involved 52 adults diagnosed with autism (Hoffman et al., 2023). The authors concluded that the clinical sample reported hypersensitivity to daily stimuli and experimental pain, with less inhibition of tonic painful stimuli.

Considering the methodological limitations highlighted by previous literature and the need for a standardized and more reproducible methodology, we decided to use the QST protocol to investigate pain perception in children and adolescents with autism. We integrated this measure with an assessment of the central processing of painful stimuli, collected through electroencephalographic (EEG) measures. Finally, we compared the data from this sample with data from an age-matched control sample. Through this combination of QST measures and EEG measures, we aimed to deepen the characterization of the sensory profile and pain perception in autism, expanding the general understanding of the peripheral and central contributions of sensory hyper- or hypo-reactivity in autism across the neurodevelopmental stages.

2 Methods and analysis

This was an observational, case-control clinical study. The study procedure involved the following steps (Steps 2 to 4 shown in Figure 1): (1) Eligibility assessment according to the inclusion and exclusion criteria, (2) Administration of questionnaires and scales for the characterization of clinical aspects of autism: the Short Sensory Profile (Tomchek and Dunn, 2007), the Autism Spectrum Quotient—Children’s Version (AQ-Child, Auyeung et al., 2008), the Vineland Adaptive Behavior Scales—Second Edition (VABS-II; Sparrow et al., 2005), and the Child Behavior Checklist (CBCL) (Achenbach and Rescorla, 2001), (3) Administration of modified QST to study sensory thresholds and perception, and (4) EEG recording at rest and while receiving heat stimuli to study cortical processing of salient thermal stimuli.

2.1 Sample

The sample included children and adolescents between the ages of 5 and 17 years selected according to the following inclusion/exclusion criteria. According to the calculation performed with the G*Power software, the sample size should be approximately 32 participants to provide a statistical power of 0.9. The sample size calculation was performed based on the effect-size parameters by Vaughan et al. (2020).

Inclusion criteria for the clinical sample

Children and adolescents between the ages of 5 and 17 years and patients with autism diagnosis according to the DSM-V TR criteria were included in the clinical sample.

Exclusion criteria for the clinical sample

Patients with the following comorbidities were excluded from the clinical sample: peripheral neuropathies, to avoid confounding

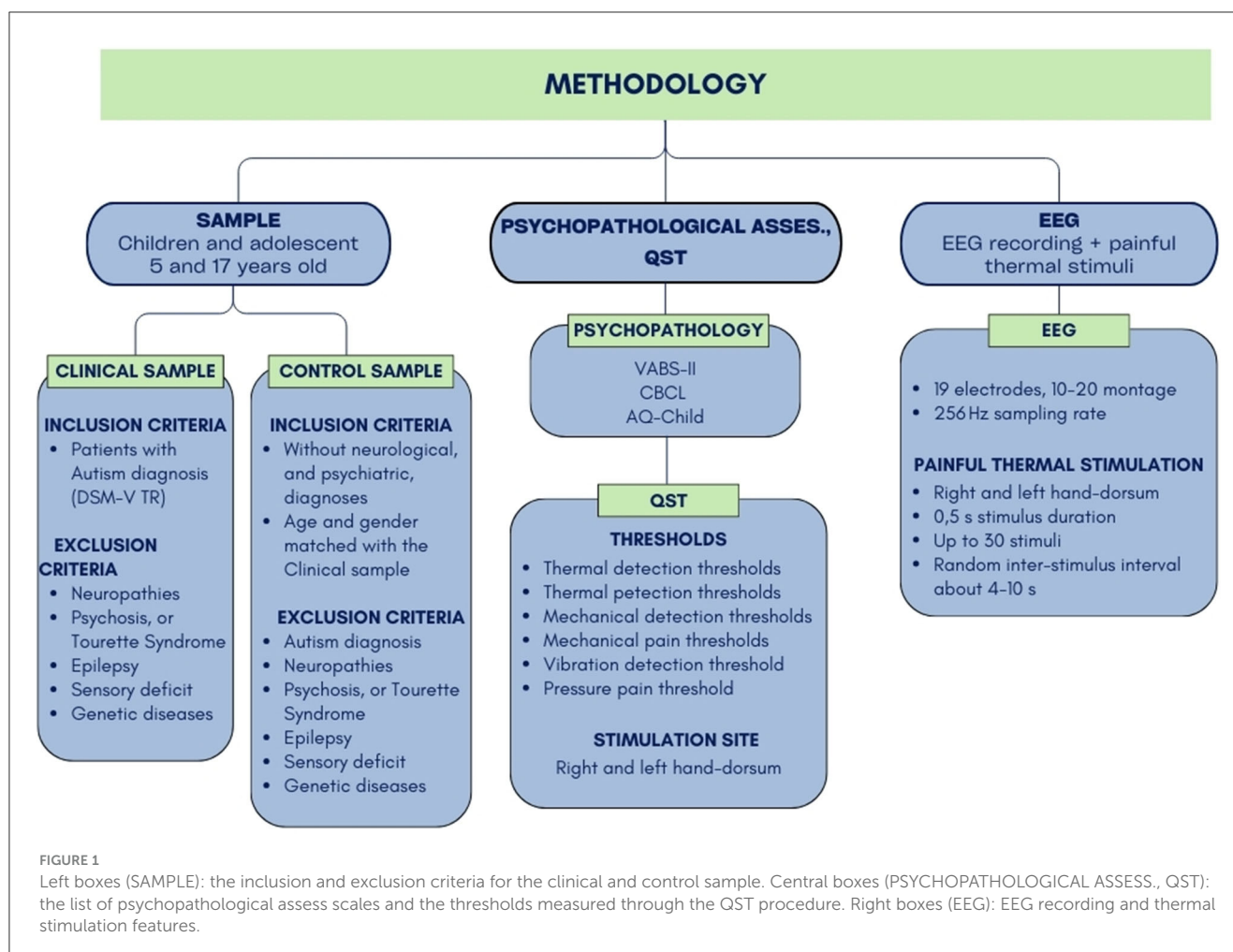


FIGURE 1

Left boxes (SAMPLE): the inclusion and exclusion criteria for the clinical and control sample. Central boxes (PSYCHOPATHOLOGICAL ASSES., QST): the list of psychopathological assess scales and the thresholds measured through the QST procedure. Right boxes (EEG): EEG recording and thermal stimulation features.

factors with respect to the QST measures; psychiatric diagnoses, such as psychosis or Tourette syndrome, to prevent interference with EEG signals; neurological diagnoses such as epilepsy, sensory deficits, or sensory loss; and genetic diseases.

Inclusion criteria for the control sample

The inclusion criteria include the following: Healthy children and adolescents between the ages of 5 and 17 years, without neurological or psychiatric diagnoses and age- and gender-matched participants within the clinical sample.

Exclusion criteria for the control sample

Children and adolescents with an autism diagnosis and those with peripheral neuropathies; psychiatric diagnoses such as psychosis or Tourette syndrome, to prevent interference with EEG signals; neurological diagnoses such as epilepsy, sensory deficits, or sensory loss; and genetic diseases were excluded.

2.2 Psychopathological assessment and dispositional measures

The psychopathological assessment (Figure 1) allowed for the characterization of clinical aspects of autism through the following

scales: the Vineland Adaptive Behavior Scales—Second Edition (VABS-II; Sparrow et al., 2005); the Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2001); and the Autism Spectrum Quotient—Children's Version (AQ-Child; Auyeung et al., 2008). Moreover, a caregiver report questionnaire was included to assess sensory processing abnormalities in children with autism and neurotypical children: the Short Sensory Profile (Tomchek and Dunn, 2007).

2.3 QST

The QST protocol (Rolke et al., 2006; Blankenburg et al., 2010) involves the administration of seven short sensory tests to measure up to 13 parameters. The overall parameters can be grouped as follows (Figure 1): thermal detection thresholds for the perception of cold, warm, and paradoxical heat sensations; thermal pain thresholds for cold and hot stimuli; mechanical detection threshold (MDT) for touch and vibration; mechanical pain threshold (MPT) and sensitivity for pinprick and blunt pressure; and vibration detection and pressure pain thresholds. Previous research using QST in neurodevelopmental disorders used a modified version of the whole protocol to make it suitable and tolerable for different

clinical conditions, such as developmental delay, including motor, communicative, and cognitive impairments (Barney et al., 2020; Symons et al., 2022). Thus, we administered the most suitable and tolerable version of the QST based on each patient's condition and needs. We selected the hand dorsum as the only stimulation site and reduced the number of stimuli for each stimulation to shorten the stimulus trial duration and enhance the tolerability of the complete procedure. For each intensity value, three stimuli were delivered on the hand dorsum for mechanical stimulation. We also divided the QST procedure into two sessions, conducted at the same time of day for each patient (i.e., both sessions in the morning or both in the afternoon). The entire procedure was conducted in a child-friendly environment—colorful and comfortable, with sensory stimuli adapted to avoid fearfulness of the stimuli. Thus, each stimulation was presented as a game to be played with a specific animal, and each device and instrument was covered with pictures of animals according to the game it represented. Overall, QST lasted ~1 h 30 min. When needed, it was divided into two sessions, each lasting ~45 min, according to the patients' needs. Our modified version of QST only included detection and pain thresholds for thermal and mechanical (pinprick, vibratory, and pressure) stimuli. We excluded the following from the original procedure: paradoxical heat sensations, the difference limen threshold for alternating cold and warm stimuli, and the number of paradoxical heat sensations, as these stimulations involved many repeated stimuli, greater unpleasantness, and less tolerability for patients. Thermal stimulation included cold and warm detection thresholds (CDT and WDT, respectively) and cold pain and heat pain thresholds (CPT and HPT, respectively). These parameters were estimated using the method of levels, implemented with a contact thermal cutaneous stimulator (TCS model II.1, QST.Lab; Strasbourg, France) to avoid variations in response times related to the method of limits (Duerden et al., 2015; Chien et al., 2020). We chose the thermode model T08, which consists of 15 Peltier elements, each with a 9 mm² surface, resulting in a total stimulation surface of ~4.5 cm². This model was selected as it is the most suitable probe for implementing the QST protocol and contact heat-evoked potentials. The mechanical detection threshold (MDT) was determined using 12 modified von Frey hairs (Optihair2-Set, Marstock Nervtest, Germany), with stimulus intensities of 0.25, 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 32, 64, 128, 256, and 512 mN. The mechanical pain threshold (MPT) was measured using weighted pinprick mechanical stimulators, with intensity forces of 8, 16, 32, 64, 128, 256, and 512 mN and a contact area of 0.2 mm in diameter. The vibration detection threshold (VDT) was measured using a Rydel-Seiffer graded tuning fork (64 H/.8/8 scale) placed on the styloid process of the ulna. The tuning fork was placed on the target bone and kept in place until the patient could no longer feel the vibration. The pressure pain threshold (PPT) was measured using a calibrated digital force gauge device (SAUTER FC) with a maximum capacity of up to 50 N and a probe area of 1 cm². Concerning possible communicative impairments, we planned to rely on parents' help in understanding the specific communication modalities of each patient, as well as to introduce the use of non-verbal pain scales, such as the Pain and Discomfort Scale (PADS; Shinde et al., 2014), when needed.

2.4 EEG recording with thermal stimulation

The EEG signal was acquired using the BRAIN QUICK EEG system (MicroMed, Treviso, Italy) with a 256 Hz sampling rate from 19 electrodes disposed according to the international 10–20 system. The reference electrode was placed on the right earlobe. The EEG recording session began with the cap montage, followed by a short accommodation with the sensory stimuli to determine an intensity value for a moderately painful stimulus to be used for the stimulation. Moderately painful stimulus refers to one that the patient perceives as painful but still tolerable, with low intensity and minimal unpleasantness. This finding ensures the procedure's tolerability and minimizes patient discomfort. After the preparation/accommodation, the EEG recording was performed with the eyes open, starting with a series of up to 30 thermal stimuli (according to the patients' tolerability) delivered to the patients' right-hand dorsum with a random inter-stimulus interval between 4 s and 10 s in the step of 1 s. Stimulus duration was 0.5 s. The entire EEG recording, lasting ~30 min, included an EEG cap montage, instructions, and stimulation, with breaks provided if needed by the patients. We did not include systematic time breaks by default, as the painful stimulation procedure lasted <10 min. However, given the age of the patients, we accounted for the possibility of breaks and included them in the 30 min time estimation.

2.5 Analysis

The primary outcome measures of this study were sensory thresholds: CDT and WDT, CPT and HPT, MDT and MPT, VDT and PPT. Another primary outcome was EEG responses, analyzed in the time domain (ERPs related to the thermal stimulus) and the time-frequency domain (power spectrum, both phase-locked and non-phase-locked with the thermal stimulus). The QST threshold data were processed according to Rolke et al. (2006), while normative values from Blankenburg et al. (2010) were used for z-transformation. Statistical analysis of the primary outcomes involved a one-way ANCOVA, with sex as a covariate, to compare the effect of the group variable (autism/neurotypical controls) on the dependent variables.

The secondary outcome measures of this study were the scores on dispositional and psychopathological measures, which were used for exploratory analysis in relation to the primary outcomes. For the explorative analysis, mixed-effects models were implemented, accounting for inter-individual variability (random intercept), and when possible (according to model convergence), for dispositional and psychopathological measures as grouping factors (random slopes).

The EEG data were processed and extracted using the EEGLAB (Delorme and Makeig, 2004) and Letswave software (www.letswave.org). Signal processing involved artifact removal through a band-pass filter. Ocular artifacts were identified and removed using independent component analysis (ICA) decomposition, implemented with the *runica* algorithm in EEGLAB (Delorme and Makeig, 2004), and re-referenced to the average reference. Further processing included signal averaging for

the extraction of event-related potentials (ERPs) in time-domain. According to previous literature and the methodology used, contact-heat evoked potentials (Chien et al., 2020; Mulders et al., 2020) were analyzed and compared between the two groups. Nonetheless, further exploratory analysis was conducted on vertex components typically related to sensory processing (Baumgartner et al., 1993; Mouraux and Plaghki, 2007). Computations, such as a fast Fourier transform or wavelet transform, were implemented to extract time-frequency domain information. Finally, explorative analyses were conducted to clarify if the psychopathological or dispositional measures contributed to group differences in sensory perception or EEG responses. In addition, we explored the relationship between subjective differences and cortical reactivity measured through EEG.

3 Discussion

To date, this is the first investigation of the sensory profile of children and adolescents with autism using the QST method. In line with previous results (Duerden et al., 2015; Fründt et al., 2017; Vaughan et al., 2020; Chien et al., 2020), we hypothesized group differences at the perceptive level. We expected to find higher variability in the clinical sample due to the presence of hyper- and hypo-sensitivity within the same sample. Moreover, we also expected to find differences in the EEG measures, indicating different cortical reactivity between the two groups. As for the perceptive profiles and EEG measures, we expected higher variability within the clinical sample. This variability could allow us to further divide this sample based on hyper- or hypo-sensitivity profiles and them as a grouping factor and choose the statistical comparison according to their presence. Moreover, with this protocol, we aimed to overcome a methodological challenge by implementing a standardized clinical protocol with children with autism, a protocol typically performed and validated on neurotypicals. The challenge concerns not only the methodology *per se* but also the topics of inclusivity and neurodiversity in research. Indeed, we adapted the protocol according to the differences and needs of the individuals with autism, increasing the protocol's tolerability for the patients. We followed the guidelines from previous studies on QST in children with intellectual and developmental disabilities (Blankenburg et al., 2018; Symons et al., 2022; Barney et al., 2020). Previous studies modified the original QST protocol to make it more tolerable in terms of the number of stimuli, time duration, and communication (Symons et al., 2022; Barney et al., 2020). Some parts of the protocol could be uncomfortable and possibly overwhelming for patients, such as the difference limen for cold and warm stimuli, paradoxical heat sensation, and dynamic mechanic allodynia, which may be due to the alternation of different stimuli in a very short time, as well as the intense, repetitive, and fast stimulation that characterizes these parts of the QST protocol. Thus, in line with the methodological aims, we decided not to administer these sessions and to collect only perceptive and pain thresholds. Moreover, we decided to stimulate both sides of the body with only three consecutive stimuli for each intensity value, except for the thermal stimuli, where the number of stimuli was determined by the threshold algorithm of the thermal stimulator. Recent findings have shown between-group differences for mechanical thresholds (Fründt et al., 2017; Vaughan et al.,

2020) and thermal thresholds (Duerden et al., 2015; Chien et al., 2020), reporting lower sensitivity for people with autism. Moreover, Chien et al. (2020) found that a subsample exhibited lower skin fiber density and higher amplitude for evoked potentials related to thermal stimuli. The authors suggested that peripheral fiber density could partially explain these results; however, only Chien included this measure in their methods. Finally, the study by Duerden et al. (2015) found lower sensitivity to thermal stimuli in people with autism. The authors used the method of limits to measure detection thresholds, which relies on participants' reaction times. Indeed, the authors suggested that their results could reflect slower response times in the population with autism. On the other hand, Cascio et al. (2008) summarized findings on tactile thresholds in adults with autism, reporting hypersensitivity compared to neurotypical controls. The methodological differences could account for conflicting results; however, it is also possible that these results reflect the higher variability within the clinical sample, where some patients show hyper-sensitivity and others show hypo-sensitivity to sensory stimuli. We claim that the stimulation protocol, the psychophysical approach, and the statistics implemented should be considered to improve the methodological approach concerning perception in autism. In line with this finding, we believe that our study could provide a robust and reproducible methodology and positively contribute to the current literature. The use of QST as the stimulation protocol, a psychophysical approach accounting for differences in reaction times, and a statistical approach that also explores inter-individual differences and grouping factors can overcome previous methodological issues. Increasing our understanding of differences in sensory reactivity and perception by considering subjective, central, and peripheral measures is crucial for planning adequate and personalized clinical intervention (Smith, 2019). Moreover, this methodological approach could contribute to future hypotheses on the causal mechanisms of observed differences. Nonetheless, the use of a non-validated modified version of QST and the sample size could be considered methodological limitations. However, the modifications we applied to the protocol align with previous research on neurodevelopmental disorders, where differences in sensory reactivity were observed when compared to typically developing children (Symons et al., 2010, 2022). If confirmed, our results could align with findings from other neurodevelopmental disorders. Within the framework of inclusivity toward neurodiversity, it is essential to adapt research methodologies that are often applied for neurotypicals. For this reason, we collaborated with patient and family organizations, discussing our methodology with them in line with the participatory research framework.

Data availability statement

The collected data will be made available by the authors, without undue reservation. Further inquiries can be directed to the corresponding author.

Ethics statement

The study protocol has been approved by the Local Ethic Committee of Istituto Tumori "Giovanni Paolo II"

– IRCCS - Bari, Italy (Prot.n. 201/CE 19/04/2023). Each participant has been provided with informed consent before enrolment. The study protocol has been registered on the [ClinicalTrials.gov](https://clinicaltrials.gov) international repository, with the protocol identifier NCT06659731. The patients/participants provided their written informed consent to participate in this study.

Author contributions

VN: Conceptualization, Funding acquisition, Methodology, Resources, Writing – original draft, Writing – review & editing. IF: Writing – review & editing. GA: Writing – review & editing. SS: Writing – review & editing. AT: Funding acquisition, Resources, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Neural mechanisms of symmetry perception: hemispheric specialization and the impact of noise on reflection symmetry detection

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Symmetry is a crucial cue for perceptual grouping in human vision. This study investigates the neural and cognitive mechanisms underlying symmetry perception, focusing on hemispheric specialization and the effects of noise on symmetry detection. Using psychophysical and electrophysiological (EEG) experiments, participants were presented with reflection symmetric patterns (full circle vs. right-left quarter-circle), under varying noise levels. Behavioral results demonstrated noise-induced impairment in accuracy ($p < 0.001$), with Cycle outperforming Quarter in noiseless conditions ($p < 0.05$), highlighting the role of contour completeness in perceptual grouping. EEG recordings revealed distinct neural mechanisms associated with different stages of symmetry processing. Early sensory processing exhibited left-hemisphere dominance, while later stages implicated the right hemisphere in noise-modulated global integration. Noise disrupted early contour integration and attenuated higher-order object recognition processes, with right-hemisphere sensitivity to noise emerging during decision-making. These findings challenge the strong version of the callosal hypothesis, highlighting the complexity of hemispheric interactions in symmetry perception. This study provides new insights into the interplay between bottom-up sensory processing and top-down hemispheric interactions in perceptual organization.

KEYWORDS

symmetry perception, hemispheric specialization, EEG, neural mechanisms, event-related potentials (ERPs)

1 Introduction

The human visual system is remarkably adept at organizing fragmented or incomplete visual input into coherent perceptual objects. This ability is governed by the principles of perceptual grouping, as outlined by the Gestalt laws of perception, which include principles such as good continuation, closure, proximity, similarity, and symmetry (Gorbunova, 2017; Mauro and David, 2024; Purves, 2024; Wang et al., 2022). Among these, symmetry has been identified as a particularly salient cue for perceptual grouping (Moscato et al., 2023;

Henle, 1963; Hu et al., 2024; Purves, 2024). Symmetry allows the visual system to efficiently segregate objects from their backgrounds and to infer the structure of partially occluded or ambiguous stimuli (Moscato et al., 2022). Ernst Mach (Mach, 1914) was among the first to systematically categorize symmetry into three types: translational (repetition) symmetry, reflectional (mirror) symmetry, and centric (rotational) symmetry. Of these, reflectional symmetry, particularly mirror symmetry, has been shown to be processed more readily and rapidly than other forms of symmetry or asymmetrical patterns (Palmer and Hemenway, 1978; Wright, 1972). This efficiency in processing mirror symmetry is thought to play a critical role in the perceptual organization of visual scenes, helping to group and segregate visual input into meaningful objects and backgrounds (Machilsen et al., 2009).

1.1 Neural mechanisms of symmetry perception

Recent advances in neuroimaging and electrophysiological techniques have provided new insights into the neural mechanisms underlying symmetry perception (Beck et al., 2005; Carr et al., 2025). Functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) studies have identified a distributed network of brain regions involved in processing symmetrical patterns. These include early visual areas such as the primary visual cortex (V1) and extrastriate areas (V2, V4), as well as higher-order regions like the lateral occipital complex (LOC) and the intraparietal sulcus (IPS) (Bertamini et al., 2018; Makin et al., 2021). These regions work in concert to encode local symmetrical features and integrate them into global perceptual representations. For example, Tyler et al. (2005) used fMRI to investigate the LOC exhibits strong neural responses to symmetry patterns (such as mirror and rotational symmetry), supporting its role in symmetry grouping and perception (Tyler et al., 2005). This suggests that the LOC plays a critical role in the perceptual grouping of symmetrical patterns. Similarly, Bertamini et al. (2018) demonstrated that symmetry processing involves both feedforward and feedback mechanisms, with early visual areas encoding local features and higher-order regions integrating these features into coherent perceptual objects (Bertamini et al., 2018).

1.2 Cognitive and contextual influences on symmetry perception

While neural mechanisms provide the foundation for symmetry detection, cognitive factors such as attention, expectation, and learning also play a significant role (Elena et al., 2021; Makin et al., 2023). Recent studies have shown that symmetry perception can be modulated by top-down processes, such as attentional focus and task demands. For instance, research by Bertamini and Makin (2014) demonstrated that attention can enhance the perception of symmetry, particularly when participants are explicitly instructed to focus on symmetrical patterns (Bertamini and Makin, 2014). This suggests that attention can amplify the neural responses to symmetry, making it more salient in the visual field. Moreover, understanding hemispheric

specialization in symmetry perception is critical for cognitive neuroscience because it reveals fundamental principles of how the brain achieves perceptual organization (Rabbito et al., 2023). The two hemispheres exhibit distinct processing biases - with the left hemisphere preferentially analyzing local features and the right hemisphere specializing in global integration (Fink et al., 1997; Makin et al., 2021; Paulraj et al., 2018). As symmetry detection requires both local element processing and global configuration analysis, it provides an ideal paradigm to investigate how divided hemispheric computations are coordinated through callosal connections.

In this study, we aim to further explore the mechanisms underlying symmetry perception, with a particular focus on the role of the two cortical hemispheres in the detection of reflection symmetric patterns. Specifically, does there exist hemisphere specialization for the detection of reflection symmetric patterns? The callosal hypothesis posits that the anatomical symmetry of the human visual system underlies the efficiency of vertical symmetry detection. However, recent evidence suggests that symmetry perception may involve more complex interactions between the two hemispheres. We aim to examine whether there is a functional specialization of the left and right hemispheres for processing different orientations of reflection symmetry.

To address these issues, we conducted a series of psychophysical and electrophysiological experiments in which participants were presented with two types of symmetrical patterns: cycle and right-left quarter-circle. These patterns were presented in the right, left, or both visual fields to assess the role of hemispheric processing in symmetry detection. By combining behavioral measures with EEG recordings, we aim to provide a comprehensive understanding of the neural and cognitive mechanisms underlying symmetry perception.

2 Materials and methods

2.1 Participants

Fifteen students (10 males; mean age = 26.3; SD = 3.4) with normal or corrected-to-normal vision from Okayama University volunteered for the experiments. They provided written informed consent for their participation in this study, which was previously approved by the ethics committee of Okayama University.

2.2 Apparatus and stimuli

We used MATLAB (v 14; the MathWorks, Okayama, Japan) and GERT, the Grouping Elements Rendering Toolbox (Demeyer and Machilsen, 2012), to construct arrays of non-overlapping Gabor elements on a uniform gray background (Figure 1). The arrays comprised 496×496 pixels. Each Gabor element was defined as the product of a sine wave luminance grating (frequency of 3 cycles per degree of visual angle and presented at 100% Michelson contrast) and a circular Gaussian (standard deviation of 3 arc min). There were 512 Gabor elements, interior 62 elements, exterior 410 elements and outline 40 elements. The number of elements inside and outside the shape outline was adjusted to

ensure a homogeneous spacing between the Gabor elements. The orientations of the inside and outside Gabors were randomly and unchanged. A subset of 40 Gabor elements were positioned along the contour outline of an artificial circle shape. The shape outline was generated by plotting the sum of 5 radial frequency components in polar coordinates. The orientation of Gabor on contour was defined by stimulus type and stimulus intensity. There were two kinds of stimulus type: circle, right-left quarter-circle, see Figure 1A. The elements had orientations parallel to the local tangent of the shape outline. For example, the orientation of left 20 Gabors were local tangent of the shape outline but right 20 Gabors were randomly when stimulus was left semicircle. In addition, we created three different noise levels by altering the orientations of the contour elements. As shown in Figure 1B, Stimuli noise 0.0 (SN0.0): The orientations of the Gabors are aligned with the local tangents of the shape contours; Stimuli noise 0.4 (SN0.4): Randomly change the orientations of the 8 Gabors; Stimuli noise 0.8 (SN0.8): Randomly change the orientations of the 16 Gabors.

2.3 Procedure and task

The subjects were instructed to perform the experiment in a dimly lit, electrically shielded and sound-attenuated room (laboratory room, Okayama University, Japan) with their head positioned on a chin rest. Stimulus presentation and response collection were conducted using E-prime 1.1 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). Figure 2 showed the experiment consisted of three sessions of 120 trials each, all stimuli were presented randomly. For each stimulus condition, subjects were presented with a central fixation cross for a randomized duration between 1200 and 1800 ms, followed by the stimulus display for 150 ms. During the experiment, participants were instructed to press the "1" key on the keyboard when a "Cycle" stimulus was displayed, the "2" key for a "left quarter-circle" stimulus, and the "3" key for a "right quarter-circle" stimulus.

2.4 EEG recording and analyses

An EEG system (BrainAmp MR plus, Gilching, Germany) was used to record EEG signals through 32 electrodes mounted on an electrode cap (Easy Cap, Herrsching-Breitbrunn, Germany). Horizontal eye movements were measured by deriving the electrooculogram (EOG) from one electrode placed about 1 cm from the outer canthi of the left eye. Vertical eye movements and eye blinks were detected by deriving an EOG from an electrode placed approximately 1.5 cm below the subject's left eye. All signals were referenced to left and right earlobe, and the impedance was maintained below 5 k Ω . Raw signals were acquired at a sample rate of 500 Hz and stored for off-line analysis.

The ERPs elicited by target stimuli were analyzed by using the Brain Vision Analyzer software (version 1.05, Brain Products GmbH, Munich, Germany). The data were band-pass filtered from 0.01 to 30 Hz. Then, the data were divided into epochs, from -100 ms before stimulus onset to 500 ms after stimulus onset, and baseline corrections were made to the data from -100 ms to stimulus onset. Epochs contaminated by artifacts (i.e., eye

movements, eye blinks, amplifier blocking) were rejected based on a threshold of $\pm 100 \mu\text{V}$ in all channels before averaging. All averaged ERP waveforms were obtained across all participants for each stimulus type in each electrode.

Therefore, our analysis was performed across electrode regions of interest focused at left occipital region (O1), right occipital region (O2), left parietal region (P3 and P7), right parietal region (P4 and P8), see Figure 3.

Murray et al. (2006) found that both correct and incorrect responses did not affect the contour integration effect or shape detection within the first 300 milliseconds (Murray et al., 2006). Therefore, four main components before 300 ms were statistically analyzed. The first component was the P/N100 complex (peaking around 100 ms after stimulus onset); the second component was the P/N130 complex (peaking around 130 ms after stimulus onset); the third component was the N190 (peaking around 190 ms after stimulus onset); the last component was P260 (peaking around 260 ms after stimulus onset). Amplitudes of these component respectively measured as an average of 20 ms duration around the peak. ANOVA (Greenhouse-Geisser corrections with corrected degrees of freedom).

3 Results

3.1 Behavioral results

Table 1 showed the proportion correct for the 6 stimuli. Analysis of the proportion correct using 2 (stimulus type) $\times$ 3 (noise level) repeated measures ANOVA revealed a significant main effect in noise level [$F(2, 28) = 190.008$, $p < 0.001$, $\eta_p^2 = 0.931$], showing that the identification ability of participants was decreased with noise enhancement. Whereas, no significant difference was found in stimulus type [$F(1, 14) = 2.663$, $p = 0.125$, $\eta_p^2 = 0.160$]. The interaction between stimulus type and noise level was significant [$F(2, 28) = 6.705$, $p = 0.012$, $\eta_p^2 = 0.324$], indicated that contour effect was different in varying noise level. The pairwise comparisons showed that for the SN 0.0 condition, the responses to cycle stimuli were significantly higher than the responses to quarter stimuli ($p < 0.05$). All reported statistics reflect Green-Geisser corrections at a significance level of 0.05.

3.2 ERP results

Figure 3 showed the ground-averaged ERPs across all participants for 6 stimuli. All stimuli evoked similar P100, N130, N190, P260 components at occipital electrode, and evoked N100, P130, N190, P260 components at parietal electrode. Analysis of the peak latency with 4 components revealed there was no significant difference in 6 stimuli across both hemispheres and electrodes (all $p > 0.05$). Analysis of the mean amplitude of 4 components (P/N100, P/N130, N190, P260) $\times$ 2 electrode (occipital, parietal) $\times$ 2 hemisphere (left, right) $\times$ 2 stimuli type (cycle, quarter) $\times$ 3 noise level (SN0.0, SN0.4, SN0.8) repeated measures ANOVA revealed a significant four-way component $\times$ electrode $\times$ hemisphere $\times$ stimuli type $\times$ noise level interaction [$F(6, 84) = 3.937$, $p = 0.015$, $\eta_p^2 = 0.219$].

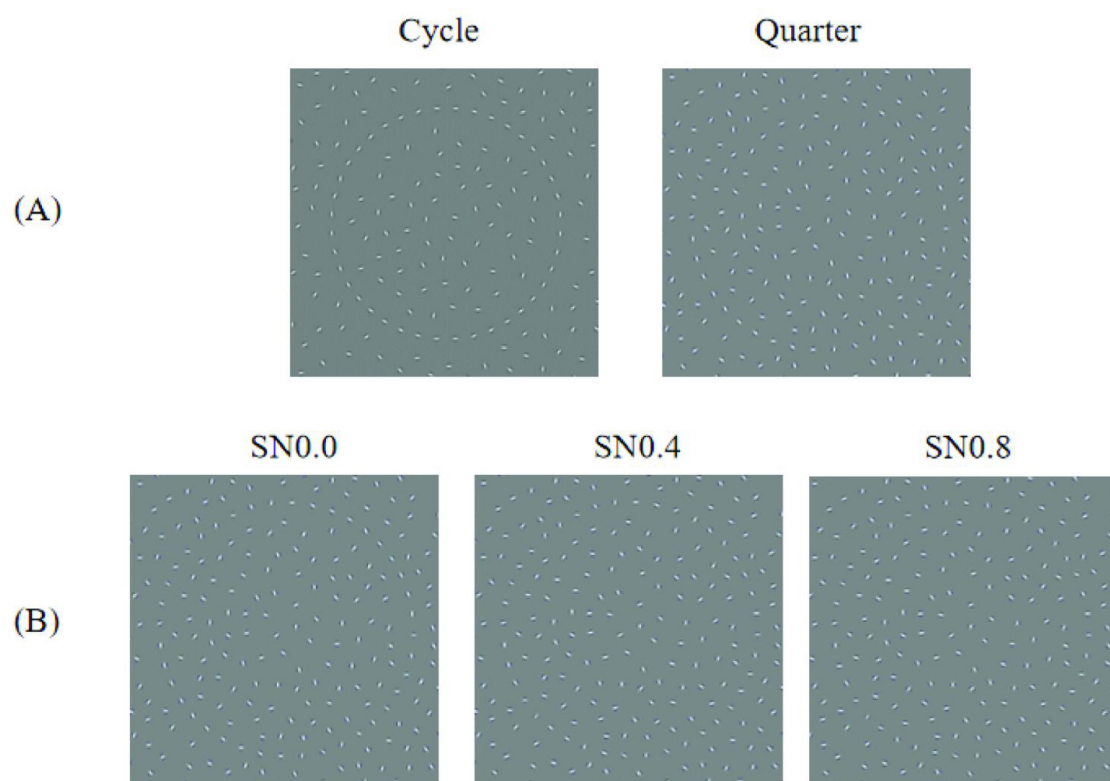


FIGURE 1
Base stimulus used in the experiment. (A) Examples of two types of stimuli. (B) Examples of three different noise levels.

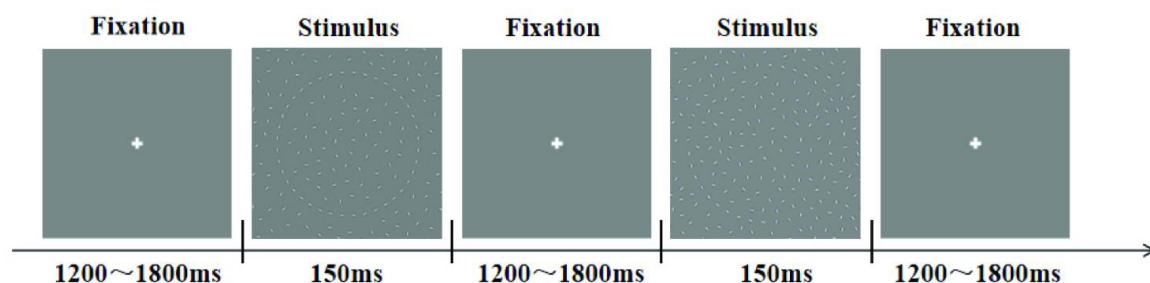


FIGURE 2
Trial structure of the experiment.

The results suggested different processing patterns for different noise conditions and for left hemisphere and right hemisphere. Therefore, we analyzed these differences in detail as follows.

3.2.1 P/N100 component

Apparently, for this component, there was a clear inversion across the electrode sites. Therefore, ANOVA tests were conducted separately for occipital and parietal electrode using the factors hemisphere, stimulus type and noise level. For the occipital electrode, the mean amplitude was submitted to a 2 hemisphere (left, right) $\times$ 2 stimuli type (cycle, quarter) $\times$ 3 noise level (SN0.0, SN0.4, SN0.8) ANOVA, no main effect or interaction were observed, see Figure 4A. Whereas, for the parietal electrode, a main effect of hemisphere was found [$F(1, 14) = 8.056$,

$p = 0.013$, $\eta_p^2 = 0.365$], with a more negative going response to left hemisphere than right hemisphere.

3.2.2 P/N130 component

Similar with P/N100 component, ANOVA tests in P/N130 component were conducted separately for occipital and parietal electrodes. The 2 hemispheres (left, right) $\times$ 2 stimuli type (cycle, quarter) $\times$ 3 noise level (SN0.0, SN0.4, SN0.8) ANOVA for occipital electrode revealed a main effect of noise level [$F(2, 28) = 6.896$, $p = 0.005$, $\eta_p^2 = 0.33$], with N130 being less negative for noise increasing, see Figure 4B. Further *post hoc* analysis revealed a significant difference between SN0.0 and SN0.4 ($p < 0.05$), a marginally difference between SN0.0 and SN0.8 ($p = 0.069$), while the difference between SN0.4 and SN0.8 was not significant

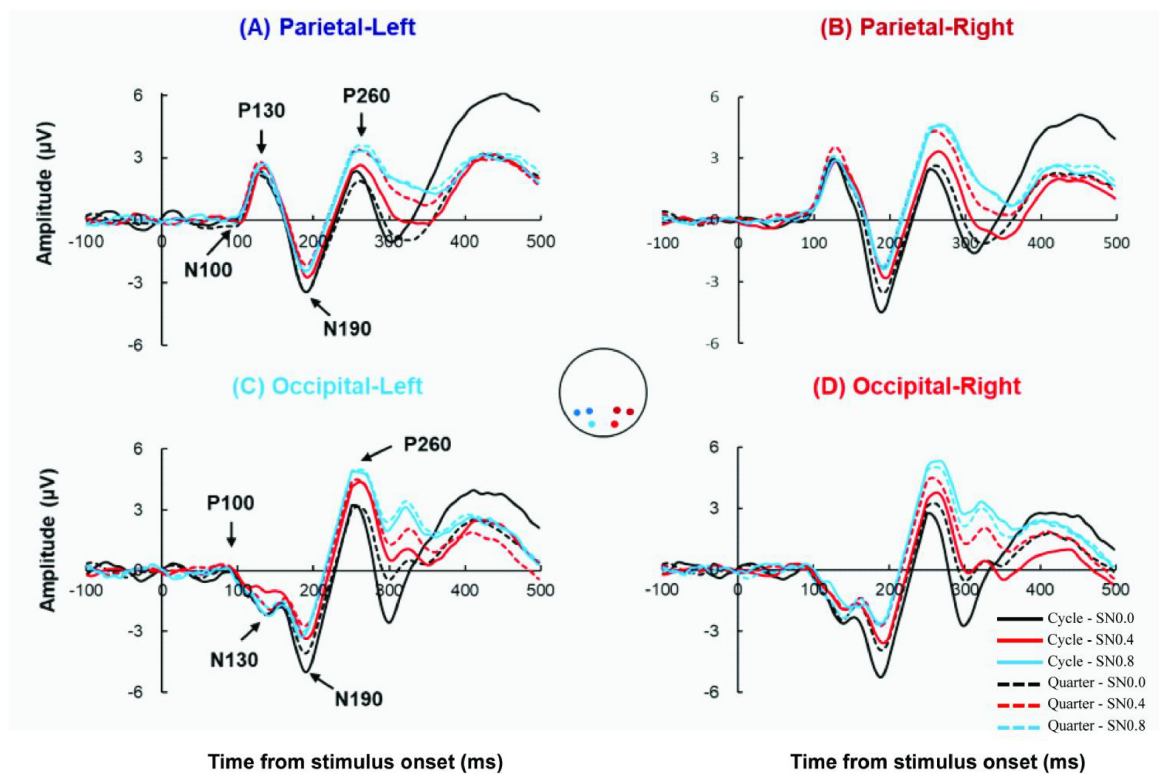


FIGURE 3 Grand-average ERP wave from 4 ROIs. (A) The Grand-average ERP waves from left parietal with 2 stimulus types (cycle: solid line; quarter: dot line) in SN0.0, SN0.4, SN0.8. Equivalent data from right parietal (B), left occipital (C) and right occipital (D).

($p > 0.05$). The 2 hemispheres (left, right) $\times$ 2 stimuli type (cycle, quarter) $\times$ 3 noise level (SN0.0, SN0.4, SN0.8) ANOVA for parietal electrode revealed that there were no main effect or interaction were observed (all $p > 0.05$).

3.2.3 N190 component

For the average amplitude of N190 component, 2 electrodes (occipital, parietal) $\times$ 2 hemisphere (left, right) $\times$ 2 stimuli type (cycle, quarter) $\times$ 3 noise level (SN0.0, SN0.4, SN0.8) ANOVA revealed a significant main effect of stimuli type [$F(1, 14) = 9.778$, $p = 0.007$, $\eta_p^2 = 0.411$], noise level [$F(2, 28) = 32.26$, $p < 0.001$, $\eta_p^2 = 0.697$]. The following two-way and three-way interactions were significant: electrode $\times$ stimuli type [$F(1, 14) = 5.957$, $p = 0.029$, $\eta_p^2 = 0.299$], hemisphere $\times$ noise level [$F(2, 28) = 4.439$, $p = 0.038$, $\eta_p^2 = 0.241$], electrode $\times$ stimuli type $\times$ noise level [$F(2, 28) = 3.936$, $p = 0.037$, $\eta_p^2 = 0.219$], hemisphere $\times$ stimuli type $\times$ noise level [$F(2, 28) = 4.962$, $p = 0.016$, $\eta_p^2 = 0.262$]. The *post hoc* analysis for stimulus type on each noise level and ROI showed that the amplitude of cycle stimulus in SN0.0 and SN0.4 was significantly more negative than that for quarter stimulus at left and right occipital (all $p < 0.05$). Whereas, this difference in parietal was only found in right hemisphere at SN0.0 ($p = 0.032$) and left parietal at SN0.4 ($p = 0.030$). However, no significant difference was found in SN0.8, see Figure 5. In addition, the *post hoc* analysis for noise level on both stimulus type revealed a significant difference between SN0.0 and SN0.4 ($p < 0.001$), between SN0.0 and SN0.8 ($p < 0.01$), while the difference between

TABLE 1 Behavior results of the proportion correct.

Conditions	SN0.0*	SN0.4	SN0.8
Cycle	0.89 $\pm$ 0.03	0.42 $\pm$ 0.06	0.01 $\pm$ 0.00
Quarter	0.78 $\pm$ 0.04	0.28 $\pm$ 0.06	0.08 $\pm$ 0.04

*Denotes statistical significance ($p < 0.05$).

SN0.4 and SN0.8 was not significant ($p > 0.05$) in all four ROIs, see Figure 4C.

3.2.4 P260 component

For the average amplitude of P260 component, the 2 electrodes (occipital, parietal) $\times$ 2 hemisphere (left, right) $\times$ 2 stimuli type (cycle, quarter) $\times$ 3 noise level (SN0.0, SN0.4, SN0.8) ANOVA revealed a significant main effect of stimuli type [$F(1, 14) = 6.569$, $p = 0.023$, $\eta_p^2 = 0.319$], noise level [$F(2, 28) = 32.679$, $p < 0.001$, $\eta_p^2 = 0.70$]. In addition, three-way interactions of electrode $\times$ stimuli type $\times$ noise level [$F(2, 28) = 6.417$, $p = 0.01$, $\eta_p^2 = 0.314$], and hemisphere $\times$ stimuli type $\times$ noise level [$F(2, 28) = 4.218$, $p = 0.028$, $\eta_p^2 = 0.232$] were also significant. The *post hoc* analysis for stimulus type on noise level and ROI showed that the amplitude of cycle stimulus in SN0.4 was significantly less positive than that for quarter stimulus at four ROIs (all $p < 0.05$). In addition, further *post hoc* analysis for noise level on both cycle and quarter stimulus revealed a significant difference between SN0.0 and SN0.4 ($p < 0.05$), between SN0.0 and SN0.8 ($p < 0.05$), and the

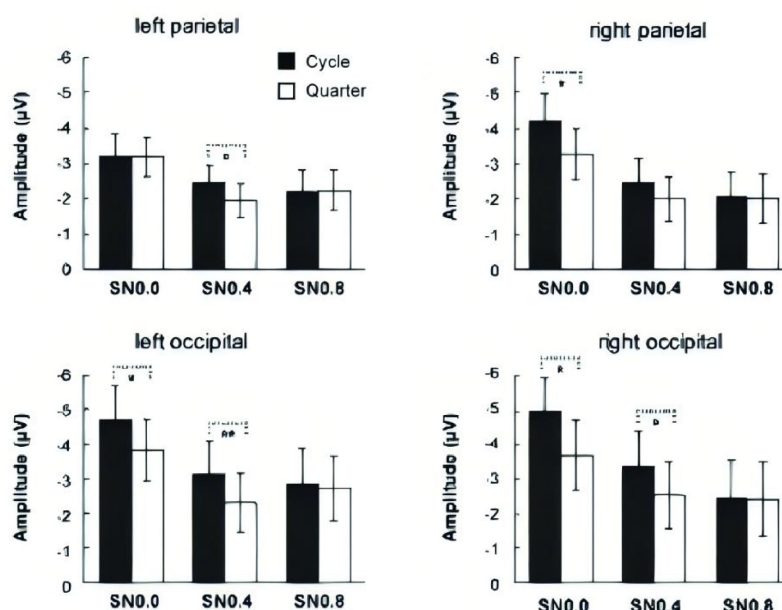
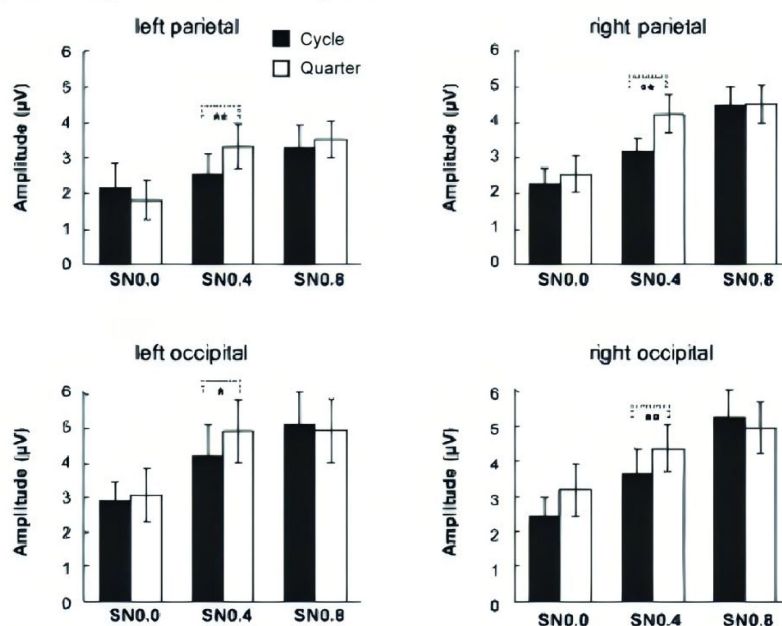
(A) Mean amplitudes in N190 component**(B) Mean amplitudes in P260 component**

FIGURE 4

Mean amplitudes of three noise level across four components. (A) Mean amplitudes of P100 in occipital. (B) Mean amplitudes of N130 in occipital. (C) Mean amplitudes of N190 ms over four ROIs. (D) Mean amplitude of P260 over four ROIs. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

difference between SN0.4 and SN0.8 was also significant ($p < 0.01$) in all four ROIs, see Figure 4D.

4 Discussion

The present study aimed to investigate the neural and cognitive mechanisms underlying the perception of reflection symmetry, with a particular focus on the role of hemispheric

specialization and the effects of noise on symmetry detection. By combining behavioral measures with high-density EEG recordings, we explored how different types of symmetrical patterns (full circle vs. quarter circle) and varying noise levels influence the efficiency of symmetry perception. Our findings provide new insights into the temporal dynamics and neural correlates of symmetry processing, as well as the interplay between bottom-up and top-down mechanisms in visual perception.

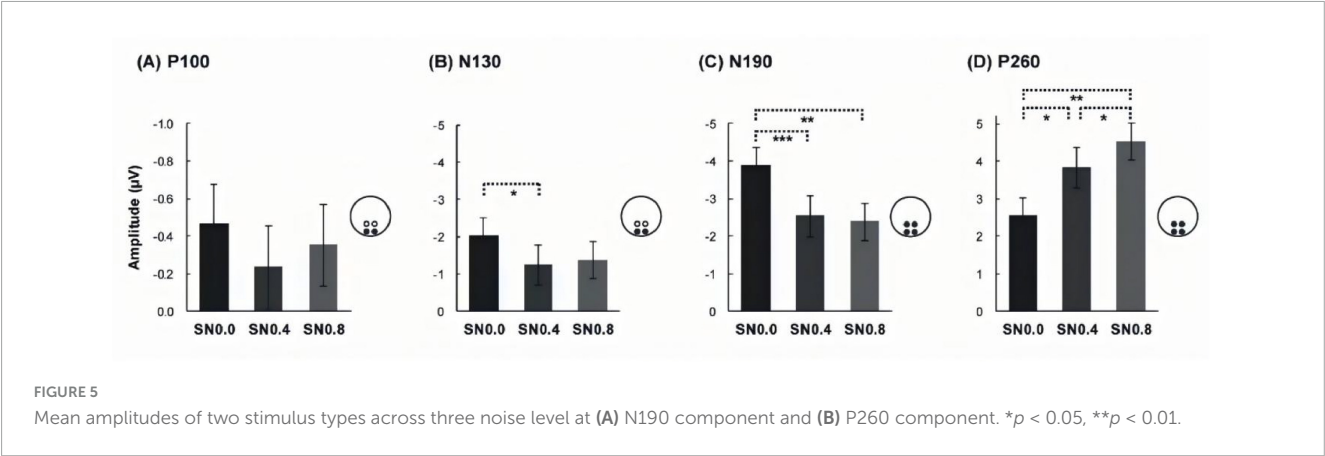


TABLE 2 Mean amplitudes of ERP components across noise levels.

Component	Electrode	Hemisphere	SN0.0	SN0.4	SN0.8
P/N100	Occipital	Left	-2.5 ± 0.3	-2.4 ± 0.3	-2.3 ± 0.3
		Right	-2.4 ± 0.3	-2.3 ± 0.3	-2.2 ± 0.3
	Parietal	Left	-3.1 ± 0.4	-3.0 ± 0.4	-2.9 ± 0.4
		Right	-2.8 ± 0.4	-2.7 ± 0.4	-2.6 ± 0.4
N130	Occipital	Left	-4.2 ± 0.5	-3.8 ± 0.5	-3.5 ± 0.5
		Right	-4.1 ± 0.5	-3.7 ± 0.5	-3.4 ± 0.5
N190	Occipital	Left	-5.6 ± 0.6	-4.8 ± 0.6	-4.0 ± 0.6
		Right	-5.5 ± 0.6	-4.7 ± 0.6	-3.9 ± 0.6
P260	Parietal	Left	3.2 ± 0.4	2.8 ± 0.4	2.4 ± 0.4
		Right	3.0 ± 0.4	2.6 ± 0.4	2.2 ± 0.4

The behavioral results revealed that participants' ability to identify symmetrical patterns decreased significantly as noise levels increased, consistent with previous studies demonstrating that noise disrupts contour integration and perceptual grouping (Field, 1992; Hess and Field, 1999; Baldwin et al., 2017). Interestingly, while there was no overall difference in accuracy between full circle and quarter circle stimuli, a significant interaction between stimulus type and noise level indicated that the contour effect was modulated by noise. Specifically, in the absence of noise (SN0.0), participants performed significantly better with full circle stimuli compared to quarter circle stimuli. This suggests that the completeness of the symmetrical contour plays a critical role in facilitating perceptual grouping under optimal viewing conditions. However, as noise levels increased, this advantage diminished, highlighting the vulnerability of contour integration to external noise. As shown in Table 1, analysis of the proportion correct using a 2 (stimulus type) $\times$ 3 (noise level) repeated measures ANOVA revealed a significant main effect of noise level [$F(2, 28) = 190.008$, $p < 0.001$, $\eta^2 = 0.931$], showing that the identification ability of participants decreased with noise enhancement. Whereas, no significant difference was found in stimulus type [$F(1, 14) = 2.663$, $p = 0.125$, $\eta^2 = 0.160$]. The interaction between stimulus type and noise level was significant [$F(2, 28) = 6.705$, $p = 0.012$, $\eta^2 = 0.324$], indicating that the contour effect was different under varying noise levels. The pairwise comparisons showed that for the

SN0.0 condition, the responses to cycle stimuli were significantly higher than the responses to quarter stimuli ($p < 0.05$).

The ERP results provided a detailed temporal profile of symmetry processing, revealing distinct neural components associated with different stages of visual perception (see Table 2). The P/N100 complex, peaking around 100 ms after stimulus onset, is thought to reflect early sensory processing in the primary visual cortex (V1) and extrastriate areas (V2/V4) (Francesco et al., 2002). In our study, the P/N100 component showed no significant differences across stimulus types or noise levels at occipital electrodes, suggesting that early sensory encoding of symmetrical patterns is relatively robust to noise. However, at parietal electrodes, a significant hemisphere effect was observed, with more negative amplitudes in the left hemisphere compared to the right. This asymmetry may reflect differential engagement of the two hemispheres in early visual processing, consistent with previous findings of hemispheric specialization in contour integration (Kovács et al., 1999).

The N130 component, peaking around 130 ms, is associated with the initial stages of contour integration and perceptual grouping (Murray et al., 2004). Our results showed that the N130 amplitude at occipital electrodes became less negative as noise levels increased, indicating that noise disrupts the early stages of contour integration. This finding aligns with the behavioral results, further supporting the idea that noise impairs the ability to group local elements into coherent global shapes.

The N190 component, peaking around 190 ms, is thought to reflect higher-order processing in the lateral occipital complex (LOC) and other extrastriate areas involved in object recognition (Kourtzi and Kanwisher, 2001). In our study, the N190 amplitude was significantly more negative for full circle stimuli compared to quarter circle stimuli, particularly at occipital electrodes and under low to moderate noise levels (SN0.0 and SN0.4). This suggests that the completeness of the symmetrical contour enhances object recognition processes, but this advantage is attenuated under high noise conditions. Additionally, the significant interactions between hemisphere, stimulus type, and noise level indicate that the two hemispheres may process symmetrical patterns differently, with the right hemisphere showing greater sensitivity to noise.

The P260 component, peaking around 260 ms, is associated with late-stage perceptual decision-making and response selection (Luck and Hillyard, 2010). Our results revealed that the P260 amplitude was less positive for full circle stimuli compared to quarter circle stimuli under moderate noise levels (SN0.4), particularly at parietal electrodes. This suggests that the completeness of the symmetrical contour facilitates decision-making processes, but this effect is modulated by noise. Furthermore, the significant differences in P260 amplitude across all noise levels indicate that noise affects not only early sensory processing but also later stages of perceptual decision-making.

4.1 Hemispheric specialization

One of the key questions addressed in this study was whether there is hemispheric specialization for the detection of reflection symmetry. Our ERP results provide partial support for this idea, with significant hemisphere effects observed at multiple stages of processing. For example, the P/N100 component showed more negative amplitudes in the left hemisphere at parietal electrodes, while the N190 and P260 components revealed significant interactions between hemisphere, stimulus type, and noise level. These findings suggest that the two hemispheres may play distinct roles in symmetry perception, with the left hemisphere potentially specializing in the processing of local features and the right hemisphere in the integration of global shapes (Fink et al., 1997; Sasaki et al., 2005). However, further research is needed to clarify the specific contributions of each hemisphere to symmetry perception.

4.2 Implications for the callosal hypothesis

The callosal hypothesis posits that the anatomical symmetry of the human visual system, particularly the role of the corpus callosum in interhemispheric communication, underlies the efficiency of vertical symmetry detection (Wright, 1972). While our findings do not directly contradict this hypothesis, they suggest that symmetry perception involves more complex interactions between the two hemispheres than previously thought. For example, the significant hemisphere effects observed in our study indicate that symmetry processing is not solely

determined by the anatomical midline but is also influenced by functional specialization and task demands. This aligns with recent reviews suggesting that the strong version of the callosal hypothesis is unlikely to fully account for the observed phenomena in symmetry perception (Bertamini et al., 2018; Treder, 2010).

5 Conclusion

In conclusion, our study provides new insights into the neural and cognitive mechanisms underlying symmetry perception. The behavioral and ERP results demonstrate that noise disrupts contour integration and perceptual grouping, with significant effects observed at multiple stages of processing. Additionally, the findings suggest that the two hemispheres may play distinct roles in symmetry perception, with the left hemisphere potentially specializing in local feature processing and the right hemisphere in global shape integration. These results challenge the strong version of the callosal hypothesis and highlight the need for a more nuanced understanding of the factors influencing symmetry perception. Future research should continue to explore the interplay between neural, cognitive, and ecological factors in shaping our perception of symmetry.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Okayama University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MW: Funding acquisition, Writing – original draft. JY: Funding acquisition, Writing – review and editing. YY: Writing – review and editing, Software. QW: Writing – review and editing, Methodology. FW: Methodology, Funding acquisition, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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fMRI-based explanations for how meditation could modulate pain processing

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Meditation is a widely recognized umbrella term encompassing a diverse range of techniques with shared foundational characteristics, celebrated for their potential to alleviate mental and physical challenges. While subjective reports and behavioral studies have long highlighted meditation's benefits, recent neuroscientific research has sought to provide tangible physiological evidence of its efficacy as a non-invasive intervention for managing physical pain. This review examines the neurophysiological mechanisms by which meditation influences brain activity in response to both acute and chronic pain experiences. Drawing on findings from functional magnetic resonance imaging (fMRI) studies, general models are categorized to explain how meditation alters cortical responses in both naïve and expert practitioners when exposed to pain stimuli. First, we discuss three major components of pain processing in the brain and analyze how meditation affects each stage. Next, we identify key brain regions consistently implicated in pain modulation through meditation, elucidating their roles in pain perception and regulation. Finally, we propose a framework for differentiating meditation techniques based on their distinct effects on pain experiences. These insights have significant implications for understanding the therapeutic potential of various meditation techniques for pain management, particularly in chronic conditions.

KEYWORDS

meditation, pain management, acute noxious pain, chronic pain, fMRI, open monitoring, focused attention

1 Introduction

Pain is a fundamental survival mechanism that protects organisms from threats by signaling disruptions in homeostatic balance. It is described as an unpleasant experience with sensory and emotional dimensions in response to actual or potential tissue damage (Merskey and Bogduk, 1994). The initiation, maintenance, perception and amplification of pain can be studied through various mechanisms, including psychosocial, movement system, and biological factors. While these mechanisms often overlap and occur simultaneously, each has distinct characteristics that contribute to the pain experience (Phillips and Clauw, 2011).

Biological factors influencing pain can be categorized into three primary mechanisms. First, nociceptive (peripheral) mechanisms arise from disruptions detected by the peripheral nervous system due to injury, or mechanical irritation. Some studies classify inflammatory pain as a subset of peripheral mechanisms (Chimenti et al., 2018), while others consider it as a distinct category (Xu and Yaksh, 2011). In this study, we categorize inflammatory mechanisms under nociceptive pain given their peripheral origin. Second, nociplastic pain mechanisms arise from non-nociceptive conditions resulting from an altered processing in the central nervous system (CNS) which can result from inflammation or central sensitization, a process characterized by heightened central excitability (Chimenti et al., 2018). Most chronic pain conditions, such as fibromyalgia and chronic migraine headache disorders, are examples of nociplastic pain

mechanisms (Buldyś et al., 2023). Finally, neuropathic pain mechanisms arise from lesions or diseases affecting the somatosensory system. This can occur such as when a nerve damage leads to pain, as seen in carpal tunnel syndrome, or when pain is a consequence of a metabolic condition such as diabetes (Phillips and Clauw, 2011).

During periods of pain, typically classified based on the biological characteristics of a noxious experience, the CNS triggers various emotional and cognitive responses. When pain becomes prolonged, individuals often engage in cycles of negative rumination and avoidance behaviors, which paradoxically intensify their pain experience (Zeidan et al., 2015). This highlights the importance of developing evidence-based strategies to help individuals regulate their behavioral and emotional responses to pain. Fostering conscious awareness through such strategies may help alleviate the perceived intensity of pain and prevents from the process of chronification.

One way to study pain responses in the CNS is through brain imaging techniques, such as functional magnetic resonance imaging (fMRI), which provide a spatial representation of cortical areas involved in sensory, cognitive, and psychological processing. fMRI measures changes in blood flow, offering high spatial resolution of functional connectivity and revealing activations and interactions among multiple brain regions during resting states or task-based conditions (Zeidan et al., 2015; Orme-Johnson et al., 1995; Gard et al., 2012).

A significant contribution of fMRI-based research is its role in refining the conceptualization of the “pain matrix,” a framework that challenges the traditional view of a single, centralized pain hub. Instead, it highlights a dynamic network of cortical and subcortical structures involved in pain processing (Garcia-Larrea and Peyron, 2013). Before exploring the connectivity patterns within this network, it is crucial for researchers to identify specific cortical and subcortical regions that have the potential to modulate pain. This understanding is particularly valuable for developing non-pharmaceutical interventions as alternative pain management strategies.

As for the frequency of pain across all different pain mechanisms, any type of pain that lasts less than 3 months is acute pain, which consistently activates certain cortical area during noxious stimuli (Jurisic et al., 2018). When pain persists for more than 3 months, it is classified as chronic pain, which is often associated with significant physiological and psychological complications and could involve with nociplastic mechanisms (Grichnik and Ferrante, 1991).

In order to alleviate pain, people can have different pharmaceutical and non-pharmaceutical alternatives, from applying a topical analgesic, taking abortive and preventative drugs, or even serotonin noradrenaline reuptake inhibitors in terms of chronic pain conditions (Chimenti et al., 2018). Recent studies indicating that prolonged use of abortive medicine to alleviate pain could itself cause the spark situations such as medication-overuse headaches (MOH) (Schwedt et al., 2022) has spurred interest in exploring non-pharmaceutical and complimentary interventions, such as meditation, alongside traditional pharmacological treatments to manage pain effectively.

Meditation encompasses a diverse range of mental training techniques that cultivate attention and heightened self-awareness to

regulate both the mind and body (Hilton et al., 2017; Pozek et al., 2016). Currently, over 309 distinct meditation techniques exist, all sharing the common goals of enhancing self-regulation and expanding consciousness (Sedlmeier et al., 2012). Historically, meditation has demonstrated significant benefits for mental health and psychological well-being (Hilton et al., 2017; McGee, 2008). However, while its application in pain management has shown promising outcomes, neuroscientific evidence in this area is still evolving.

From a psychological perspective, meditation techniques engage multiple cognitive faculties, including attention, emotion regulation, reasoning, visualization, memory, and interoception (i.e., bodily awareness) (Shear, 2006) which could help with a modulated pain perception experience. The nature of these techniques varies, ranging from active to passive, effortless to disciplined exercises. Moreover, while attentional shifting is a fundamental aspect of meditation in healthy individuals, different techniques guide attention toward various focal points, such as thoughts, imagery, concepts, internal energy, bodily sensations, love, or spiritual entities (Sedlmeier et al., 2012). In pain conditions, individuals can learn to sustain their attention on or away from the painful stimulus based on the level of expertise and type of meditation.

Neuroscientific research commonly categorizes meditation techniques into two primary types (Sperduti et al., 2012; Lutz et al., 2008; Nash et al., 2013), particularly when studying its role in pain modulation (Tang et al., 2015): (1) Focused Attention (FA), which involves sustaining attention on a specific object while enhancing the ability to detect and disengage from distractions, and (2) Open Monitoring (OM), which fosters non-judgmental awareness of arising experiences within the mental continuum without fixating on a particular object (Deolindo et al., 2020). This dichotomy is well-supported in psychology and neuroscience (Shear, 2006; Goleman, 1988; Kristeller and Rikhye, 2008; Naranjo and Ornstein, 1971; Feuerstein, 2001; Walsh and Shapiro, 2006).

Despite their distinctions, FA and OM techniques are interrelated and share common neural mechanisms, involving brain regions such as the insula and precuneus (Wang et al., 2011). Consequently, some neuroscientific models conceptualize meditation as a spectrum, with concentrative meditation (emphasizing FA techniques) at one end and mindfulness meditation (predominantly OM-oriented) at the other (Cahn and Polich, 2006). Nonetheless, given the fundamental role of attention in meditation, the FA-OM dichotomy remains a widely accepted framework for classifying meditation techniques.

A defining characteristic of FA techniques is the use of an anchor, such as a mental image, breathing rhythm, or mantra, to maintain focus while inhibiting the processing of extraneous mental or environmental stimuli. These techniques are foundational in many traditional and spiritual practices, including Transcendental Meditation (TM) (Sedlmeier et al., 2012). In contrast, OM techniques cultivate deep awareness of thoughts, emotions, and bodily sensations without triggering reactive responses in the form of secondary thoughts or emotions. Notable examples of OM techniques include Vipassana, i.e., a Theravāda Buddhist meditation practice, and Mindfulness-Based Stress Reduction (MBSR), developed by Kabat-Zinn (1994), both of which aim to enhance individuals' ability to monitor and regulate their physical and emotional states particularly during pain.

The application of meditation techniques as a cost-effective, accessible, and side-effect-free alternative for pain management is

Abbreviations: ACC, anterior cingulate cortex; CNS, central nervous system; DLPFC, dorsolateral prefrontal cortex; FA, focused attention; fMRI, functional magnetic resonance imaging; NPS, neurological pain signature; OFC, orbitofrontal cortex; OM, open monitoring; RCT, randomized controlled trial.

promising (Pozek et al., 2016; la Cour and Petersen, 2015). Early research on meditation and pain primarily relied on behavioral and clinical evidence, including subjective self-reports (Gard et al., 2012), which were susceptible to response biases. Additionally, randomized controlled trials (RCTs) have also traditionally depended on participants' self-reported pain experiences during or after meditation practices (la Cour and Petersen, 2015; Hoge et al., 2013; Lin et al., 2022).

More recently, neuroscientific exploration using brain imaging has provided an understanding of how meditation influences cortical processing, further validating its efficacy in pain management. Brain imaging studies have identified distinct patterns of cortical activity and connectivity, which illustrate how meditation alters neural function in healthy individuals (Tang et al., 2015).

A meta-analysis of over 10 studies highlighted three key brain regions involved in attentional disengagement from irrelevant stimuli: the caudate, entorhinal cortex, and medial prefrontal cortex (Sperduti et al., 2012). However, concerns remain regarding the generalizability of these findings, as the studies included in the meta-analysis primarily examined traditional meditation styles mostly across expert individuals. More broadly, evidence suggests that OM techniques are associated with the activation of regions such as the anterior cingulate cortex (ACC), prefrontal cortex (PFC), insula, and striatum, while they are also linked to the deactivation of the posterior cingulate cortex (PCC) and amygdala (Tang et al., 2015).

Despite advancements in understanding the cortical mechanisms underlying OM techniques, much remains to be explored regarding how meditation practices across OM and FA categories differentially affect brain regions involved in various pain mechanisms—particularly in distinguishing between responses to induced pain in healthy subjects and chronic pain conditions. The primary objective is to identify the brain regions consistently involved across all types of pains conditions, whether acute or chronic, during meditation. Moreover, we aim to determine which meditation category, OM or FA, is more effective in managing chronic pain, given its greater complexity and impact on sufferers.

In this perspective article, we selected large-scale, gold standard studies that emphasize fMRI evidence of cortical activity associated with meditation during pain-induced and chronic pain conditions (Table 1). These studies serve as the foundation for our proposed perspective, which differentiates between OM and FA techniques in their application to various pain conditions.

We begin by discussing the “three-tiered hierarchical model” of pain processing, which provides a broad framework for understanding meditation's influence on pain-related neural networks. We then highlight key brain regions from the “neurological pain signature” (NPS) model which prior research has consistently identified as being modulated by meditation.

2 Three-tiered hierarchical perspective of pain processing in meditation

The three-tiered hierarchical model is proposed to organize pain-related neural networks into three categories based on the shared levels of processing that may involve specific brain regions: sensory, affective, and cognitive perceptive networks (Garcia-Larrea and

Peyron, 2013). This perspective over pain processing separates the affective and cognitive dimensions due to their differing levels of consciousness and emotional influence; this is unlike some previous models which keep a dualistic approach by merging affective and cognitive components under one category (Garland et al., 2017).

2.1 Sensory-discriminative (nociception) network

Sensory network is responsible for processing signals transmitted from the spinal cord to the posterior thalamus before they reach conscious awareness. It plays a fundamental role in encoding the sensory aspects of pain, including its intensity, location, and duration. A key focus in pain research is determining whether specific techniques, such as meditation, can modulate this foundational level of pain perception. Investigating the extent to which meditation influences this network is essential for understanding its potential as an intervention for pain management. The primary brain regions involved in the sensory processing network of pain include the thalamus, which serves as a central relay for nociceptive signals (Habit et al., 2023), the posterior insula, which contributes to interoceptive awareness of pain (Bastuji et al., 2018), the cerebellum, which has been increasingly recognized for its role in pain sensation and modulation (Li et al., 2024), and both the primary and secondary somatosensory cortices, which encode detailed sensory characteristics of pain (Huang et al., 2020).

In fact, research on effects of meditation on this network has yielded mixed results. While some studies have found no changes in sensory pain processing due to OM practice, (Orme-Johnson et al., 2006; Mills and Farrow, 1981), others, such as Brown and Jones (2010), reported a significant attenuated activation in the secondary somatosensory cortex (S2), posterior insula and the thalamus. Similarly, Grant et al. (2010) demonstrated that Zen meditation can alter the activation of brain regions involved in the sensory encoding of a noxious pain stimulus in regions such as the insula, S2, and the thalamus. In alignment with these findings, Kober et al. (2019) observed reduced activity in sensorimotor regions such as postcentral gyri, pre-supplementary motor area (pre-SMA), posterior insula, the thalamus, and cerebellum, following the states of mindfulness and acceptance, a form of OM meditation. In relation to this network, meditation appears to modulate the perceived sensory properties of pain, yet more information is required to realize the degree of this impact. Despite having found a wider alteration in the sensory network through OM techniques (Brown and Jones, 2010; Kober et al., 2019), the contribution across all fMRI based studies on FA was the modulation of this system during pain (Orme-Johnson et al., 2006; Kober et al., 2019; Kakigi et al., 2005).

2.2 Affective-reappraisive (emotional) network

This category encompasses emotional arousal and escape responses to pain and is found to be altered across both FA and OM techniques in painful conditions. While there is major overlap in cortical regions between this network and the cognitive network involved in pain processing, distinguishing between salience

TABLE 1 Description of previous literature on fMRI-based studies of pain modulation via meditation techniques.

Articles	Key highlights	Significant brain regions	Pain stimuli	Type of meditation	Participants	fMRI Indications	Focused attention or open monitoring?	Default mode network (DMN) or Salience network (SN)
Aytur et al. (2021)	improved functional connectivity across networks (DMN, SN, and FPN) correlate with behavioral outcomes, such as reduced depression, lower pain interference, and increased social participation.	DMN: mPFC, PCC, AG. SN: AI, ACC. FPN: dlPFC, IPL	Chronic musculoskeletal pain	4-week of ACT(two sessions of 90 min per week)	9 adult women with chronic musculoskeletal pain	DMN: Decreased connectivity in mPFC and PCC (reflecting self-focused rumination and present-focused attention). SN: changes in AI, and ACC (suggesting reduced emotional reactivity and improved emotional regulation). Reduced coupling between DMN and SN indicate overlap between self-referential thinking and emotional processing of pain.	OM	DMN, SN
Berry et al. (2020)	Changes in both SN and DMN are associated with self-referential processing, salience detection and emotion regulation.	vPCC, TPJ, and dlPFC	Chronic low back pain	8-h self-compassion training	22 participants with low back pain.	Changes in vPCC activation (reduced emotional distress associated with pain), and TPJ (a shift in perceiving pain in relation to the self). Increased activation of dlPFC (better regulation of emotional response to pain).	OM	DMN, SN
Riegner et al. (2023)	The decoupling of the thalamus from the DMN interrupts connection between sensory pain signals and the self-referential processing that intensifies pain perception.	Thalamus, ACC, Insula, S1	Induced thermal pain	Mindfulness Meditation	40 healthy participants; 20 in mindfulness group and 20 in controlled audiobook listening group.	Improved functional connectivity across networks (DMN, and SN) correlate with behavioral outcomes, such as reduced depression, lower pain interference, and increased social participation.	OM	DMN

(Continued)

TABLE 1 (Continued)

Articles	Key highlights	Significant brain regions	Pain stimuli	Type of meditation	Participants	fMRI Indications	Focused attention or open monitoring?	Default mode network (DMN) or Salience network (SN)
Kober et al. (2019)	Altered activity of DMN promotes a more detached, less self-focused processing of pain and reduced activation of SN helps decreased emotional salience, and intensity of pain via neutral and nonjudgmental experience of sensation.	ACC, PFC, insula, S1, dlPFC	Induced thermal pain	Mindfulness Meditation	18 healthy naive meditators	Decreased activity in ACC (reduction in emotional distress), altered activation in insula (less emotional response to pain), activation of dlPFC (help with down-regulation or negative emotions.)	OM	DMN, SN
Hunt et al. (2023)	Focusing Mesocorticolimbic System Functional Connectivity. Greater vmPFC-rNAcc connectivity as a result of MSBR showed greater reductions in headache frequency. MSBR could improve pain catastrophizing, but headache severity could still remain the same.	rNAcc, vmPFC	Migraine headache pain	12-week MSBR training	98 participants with migraine headaches (50 receiving MSBR and 48 receiving stress management for headaches)	MBSR was associated with significant seed-to-voxel functional connectivity between rNAcc and vmPFC.	OM	SN
Fedeli et al. (2024)	mindfulness caused improved SN-insula connectivity was correlated with reductions in depression scores as a function of mindfulness.	Left PI, S1, ACC	Chronic Medication Overuse Headache (MOH)	Mindfulness Meditation (added to treatment as usual)	34 participants with chronic medication overuse headaches (17 mindfulness plus treatment and 17 treatment only)	Increased connectivity between SN and the left posterior insula and sensorymotor cortex (causing pain modulation and body awareness). Increased cortical thickness in ACC and the insular cortex (emotion regulation, and pain perception).	OM	DMN, SN

(Continued)

TABLE 1 (Continued)

Articles	Key highlights	Significant brain regions	Pain stimuli	Type of meditation	Participants	fMRI Indications	Focused attention or open monitoring?	Default mode network (DMN) or Salience network (SN)
Chen et al. (2023)	MBSR has the potential to influence brain structure and activity related to chronic pain and emotional processing.	AG, MFG, PHG, left AI and PI, SFGmed, SPL, postCG	Chronic pain	8-week MBSR	67 participants with chronic pain received MBSR ($n = 40$); and treatment as usual ($n = 27$)	MBSR was associated with increase in GMV, decreased amplitude of low-frequency fluctuations, and increased regional homogeneity.	OM	NA
Hatchard et al. (2022)	The control group of this study showed a decreased GMV of PHG, precuneus, MFG and right cuneus; probably due to the chronic pain experience.	AG, MFG, rPHG, right cuneus	Chronic neuropathic pain	8-week MBSR	23 participants with chronic pain: 10 MBSR trainees and 10 waitlisted control	MBSR caused increased GMV in angular gyrus, middle frontal gyrus, right parahippocampal gyrus.	OM	NA
Smith et al. (2021)	The reduced functional connectivity may be related to both the descending motor and pain pathways.	S1, precuneus, dlPFC	Chronic neuropathic pain	8-week MBSR	23 participants with chronic pain: 10 MBSR trainees and 10 waitlisted control	Reduced BOLD activity in somatosensory cortex, precuneus, and dorsolateral prefrontal cortex (correlated with decreased pain interference and improved emotional reactivity)	OM	DMN
Su et al. (2016)	Empathy, emotional awareness and their significant effect on attention switching	AIC, daMCC	Chronic pain	6-week MBSR: body scan, sitting meditation, Hatha yoga, walking meditation	34 participants: (18 pain afflicted and 16 controls with pain less than 1 score in McGill Pain Questionnaire)	Significant interaction between AIC and daMCC activity. A significant negative correlation between the results of "Short Form McGill Pain Questionnaire" and AIC-daMCC connection strength. Pain decreased significantly in pain-afflicted group but not in the control group after training, meditation may cause a significant change of attention to pain.	OM	SN

(Continued)

TABLE 1 (Continued)

Articles	Key highlights	Significant brain regions	Pain stimuli	Type of meditation	Participants	fMRI Indications	Focused attention or open monitoring?	Default mode network (DMN) or Salience network (SN)
Orme-Johnson et al. (2006)	ACC showed the least significant change when associated with meditation.	Thalamus, ACC, PFC, central coordinates (medialateral, anterior-posterior, and dorsoventral cortex)	Induced thermal pain	4-day Transcendental meditation (20 min daily)	24 participants (12 healthy controls and 12 long-term meditators with an average of 31 years of practice)	Long-term meditators show less cerebral blood flow in ACC, PFC, and thalamus in response to the painful stimulus. The changes brought by meditation is usually related to motivational-affective level than the sensory level.	FA	DMN, SN
Kakigi et al. (2005)	Professional practice of meditation may significantly modulate sensory processing of pain	Thalamus, S2-insula, ACC	Induced thermal pain	Yoga (abdominal breathing pattern)	One yoga master (38 years of experience)	Modulated activity of thalamus, SII-insula and cingulate cortex. The meditator claimed no sense of pain during meditation. Increased signal activities in frontal lobe, parietal lobe, midbrain increase during meditation	FA	SN
Grant et al. (2010)	The effect of meditation training levels on neural activations of pain	dIPFC, amygdala, MFG, hippocampus, mPFC/OFC, dACC, thalamus, insula	Induced thermal pain	Zen Meditation (Zazen)	13 professional meditators and 9 healthy controls	A negative correlation between pain-related activation and meditation experience. During the induced pain, there was a higher activation in dACC, thalamus, and insula in meditation group. Meditators showed a lower baseline pain sensitivity, no typical attention-related pain increases, and decreased sensory and affective components during mindful attention.	FA	SN

(Continued)

TABLE 1 (Continued)

Articles	Key highlights	Significant brain regions	Pain stimuli	Type of meditation	Participants	fMRI Indications	Focused attention or open monitoring?	Default mode network (DMN) or Salience network (SN)
Zeidan et al. (2015)	A “gold standard” study comparing the analgesic mechanisms of mindfulness meditation with placebo and sham mindfulness	S2, ACC, putamen, dlPFC, hippocampus, OFC, ACC, IFG, MFG	Induced thermal pain	Mindfulness meditation (breathing technique, full flow of breath)	75 healthy naive meditators	Reductions in DLPFC, mPFC, PCC. Greater activation in bilateral OFC, subgenual ACC, right anterior insula, and putamen. Pain intensity and pain unpleasantness reported to have the highest reduction in mindfulness meditation before and after the intervention when compared to other groups.	OM	SN, DMN
Kober et al. (2019)	No significant neural markers of PFC in response to negative emotion in meditating groups. Evidence showing that meditation acts differently from an emotion regulation strategy. The impact of meditation on Neural Pain Signature	Amygdala, PFC, ACC, thalamus	Induced thermal pain	Mindfulness meditation (breathing technique, full flow of breath)	17 naive meditators	Negative images: the activity in right amygdala reduced in accepting cue, pretty similar between neutral and negative images. Pain: daCC, medial frontal gyrus, sensorimotor regions: precentral and postcentral gyri, pre-SMA, anterior and posterior insula, thalamus, and cerebellum.	OM	SN
Zeidan et al. (2011)	Direct relation between meditation-related activation of some brain regions with pain modulation	ACC, AI, OFC	Induced thermal pain	Mindfulness meditation (attention to breath)	18 healthy subjects	Additional activation in ventral striatum, ventrolateral PFC, and amygdala (Meditation is different from a relaxing mode). changes in pain intensity and pain unpleasantness ratings	OM	SN

(Continued)

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Articles	Key highlights	Significant brain regions	Pain stimuli	Type of meditation	Participants	fMRI Indications	Focused attention or open monitoring?	Default mode network (DMN) or Salience network (SN)
Lutz et al. (2013)	Expert meditation practice enhances neural mechanisms associated with attentional focus and emotion regulation during pain.	AI, aMCC	Induced thermal pain	Open Presence meditation (OM) compared to FA	14 long-term meditators (10,000 h of practice) and 14 novice controls	Neural habituation in aMCC. Meditation expertise can decrease the baseline activity prior to pain. Expert meditation practice-anticipation of a safe condition reduces activity in AI.	OM	SN
Gard et al. (2012)	Staying focused on the pain inducer and pain sensation. Top-down modulation of pain and decreased activation of brain regions involved in pain (e.g., insula/S2)	rACC, PFC, PI, S2, thalamus	Induced pain with an electrical stimulator	Mindfulness (Vipassana meditation)	34 (17) meditators and 17 controls	Reduced unpleasantness (22%) and anxiety (29%). Decreased activation of IPFC and increased activation in posterior insula during pain stimulation and increased activity in rACC during anticipation of pain	OM	NA

ACT = acceptance and commitment therapy; IFG = inferior frontal gyrus; rACC = rostral anterior cingulate cortex; AG = angular gyrus; IPL = inferior parietal lobe; rNAcc = rostral nucleus accumbens; AI = anterior insula; MBSR = mindfulness-based stress reduction; rPHG = right parahippocampal gyrus; ACC = anterior cingulate cortex; MFG = middle frontal gyrus; S1 = primary somatosensory cortex; aMCC = anterior midcingulate cortex; mPFC = medial prefrontal cortex; S2 = secondary somatosensory cortex; BOLD = blood oxygen level dependent; OM = open monitoring; SFGmed = superior medial frontal gyrus; DMN = default mode network; OFC = orbitofrontal cortex; SN = salience network; dACC = dorsal anterior cingulate cortex; PI = posterior insula; SMA = supplementary motor area; daMCC = dorsal anterior midcingulate cortex; PHG = parahippocampal gyrus; SPL = right superior parietal lobule; dlPFC = dorsolateral prefrontal cortex; PCC = posterior cingulate cortex; TPJ = temporoparietal junction; FA = focused attention; PFC = prefrontal cortex; vPCC = ventral posterior cingulate cortex; FPN = frontoparietal network; postCG = post central gyrus; vmPFC = ventromedial prefrontal cortex GMV = gray matter volume.

processing and attention-based networks is crucial in meditation studies. The affective-reappraisal network is primarily responsible for the rapid, impulsive evaluation of pain based on previously learned experiences and emotional associations. This network plays a key role in shaping an individual's immediate reaction to pain, often triggering automatic avoidance behaviors or heightened emotional responses. However, when constructively activated, it can facilitate a more adaptive, motivational, and reappraisal-based processing of pain (Seno et al., 2018). This shift allows individuals to reinterpret their pain experience, fostering greater self-empathy and resilience. Over time, such reappraisal mechanisms can contribute to improved emotion regulation, reducing the distress associated with pain and enhancing overall psychological well-being (Naor and Rohr, 2020).

The main brain regions involved in this network are ACC (Huang et al., 2020), anterior insula (Bastuji et al., 2018), and the amygdala (Seno et al., 2018). Studies suggest that the affective/motivational

dimension of pain perception is often more impacted by meditation than the sensory dimension (Singer et al., 2004; Villemure and Bushnell, 2002). In the context of meditation techniques, this dimension is variably influenced and modified during pain processing. On one hand, increased activation in brain regions such as the ACC and anterior insula has been linked to reducing pain expectations and anticipation during meditation (Brown and Jones, 2010). On the other hand, some studies report a significant decrease in the activity of emotion-related brain networks such as the connection between the amygdala with hippocampus which plays an important role in associating contextual learning about previous experiences of pain (Garcia-Larrea and Peyron, 2013; Garland et al., 2017).

Evidently, the affective-motivational aspect of meditation plays a crucial role in regulating empathy; the same network which is central to managing stress, anxiety, and pain-related distress. Early pain sensations often trigger negative appraisals by associating current

experiences with past pain memories, which amplifies distress. Meditation appears to weaken this association, enabling individuals to disengage from pain catastrophizing and approach pain with reduced emotional reactivity (Zeidan et al., 2015).

2.3 Cognitive-evaluative (attentional) network

This network which shares some brain areas with the reappraisal-motivational network (Garcia-Larrea and Peyron, 2013) and is sometimes grouped together with it due to overlapping functions, despite the cognitive-perceptive network's engagement in higher-order processes. During pain experiences, attentional processing of noxious stimuli and orientation toward the pain source can significantly alter the perception of pain, meaning that anticipating pain can enhance synchrony among brain regions encoding the sensory properties of noxious stimuli (Ohara et al., 2006).

Studies have shown that individuals with a heightened fear of pain exhibit attentional biases toward potential threats, often specific to their condition (Koster et al., 2006; Vago and Nakamura, 2011; Okifuji and Turk, 2016). While attention orienting is a core component of meditation, most meditation techniques go far beyond a simple redirection of attention (Zeidan et al., 2015). Instead, they can significantly reduce emotional responses and catastrophizing behaviors by flexibly orienting attention toward or away from pain, depending on the practice. It seems like mindfulness techniques such as decentering involve actively observing the source of physical pain, redirecting attention to the emotions elicited by the pain, and ultimately maintaining awareness of the pain from a detached perspective (Kober et al., 2019).

Meditation techniques differ widely in their approach to attentional practice (Grant et al., 2010). Yet what remains the same is that all meditation techniques contribute to an attentional shift to/from the source of pain. Meditation also enhances inhibitory control, helping individuals dissociate current pain from previous painful experiences (Lutz et al., 2013). Rather than being trapped in the pain sensation, meditation enables a flexible and fluid transformation of attention and responses.

As could be seen, evidence supports that meditation influences all categories of the three-tiered hierarchical model of pain processing. Nevertheless, the concern with this model is regarding the overlapping cortical regions which make it hard to distinguish if meditation is mostly helpful at either the sensory, emotional or the cognitive level. Therefore, we further discuss meditation experience from another perspective which mainly focuses on pinpointing most mentioned regions in literature reviews.

3 Neurological pain signature (NPS) of brain areas involved in meditation

The NPS is an objective, multivariate neural pattern that encompasses brain regions consistently activated during nociception and pain processing (Wager et al., 2013). By comparing individual neural data against the NPS, the intensity of pain can be reliably predicted, offering a valuable tool for objectively assessing pain experiences. The main role of NPS has been to learn about efficacy of analgesic treatments (Kober et al., 2019; Wager et al., 2013; López-Solà

et al., 2022), but such a signature can also elaborate more on non-pharmaceutical techniques, such as meditation, to ensure if a technique is appropriately implemented and whether it is functional for subjects or not.

Given the importance of reaching NPS model for meditation techniques, here we specify some fMRI evidence of the most frequently mentioned brain regions in both pain-induced and chronic pain conditions encouraging future studies to elaborate on the connectivity of such areas with each other.

3.1 Dorsolateral prefrontal cortex (DLPFC)

Dorsolateral prefrontal cortex is a frequently cited brain region in fMRI studies investigating pain and meditation experiences (Zeidan et al., 2015; Grant et al., 2010; Kober et al., 2019; Berry et al., 2020; Smith et al., 2021). It plays a critical role in moderating pain signals and contributes to a more regulated perception of pain. Specifically, research indicates that the DLPFC acts as a key player in bridging cognitive and emotional regulation in individuals experiencing pain, particularly as influenced by OM techniques (Berry et al., 2020; Smith et al., 2021).

A central function of DLPFC is its role in empowering non-judgmental awareness of sensations, a hallmark of OM techniques (Lutz et al., 2013). Studies have demonstrated that this region exhibits increased activation during meditation for chronic pain (Berry et al., 2020; Kober et al., 2019). Considering the literature demonstrating an association between heightened activation of the DLPFC in chronic musculoskeletal and low back pain, it can be inferred that this region plays a crucial role in the top-down modulation of pain through mechanisms such as neuroplasticity, nociception, and neuropathy. The activation of the DLPFC also reflects its involvement in working memory, a function that is particularly relevant to OM meditation. In contrast, during acute pain among healthy controls, DLPFC's activation appears to be decreased instead when participants were doing OM (Grant et al., 2010). Such a deactivation in this region could be associated with a shift away from the cognitive effort toward effortless pain modulation, and therefore a reduced pain perception. While these studies primarily focus on OM strategies, the observed changes in DLPFC activation may be associated with the type of pain, whether induced or chronic.

3.2 Anterior cingulate cortex (ACC)

Anterior cingulate cortex plays a pivotal role in both pain processing and mindfulness, serving as a key hub for emotional and cognitive regulation (Tang et al., 2015; Zeidan et al., 2011). Based on our review, ACC is one of the most frequently cited regions associated with interpreting unpleasant states and emotional distress linked to pain in both meditation categories and across induced pain and chronic pain conditions. It ultimately regulates pain perception through various cognitive strategies (Zeidan et al., 2015; Gard et al., 2012; Orme-Johnson et al., 2006; Kober et al., 2019; Zeidan et al., 2011; Fedeli et al., 2024; Riegner et al., 2023; Aytur et al., 2021; Zeidan et al., 2011; Chen et al., 2023).

Meditation practices target ACC to enhance its functions, including sustaining attention on the present moment, detecting

discrepancies between actions and expected outcomes in critical conditions, and, most importantly, regulating emotion by supporting metacognition and heightened self-awareness during painful situations. This suggests that ACC contributes to fostering a positive attitude and acceptance toward impending stimuli, which may enhance coping strategies during pain.

Anterior cingulate cortex is commonly implicated in OM practices (Zeidan et al., 2015; Kober et al., 2019; Zeidan et al., 2011; Fedeli et al., 2024; Riegner et al., 2023; Aytur et al., 2021; Zeidan et al., 2011; Chen et al., 2023), although it is also found to play a role in FA techniques (Xu and Yaksh, 2011; Nash et al., 2013). Most studies reporting ACC activation involve healthy subjects receiving an induced pain (Zeidan et al., 2015; Gard et al., 2012; Orme-Johnson et al., 2006; Grant et al., 2010; Kober et al., 2019; Zeidan et al., 2011; Riegner et al., 2023). Compared to the DLPFC, fewer studies have linked ACC modulation to improved chronic pain outcomes through meditation (Fedeli et al., 2024; Aytur et al., 2021). Fedeli et al.'s study on chronic migraine and medication-overuse headaches (MOH) found increased cortical thickness in the ACC among individuals with MOH compared to healthy controls (Fedeli et al., 2024). Another study on chronic musculoskeletal pain suggests that the salience network is diminished, as indicated by reduced activity in the ACC along with the primary somatosensory cortex (S1). Although the existing literature does not allow for definitive conclusions across all pain mechanisms, the ACC serves as a hub for embedding an automatic state of non-reactivity to pain stimuli. It is more closely associated with nociceptive pain mechanisms, as observed in studies of induced pain in healthy controls. In general, it can be inferred that meditation practices, particularly OM techniques, modulate ACC activity by reframing pain as a neutral sensory experience through constructive cognitive strategies.

3.3 Insula

The insula is another frequently cited brain region in fMRI studies (Zeidan et al., 2015; Gard et al., 2012; Grant et al., 2010; Kober et al., 2019; Kakigi et al., 2005; Fedeli et al., 2024; Riegner et al., 2023; Aytur et al., 2021; Zeidan et al., 2011; Chen et al., 2023; Nakata et al., 2014) and is involved in enhancing interoceptive awareness, moderating emotional reactivity, and improving cognitive control. This region is one of the key hubs for bridging the sensory and emotional processing of pain to each other with the posterior insula receiving direct input from spinothalamic pathway and evaluating pain intensity, location and sensory recognition of a noxious stimulus and connecting it to the anterior insula for more emotional processing and connecting the information to the rest of the limbic system (Bastuji et al., 2018).

Chronic pain conditions are often associated with hyperactivation of the insula, reflecting increased maladaptive interoceptive awareness of pain indicators, which can lead to heightened emotional distress in individuals experiencing pain (Zeidan et al., 2015; Zeidan et al., 2011).

Evidence suggests that meditation can increase insula activation in response to acute pain (Zeidan et al., 2015; Grant et al., 2010). However, in chronic pain, meditation generally moderates emotional responses through the modulation of insula activity (Fedeli et al., 2024; Aytur et al., 2021; Chen et al., 2023). Additionally, the involvement of the insula in meditation techniques is not limited to OM strategies; FA practices have also been shown to modulate insula activity as well (Grant et al., 2010; Kakigi et al., 2005).

Overall, meditation appears to regulate insular activation, helping to control hypervigilance and catastrophizing responses to pain. The key factor is not just the activation of this region but also its connectivity within the salience network (SN), particularly with the ACC (Fedeli et al., 2024; Aytur et al., 2021). This regulation is crucial, as it may help delay the chronification process associated with prolonged negative emotional responses across different pain mechanisms.

3.4 Thalamus

The thalamus is known for its role in mediating and integrating different forms of somatosensory, noxious, and vestibular stimuli (Habig et al., 2023). As a relay station for the sensory perception of pain, the thalamus plays a critical role in mediating pain relief through meditation practice specifically when a mechanical pain is induced. In the thalamus, critical sensory information, including nociceptive signals, is processed before reaching other areas of the cortex. fMRI evidence demonstrates decreased thalamic activity during meditation, suggesting that meditation effectively filters nociceptive information and modulates the sensory transmission of pain signals to higher cortical regions (Gard et al., 2012; Orme-Johnson et al., 2006; Grant et al., 2010; Kober et al., 2019; Kakigi et al., 2005; Riegner et al., 2023).

Changes in thalamic activity is often observed in professional meditators. For example, the thalamus was found a key factor in a study observing a yoga master during practice (Kakigi et al., 2005), a result consistent across various meditation techniques (Gard et al., 2012; Grant et al., 2010). This highlights meditation's impact, which extends beyond modulating the affective aspects of pain to directly influencing sensory processing, particularly at professional levels of practice. Research shows that both FA practices (Orme-Johnson et al., 2006; Grant et al., 2010; Kakigi et al., 2005) and OM techniques (Gard et al., 2012; Kober et al., 2019; Riegner et al., 2023) have a comparable impact on thalamic modulation; yet FA practices highlight this area as critically impacted region during practice (López-Solà et al., 2022).

In general, the thalamus is one of the initial regions where sensory pain signals and nociceptive inputs to higher emotional and cognitive levels can be decoupled (Riegner et al., 2023) and evidence supports the assertion that long practice of meditation has a clear impact on sensory modulation, as demonstrated by mediated activation in areas such as the thalamus and cerebellum in response to noxious stimuli (Kober et al., 2019; Nakata et al., 2014). However, there is currently no evidence to suggest that meditation modulates thalamic activation in chronic pain conditions. This suggests that meditation, particularly OM, may be more effective at addressing the emotional and cognitive dimensions of pain rather than its sensory aspects in individuals with chronic pain.

4 Discussion

We discussed how fMRI studies support a categorical theory of pain (i.e., three-tiered hierarchical perspective of pain) and pinpointed some common regions which could inspire further studies on a holistic model of pain (i.e., NPS) during meditation. Figure 1 elaborates on cortical regions at each of the three-tiered networks in association with OM and FA techniques. Here we provide a practical

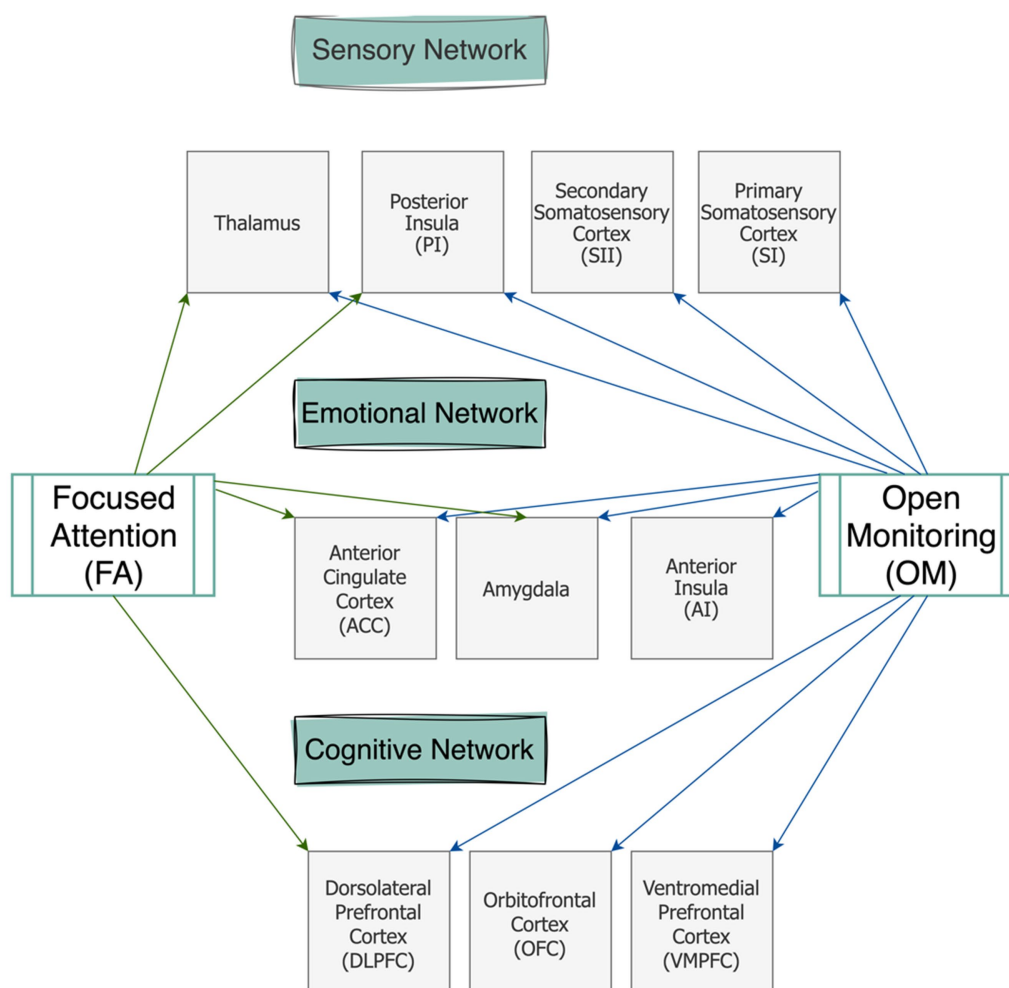


FIGURE 1

Schematic representation of the brain regions involved in the three-tiered networks of pain modulation during two meditation categories (FA and OM).

perspective for meditation's efficacy in pain management discussing which category of meditation may be more suitable for addressing chronic pain conditions.

4.1 Meditation practice beyond placebo effect

The fMRI studies show that meditation can alleviate pain through multiple mechanisms. It promotes self-compassion and grounding in the present moment, reducing pain-related stress and emotional discomfort (Su et al., 2016; Okifuji and Turk, 2016). Additionally, meditation may attenuate physiological reactions to pain-related distress, potentially by increasing the secretion of endogenous endorphins (Orme-Johnson et al., 2006). Meditation techniques are also associated with key hypometabolic changes, such as lower respiration and heart rates, which significantly influence the pain experience (Beary and Benson, 1974). An ongoing debate concerns whether meditation operates distinctly from placebo effects.

Some studies attribute its benefits to factors such as facilitator attention, body posture, practice characteristics, and the environment

(Zeidan et al., 2015; Tang et al., 2015; Zeidan et al., 2012). Notably, DLPFC plays a role in both meditation and placebo analgesia, potentially explaining why placebo effects can similarly reduce perceived pain (Wager and Atlas, 2015). However, a gold-standard fMRI study by Zeidan et al. (2015) found that reduced DLPFC activity during mindfulness meditation differs significantly from placebo and sham meditation groups. Behavioral reports from this study, such as decreased pain unpleasantness and intensity in the meditation group, further support meditation's unique, non-placebo benefits.

4.2 Practical implications of meditation for chronic pain

Knowing that pain mechanisms are different from one another, here we explained how meditation techniques have been found helpful for three categories of nociceptive, neuroplastic, and neuropathic pain. A key question here is which meditation technique is most effective for pain management of different pain mechanisms. Previous research supports our perspective that FA and OM categories act distinctively in addressing acute or chronic pain conditions. Building on the three-tiered hierarchical perspective of pain, we differentiate between FA and

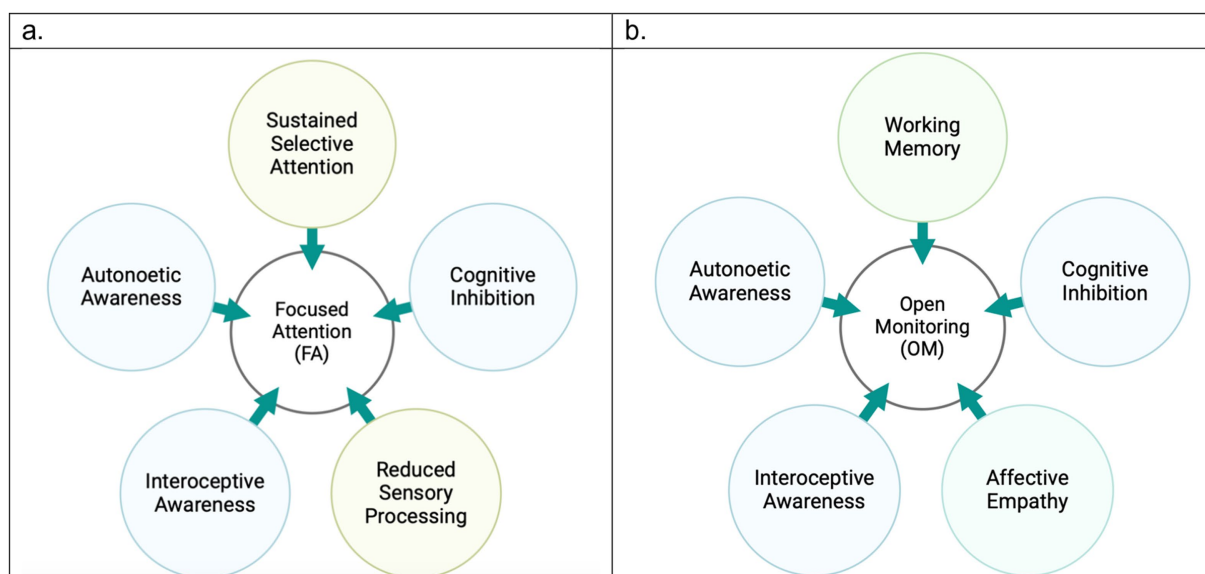


FIGURE 2
Major factors contributing to pain modulation in the two meditation categories.

OM meditation techniques in pain management. Figure 2 highlights the key factors associated with each of the techniques during pain modulation particularly by emphasizing that while OM is more potential to engage working memory, FA requires sustained attention on a task, so it reduces sensory processing of pain. We also assert that FA techniques require greater levels of expertise and are particularly effective for acute pain. In contrast, OM techniques are more accessible and beginner-friendly practices that foster a broader, non-reactive awareness of pain, making it especially beneficial for chronic pain conditions. We underscore that while FA primarily modulates sensory and emotional responses, OM engages a more comprehensive framework, integrating emotional, cognitive, and sensory regulation.

Based on the previous research, OM practices engage a wide range of cortical regions, including the superior temporal gyrus, superior parietal lobule, inferior frontal gyrus, precuneus, OFC, transverse temporal gyrus, fusiform gyrus, parahippocampus, and amygdala (Zeidan et al., 2015; Aytur et al., 2021; Zeidan et al., 2011; Manna et al., 2010). Behavioral studies indicate that naïve OM practitioners report reduced pain unpleasantness without significant changes in pain intensity (Perlman et al., 2010), suggesting a stronger link to affective network activation, particularly within the limbic system (Nakata et al., 2014).

In contrast, FA predominantly activates regions such as the ACC, and the thalamus (Wang et al., 2011; Orme-Johnson et al., 2006; Grant et al., 2010; Kakigi et al., 2005). However, fMRI evidence implies that FA's efficacy is more pronounced in long-term or expert meditators (Orme-Johnson et al., 2006; Grant et al., 2010; Kakigi et al., 2005; Manna et al., 2010). While FA may mediate sensory aspects of pain perception along with affective and cognitive levels, its generalizability for chronic pain remains uncertain due to a lack of fMRI-based studies on FA practices in chronic pain conditions.

Behavioral comparisons between OM and FA suggest that OM is more effective in reducing pain unpleasantness, even without altering pain intensity (Villemure and Bushnell, 2002). This makes OM techniques particularly suitable for naïve meditators seeking pain management, as they may more effectively promote acceptance and

coping strategies in individuals with little or no prior meditation experience compared to FA techniques (Perlman et al., 2010; Ochsner et al., 2012). Additionally, OM helps individuals remain present in their experience of chronic pain by reducing hippocampal activity, which diminishes the mental and emotional processing of short-term pain into long-term memory (Hunt et al., 2023; Hatchard et al., 2022). This reduction in hippocampal activity enables individuals to moderate their behavioral reactivity by learning to dissociate their lived experience of pain from their current state, thereby reducing tendencies toward catastrophizing or hypervigilance about future pain. Figures 3 displays a summary of our perspective regarding the efficacy of OM and FA techniques for different pain mechanisms and different conditions of acute and chronic pain.

In sum, fMRI evidence provides compelling support for the efficacy of meditation as a valuable non-pharmaceutical alternative for managing pain, especially in chronic conditions. While this review has identified distinct patterns of brain activation associated with various meditation techniques, it also underscores the need for further research to explore these differences in greater detail. For instance, future studies could focus on delineating how FA and OM differentially activate brain regions and networks involved in pain perception and regulation. Such investigations would not only enhance our understanding of the neural mechanisms underpinning meditation's efficacy but also help identify optimal meditation techniques for specific pain conditions, tailoring interventions to maximize therapeutic outcomes. By bridging the gap between neuroscience and clinical practice, these advancements could further establish meditation as a cornerstone in the management of chronic pain and related disorders.

5 Conclusion

Meditation encompasses a spectrum of techniques, ranging from focused attention (FA) to open monitoring (OM) strategies, which foster an aware mental state that enables individuals to focus on the sensory

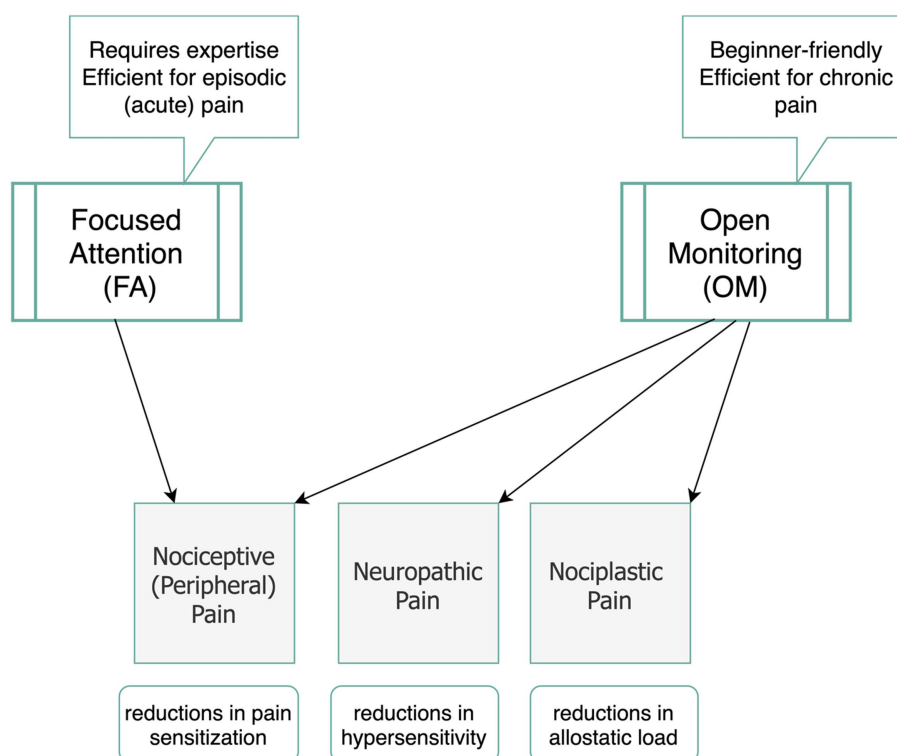


FIGURE 3

Suggested meditation categories (OM and FA) and their potential efficacy in modulating pain mechanisms.

aspects of a noxious stimulus while voluntarily modulating their cognitive processing and emotional reactivity to painful experiences. fMRI-based evidence highlights the multidimensional influence of meditation on the brain in mitigating pain. This review explored the impact of meditation on three key layers of pain processing; sensory, cognitive, and emotional, in both acute and chronic pain conditions, elaborating on the most implicated brain regions involved in pain management through meditation techniques. In this perspective article, we propose that the primary distinction between FA and OM strategies lies in the level of the practitioner's proficiency. Most fMRI evidence for FA techniques has been derived from studies on experienced meditators undergoing acute pain induction. From a neuroscientific perspective, we suggest that OM may be a more practical and accessible technique for chronic pain management in naïve meditators, as it facilitates acceptance, reduces pain-related emotional distress, and promotes coping strategies even without extensive prior training.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

FG: Conceptualization, Resources, Writing – original draft, Writing – review & editing. MM: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Effects of visual spatial frequency on audiovisual interaction: an event-related potential study

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Spatial frequency is a fundamental characteristic of visual signals that modulates the audiovisual integration behavior, but the neural mechanisms underlying spatial frequency are not well established. In the present study, the high temporal resolution of event-related potentials was used to investigate how visual spatial frequency modulates audiovisual integration. A visual orientation discrimination task was used, and the spatial frequency of visual stimuli was manipulated under three conditions. Results showed that the influence of visual spatial frequency on audiovisual integration is a dynamic process. The earliest audiovisual integration occurred over the left temporal-occipital regions in the early sensory stage (60–90 ms) for high spatial frequency conditions but was absent for low and middle spatial frequency conditions. In addition, audiovisual integration over fronto-central regions was delayed as spatial frequency increased (from 230–260 ms to 260–320 ms). The integration effect was also observed over parietal and occipital regions at 350–380 ms, and its strength gradually decreased at higher spatial frequencies. These discrepancies in the temporal and spatial distributions of audiovisual integration imply that the role of spatial frequency varies between early sensory and late cognitive stages. The findings of this study offer the first neural demonstration that spatial frequency modulates audiovisual integration, thus providing a basis for studying complex multisensory integration, especially in semantic and emotional domains.

KEYWORDS

spatial frequency, visual orientation discrimination, audiovisual integration, early sensory stage, late cognitive stage, event-related potentials

1 Introduction

In our daily life, the brain continuously receives and processes sensory inputs from multiple modalities, such as vision, sound, touch, and smell. In particular, when auditory and visual signals are spatiotemporally congruent, the brain integrates them into unified perceptual representations to optimize behavioral responses—a phenomenon termed “audiovisual integration.” Previous studies have shown audiovisual integration across diverse domains, including spatial localization (Frassinetti et al., 2002), temporal judgment (Adams, 2016; Takeshima, 2024), object identification (Amedi et al., 2005; Van der Burg et al., 2011), and speech perception (Micheli et al., 2020; Stevenson and James, 2009). Audiovisual integration confers behavioral advantages such as faster response times (RTs) and higher accuracy for bimodal stimuli than for unimodal stimuli presented in isolation.

Audiovisual integration strongly depends on stimulus features such as the intensity and frequency of auditory stimuli (Green et al., 2019; Senkowski et al., 2011; Yang et al., 2015). Visual signal has two basic features: contrast and spatial frequency (SF). Previous studies have shown that a lower visual contrast leads to more audiovisual interactions than a higher visual contrast (Noesselt et al., 2010). Moreover, event-related potential (ERP) studies have shown that audiovisual integration is elicited by lower-contrast stimuli but not by higher-contrast stimuli 40–60 ms after stimulus presentation when visual and auditory stimuli are presented simultaneously (Senkowski et al., 2011). SF is an important characteristic of the visual system. Previous behavioral studies have established that contrast sensitivity across SFs in humans follows a characteristic inverted-U-shaped profile, showing maximum sensitivity to midrange frequencies, which decreases toward higher and lower frequencies (Campbell and Robson, 1968). The multichannel theory proposes that the visual system employs multiple independent, parallel channels to process visual information. Each channel is selectively attuned to a specific SF range—high frequencies for fine details (e.g., texture) and low frequencies for global structures (e.g., shape)—allowing for efficient hierarchical analysis of complex scenes. Indeed, some studies have shown that the primary visual cortex selectively processes visual-information-based visual SFs in both animals (De Valois et al., 1982; Issa et al., 2000) and humans (Sara and Sam, 2018). Furthermore, studies have been carried out on the human brain to investigate the neural mechanisms underlying the processing of changes in visual SFs (Baas et al., 2002; Musselwhite and Jeffreys, 1985). For example, an ERP study has revealed that the latency of the C1 component became longer with an increase in the SF (Musselwhite and Jeffreys, 1985). However, little is known about the interactions between visual stimuli of different SFs and auditory stimuli.

Several behavioral studies have investigated the influence of visual SF on audiovisual processing (Green et al., 2019; Jaekl and Soto-Faraco, 2010; Pérez-Bellido et al., 2013; Takeshima, 2024). In a visual orientation discrimination task, Jaekl and Soto-Faraco (2010) showed that auditory input selectively enhances contrast sensitivity at low SFs, as evidenced by significantly lower contrast thresholds in audiovisual stimuli than in visual-only stimuli. This integration effect of low SFs was further confirmed by Pérez-Bellido et al. (2013). Pérez-Bellido et al. (2013) instructed participants to detect visual speed to distinguish audiovisual enhancement due to stimulus-driven changes from those accounted for by decision-level contributions (Pérez-Bellido et al., 2013). Their results revealed that sound-induced visual enhancement was more selective for low-SF stimuli than for high-SF stimuli. Furthermore, Green et al. (2019) used an audiovisual simultaneity judgment task designed with different audiovisual stimulus onset asynchronies to investigate the role of visual SF in audiovisual integration (Green et al., 2019). Their results indicated that the temporal window of integration inside the human sensitivity range (1–12 c/d) was wider than that outside the human sensitivity range (Green et al., 2019). In a recent audiovisual simultaneity judgment study, Takeshima (2024) manipulated SF to probe its impact on temporal recalibration and revealed no significant differences in recalibration magnitude between low-SF (1.0 c/d) and high-SF (5.0 c/d) conditions (Takeshima, 2024). These behavioral studies demonstrate that visual SF differentially modulates audiovisual integration depending on task demands. However, there is little research on the role of SFs in the neural processing of audiovisual integration, and integration effects are yet to be investigated in detail.

In the present study, the neural mechanism underlying the effect of SFs on audiovisual integration was examined via the high temporal resolution of electroencephalogram (EEG). For this purpose, a visual orientation discrimination task was designed, and the SF of visual stimuli was manipulated under three conditions, namely low, middle, and high SFs. The nature and timing of audiovisual integration was analyzed by comparing the ERPs elicited by the audiovisual stimuli with the sum of the ERPs elicited by the unimodal auditory and unimodal visual stimuli. By comparing the differences in audiovisual integration among the three SFs, fundamental patterns regarding the influence of SF on audiovisual integration were identified: different stages and different SF modulation effects occur.

2 Materials and methods

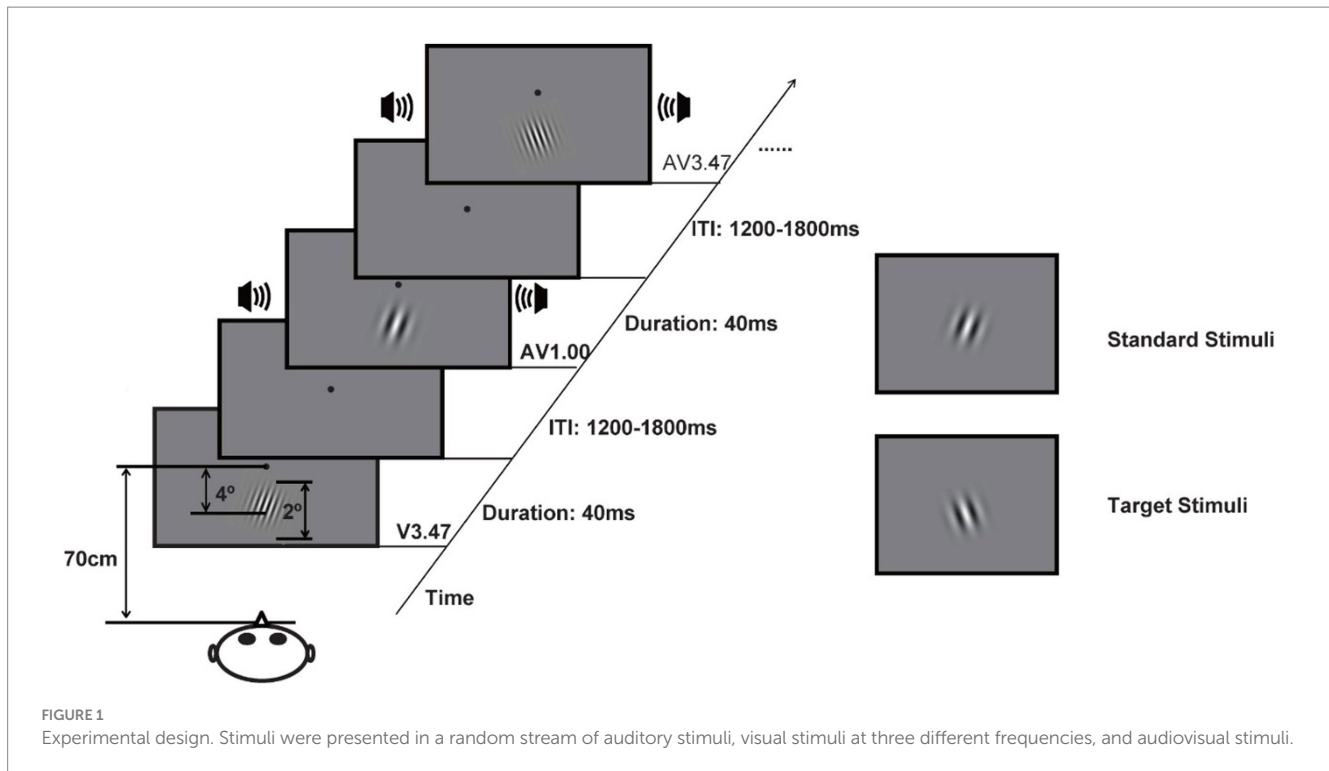
2.1 Participants

Sixteen healthy volunteers (aged 22–29 years, mean age 24.1 years) from Okayama University participated in this experiment. All participants had normal or corrected-to-normal vision and were right-handed, with no neurological or psychiatric disorders and no hearing problems. The experimental protocol was approved by the Ethics Committee of Okayama University.

2.2 Stimuli and task

Stimuli presentation and response collection were carried out using MATLAB Release 14 with the Psychophysics Toolbox (PTB-3, a free, open-source collection of MATLAB and GNU Octave functions designed for designing and executing experiments in psychology research) (Brainard and David, 1997). The experiment consisted of three stimulus types: unimodal visual, unimodal auditory, and bimodal audiovisual (auditory and visual stimuli were presented simultaneously). The visual (V) stimuli consisted of a Gabor grating (2° visual angle, 30% contrast) with three SFs: 1.00 c/d, 1.86 c/d, and 3.47 c/d. These three SFs were selected based on previous studies (Campbell and Robson, 1968). The visual stimuli were presented on a 17-in. CRT monitor (100 Hz, 1,280 × 1,024 pixels, with a background luminance of 10 cd/m²) approximately 4° below the fixation point and included two subtypes with different orientations: clockwise 10° and anticlockwise 10°. The auditory stimulus (A) was a 3,000 Hz pure tone (65 dB SPL, 40 ms in duration, 5 ms rise and fall periods) that was presented through earphones. Bimodal audiovisual (AV) stimuli were presented at three levels, with the visual stimuli of 1.00 c/d (AV1.00), 1.86 c/d (AV1.86), and 3.47 c/d (AV3.47), as shown in Figure 1.

The experiment was performed in a dimly lit, electrically shielded, and sound-attenuated room (laboratory room, Okayama University, Japan). Each subject participated in 12 blocks, with each block lasting approximately 6 min. In six blocks, 10° clockwise was defined as the target visual stimulus, and 10° anticlockwise was defined as the standard reverse stimulus in the other six blocks. The order of orientation for the target stimulus was balanced between participants. Each block consisted of 54 visual stimuli (3 SFs × 15 standards and 3 SFs × 3 targets), 54 audiovisual stimuli (3 SFs × 15 standards and 3 SFs × 3 targets), 15 auditory stimuli, and 15 catch trials. The interstimulus interval varied randomly between 800 and 1,200 ms. At the beginning of each block, the participants were presented with a fixation point for 3,000 ms, and then, the stimuli were



presented randomly for 40 ms. The participants were instructed to press the button as accurately and quickly as possible when the target stimuli were presented regardless of whether an auditory stimulus was presented, as shown in Figure 1.

2.3 Apparatus

An EEG system (BrainAmp MR plus, Gilching, Germany) was used to record EEG signals through 32 electrodes mounted on an electrode cap (Easy Cap, Herrsching-Breitbrunn, Germany). Horizontal eye movements were measured by deriving the electrooculogram (EOG) from one electrode placed approximately 1 cm from the outer canthi of the left eye. Vertical eye movements and eye blinks were detected by deriving an EOG from an electrode placed approximately 1.5 cm below the participant's left eye. All signals were referenced to the left and right earlobes, and the impedance was maintained below 5 k Ω . Raw signals were acquired at a sample rate of 500 Hz and stored for offline analysis.

2.4 Behavioral data analysis

Hit rates, false alarms, and RTs were computed separately for each participant. RTs were calculated based on the responses falling within the mean RT $\pm$ 2.5 standard deviations (SDs). Hit rate was calculated as the percentage of correct responses relative to the total number of target stimuli, and false alarm rate was calculated as the percentage of incorrect responses relative to the total number of standard stimuli. In addition, perceptual sensitivity ($d' = z(\text{HR}) - z(\text{FA})$) and response bias ($c = -0.5 \times [z(\text{HR}) + z(\text{FA})]$) were calculated for each participant. These measures were then analyzed using a 3 SF (1.00, 1.86, and 3.47 c/d) $\times$ 2 stimuli type (V and AV) repeated-measures ANOVA, followed by post-hoc tests with Bonferroni adjustment.

2.5 ERP data analysis

The EEG signals elicited by the standard stimuli were analyzed using BrainVision Analyzer software (version 1.0, Brain Products GmbH, Munich, Germany). First, the data were re-referenced to the average of left and right mastoids and bandpass-filtered from 1 to 30 Hz at a sample rate of 500 Hz. Next, the data were divided into epochs from -100 to 600 ms after stimulus onset, and baseline corrections were made from -100 to 0 ms. Then, epochs with a voltage exceeding $\pm 100 \mu\text{V}$ at any electrode location were excluded from the analysis. In addition, responses associated with false alarms were rejected. Finally, grand-averaged ERPs were obtained across all participants for each stimulus type. Three participants were excluded from further analysis due to the loss of more than 70% of the epochs over at least one stimulus type.

To establish the presence of audiovisual integration, statistical analysis was conducted in three steps, following previous studies (Ren et al., 2018; Senkowski et al., 2011). First, the ERPs for bimodal AV stimuli were compared with the linear summation of unimodal auditory and unimodal visual ERPs (A+V) via pointwise running t -tests (two-tailed) for each electrode under each condition (1.00, 1.86, and 3.47 c/d). Significant differences were plotted when at least 12 consecutive data points met the alpha criterion of being < 0.05 (24 ms at a 500 Hz digitization rate was defined as audiovisual integration, Figure 2; Ren et al., 2018; Yang et al., 2015). Then, the regions of interest (ROI) and integration time intervals where and when significant audiovisual integration occurred were chosen based on the statistical analysis and topographical response patterns (Figure 3). In the second level of analysis, repeated-measures ANOVA were conducted for the three SFs of visual stimuli for the time interval and were selected based on an overview of the significant differences observed in the first step. Mean amplitude data were analyzed while accounting for the between-subject factors of stimulus types, conditions, electrodes, and time intervals. If a significant interaction between stimulus type,

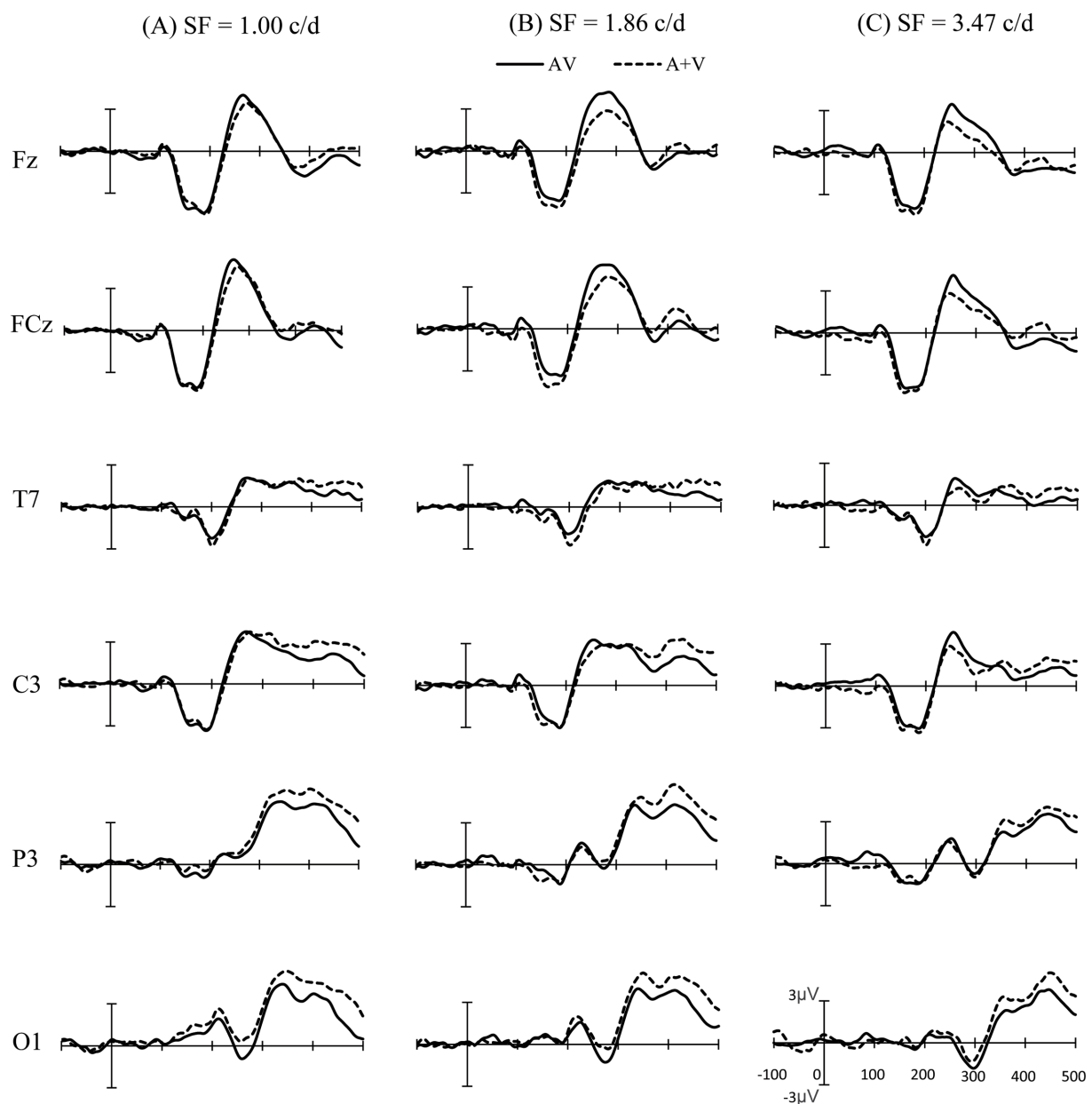


FIGURE 2

Event-related potentials of the sum of the unimodal stimuli (A+V) and bimodal (AV) stimuli at a subset of electrodes are shown from 100 ms before the stimulus to 500 ms after stimulus onset. (A) For the 1.00 c/d condition. (B) For the 1.86 c/d condition. (C) For the 3.47 c/d condition.

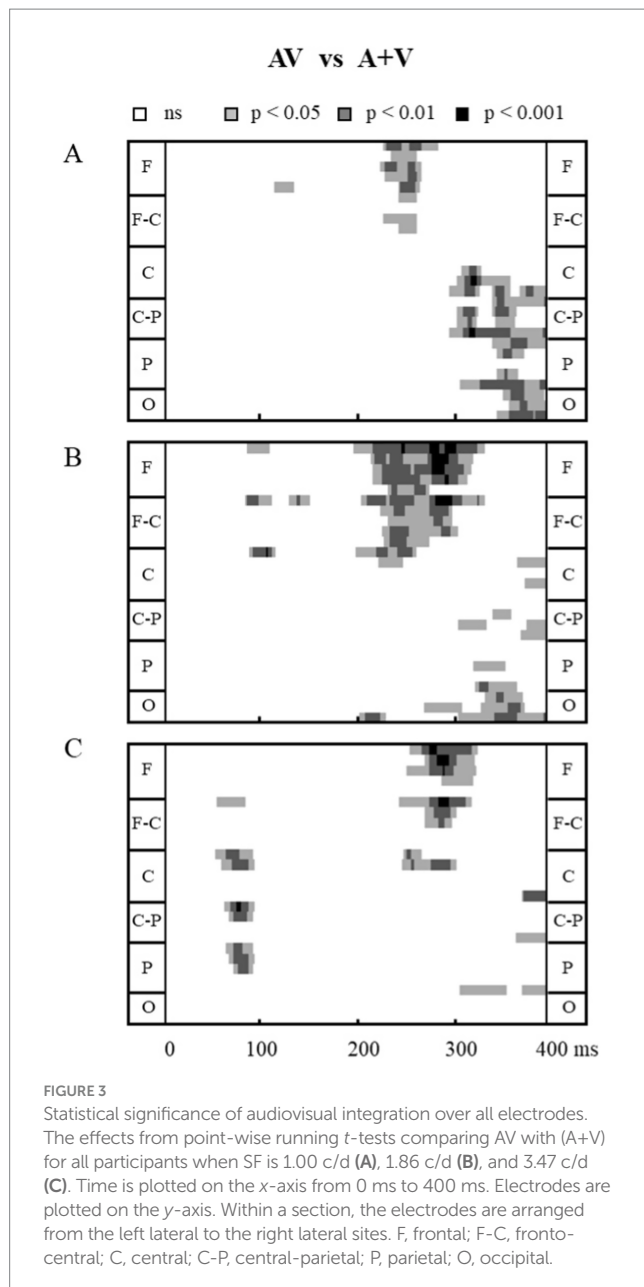
condition, or electrode and time interval was observed, the third phase of the analysis was carried out. In the third step, ANOVA were conducted separately for each of the ROI using the factor stimulus type (AV, A+V).

3 Results

3.1 Behavioral results

The RTs, hit rates, false alarm rates, perceptual sensitivity (d'), and response bias (c) are shown in Table 1. The 3 SF (1.00, 1.86, and 3.47 c/d) $\times$ 2 stimuli type (V and AV) repeated-measures ANOVA on RTs showed a main effect of stimuli type [$F(1, 15) = 22.99, p = 0.000$,

$\eta_p^2 = 0.605$], indicating a faster response for AV stimuli than for V stimuli. In addition, a significant interaction was observed between stimuli type and SF [$F(2, 30) = 8.86, p = 0.001, \eta_p^2 = 0.371$]. Post-hoc comparisons showed significantly faster responses for AV versus V stimuli at SF 1.00 c/d ($p < 0.01$) and SF 1.86 c/d ($p < 0.001$), but not at SF 3.47 c/d. The 3 SF (1.00, 1.86, and 3.47 c/d) $\times$ 2 stimuli type (V and AV) repeated-measures ANOVA on hit rates revealed a significant main effect of SF [$F(2, 30) = 13.65, p = 0.002, \eta_p^2 = 0.477$], with a higher accuracy for SF 1.00 c/d ($p = 0.005$) and SF 1.86 c/d ($p = 0.006$) than for SF 3.47 c/d. Furthermore, a main effect of stimuli type was observed [$F(1, 15) = 9.05, p = 0.009, \eta_p^2 = 0.376$], where AV stimuli elicited larger hit rates than V stimuli. This auditory enhancement was significant only for SF 1.86 c/d ($p = 0.049$) and SF 3.47 c/d ($p = 0.037$).



However, the interaction between SF and stimuli type was not significant [$F(2, 30) = 1.55$, $p = 0.233$, $\eta_p^2 = 0.094$]. The 3 SF (1.00, 1.86, and 3.47 c/d) * 2 stimuli type (V and AV) repeated-measures ANOVA on false alarm rates revealed a significant main effect of stimuli type [$F(1, 15) = 7.39$, $p = 0.016$, $\eta_p^2 = 0.330$], with higher false alarms for AV stimuli than for V stimuli. The 3 SF (1.00, 1.86, and 3.47 c/d) * 2 stimuli type (V and AV) repeated-measures ANOVA on d' showed a main effect of SF [$F(2, 30) = 4.58$, $p = 0.035$, $\eta_p^2 = 0.234$], indicating decreased sensitivity with increasing SF. No significant interaction was observed [$F(2, 30) = 1.78$, $p = 0.192$, $\eta_p^2 = 0.106$] though a marginal difference between V and AV stimuli emerged at SF 3.47 c/d ($p = 0.062$). The 3 SF (1.00, 1.86, and 3.47 c/d) * 2 stimuli type (V and AV) repeated-measures ANOVA on c showed a main effect of SF [$F(2, 30) = 9.16$, $p = 0.004$, $\eta_p^2 = 0.379$] and a main effect of stimuli type [$F(1, 15) = 11.29$, $p = 0.004$, $\eta_p^2 = 0.429$], but no interaction was observed.

3.2 ERP results

The average ERPs across the three experimental conditions are shown in Figure 2. The results of pointwise running *t*-tests comparing AV and A+V conditions at the three different SFs are shown in Figure 3. Based on the statistical analysis and topographical response patterns, six ROI (frontal: F7, F3, Fz, F4, F8; fronto-central: FC5, FC1, FCz, FC2, FC6; central: C3, Cz, C4; parietal: P3, Pz, P4; occipital: O1, Oz, O2; and temporal: T7, T8) and three integration time windows (60–90 ms, 230–320 ms, and 350–380 ms) were selected. Due to significant lateralization effects in the early time interval of 60–90 ms (Figure 4 topography), bilateral electrodes within each ROI were selected for subsequent analyses (left: F3, FC1, T7, C3, P3 and O1; right: F4, FC2, T8, C4, P4 and O2). A 3 SF (1.00, 1.86, and 3.47 c/d) * 2 stimuli type (AV and A+V) * 3 time interval (60–90 ms, 230–320 ms, and 350–380 ms) * 6 ROI (frontal, fronto-central, temporal, central, parietal, and occipital) * 2 electrode (left and right) repeated-measures ANOVA on mean amplitudes revealed a significant five-way interaction [$F(20, 240) = 2.64$, $p = 0.016$, $\eta_p^2 = 0.180$]. This indicates the distinct audiovisual integration patterns for different SF conditions in different time intervals. Therefore, these differences were analyzed in detail in the following sections.

3.2.1 Audiovisual integration for 60–90 ms

In the early stage of 60–90 ms, audiovisual integration occurred for SF 3.47 c/d, but not for SF 1.00 and SF 1.86 c/d (Figures 2, 4). A 2 stimuli type (AV and A+V) * 6 ROI (frontal, fronto-central, temporal, central, parietal, and occipital) * 2 electrode (left and right) repeated-measures ANOVA was conducted for SF 3.47 c/d. A significant main effect of stimuli type was observed [$F(1, 12) = 13.04$, $p = 0.004$, $\eta_p^2 = 0.521$], with more positive amplitudes for the ERPs elicited by AV than those elicited by A+V. In addition, a significant interaction between stimuli type * ROI * electrode was observed [$F(5, 60) = 4.48$, $p = 0.008$, $\eta_p^2 = 0.272$]. Post-hoc analyses revealed a significant difference at electrodes FC1, T7, C3, P3, P4, and O1 (all $p < 0.05$). These results indicate that significant early audiovisual integration occurred for high-SF stimulus over left temporal-occipital regions, as shown in Figure 4C.

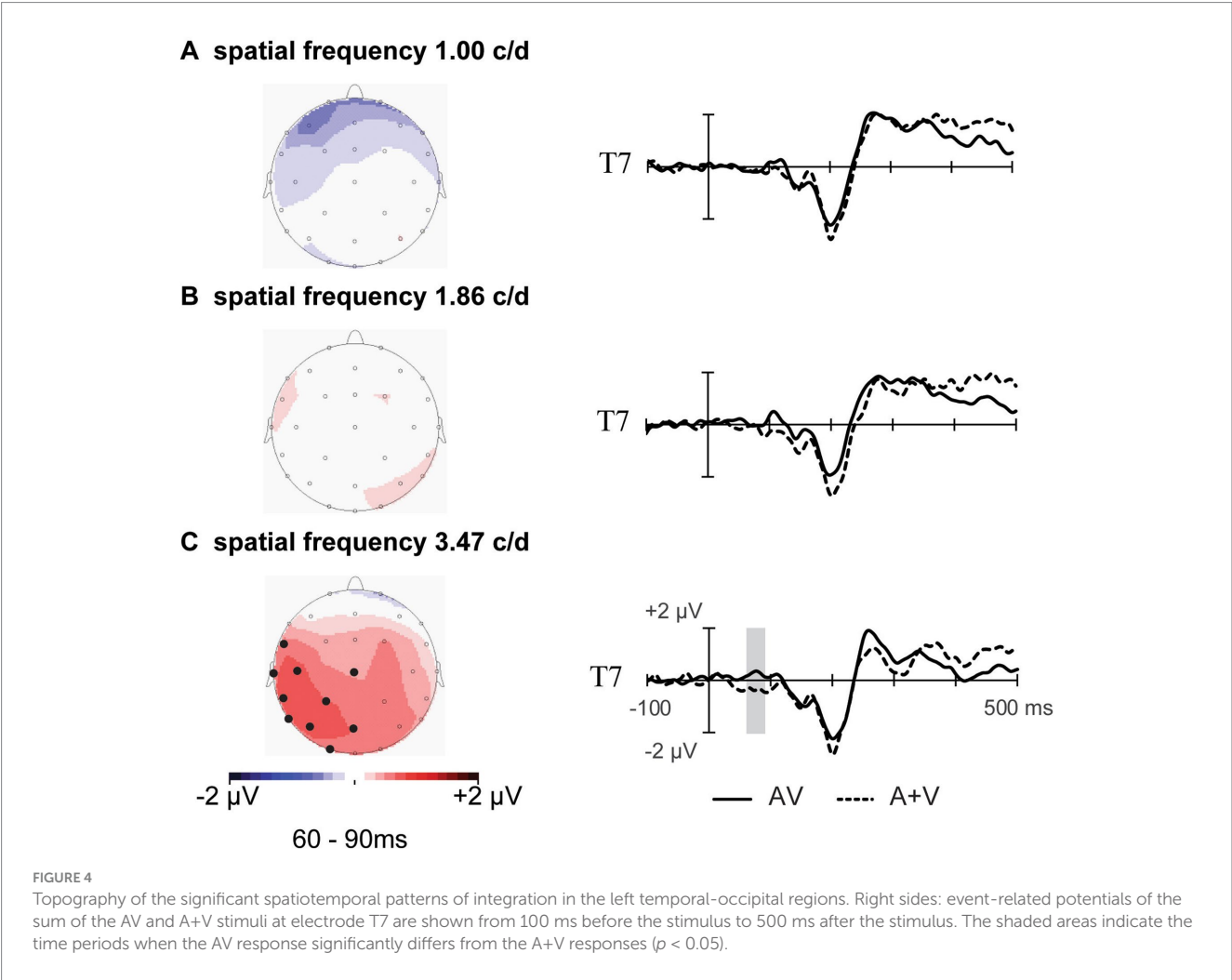
3.2.2 Audiovisual integration for 230–320 ms

The ERPs and topography maps within the 230–320 ms window are shown in Figure 5. The onset time and duration of audiovisual integration differed significantly across the three SF conditions in frontal and fronto-central regions. Separate three-way ANOVA (2 stimuli type (AV and A+V) * 6 ROI (frontal, fronto-central, temporal, central, parietal, and occipital) * 2 electrode (left and right)) was carried out for each condition using average ERP amplitudes. For SF 1.00 c/d, audiovisual integration occurred within 230–260 ms. ANOVA revealed a significant main effect of ROI [$F(5, 60) = 7.40$, $p = 0.009$, $\eta_p^2 = 0.381$] and a significant ROI * stimuli type interaction [$F(5, 60) = 7.80$, $p = 0.003$, $\eta_p^2 = 0.374$]. Post-hoc analyses showed a larger amplitude for AV than for A+V in frontal ($p = 0.004$) and fronto-central ($p = 0.027$) regions. For SF 1.86 c/d, audiovisual integration was observed in 230–320 ms, with a significant main effect of ROI [$F(5, 60) = 7.44$, $p = 0.010$, $\eta_p^2 = 0.383$] and a significant ROI * stimuli type interaction [$F(5, 60) = 11.32$, $p = 0.001$, $\eta_p^2 = 0.485$]. Post-hoc tests indicated significant audiovisual integration in frontal ($p = 0.003$), fronto-central ($p = 0.006$), and temporal regions ($p = 0.015$). For SF 3.47 c/d, audiovisual integration occurred later, within 260–320 ms, showing a significant main effect of ROI [$F(5, 60) = 14.12$,

TABLE 1 Mean behavioral data for all participants in the experiment.

Stimulus types	Response times (ms)	Hit rates (%)	False alarm rates (%)	d'	c
V1.00	533.6 ± 14.52	95.3 ± 1.14	0.71 ± 0.14	4.31 ± 0.15	0.36 ± 0.07
V1.86	542.9 ± 16.41	92.6 ± 1.86	1.04 ± 0.26	4.01 ± 0.17	0.39 ± 0.08
V3.47	581.6 ± 18.93	78.9 ± 4.61	0.67 ± 0.23	3.53 ± 0.18	0.76 ± 0.12
AV1.00	508.1 ± 15.77	95.6 ± 1.44	1.04 ± 0.22	4.29 ± 0.15	0.29 ± 0.08
AV1.86	497.1 ± 11.51	95.0 ± 1.21	1.47 ± 0.36	4.05 ± 0.14	0.26 ± 0.07
AV3.47	580.1 ± 17.73	84.8 ± 3.67	0.66 ± 0.22	3.73 ± 0.18	0.65 ± 0.09

Data are presented as the mean ± standard error of the mean (SEM). V, visual stimulus; AV, audiovisual stimulus.



$p = 0.001$, $\eta_p^2 = 0.541$] and a significant ROI*stimuli type interaction [$F(5, 60) = 9.20$, $p = 0.001$, $\eta_p^2 = 0.434$]. Post-hoc analyses confirmed audiovisual integration in frontal ($p = 0.013$) and fronto-central ($p = 0.041$) regions. This finding is of particular interest because it shows that the effects of higher SF stimuli on audiovisual integration processes can occur later.

3.2.3 Audiovisual integration for 350–380 ms

The ERPs and topography maps within the 350–380 ms window are shown in Figure 6. For SF 1.00 c/d, ANOVA revealed a significant main effect of stimuli type [$F(1, 12) = 7.45$, $p = 0.018$, $\eta_p^2 = 0.383$] and

ROI [$F(5, 60) = 12.86$, $p = 0.002$, $\eta_p^2 = 0.517$]. Post-hoc comparisons showed significantly smaller amplitudes for AV than for A+V stimuli in central ($p = 0.038$), parietal ($p = 0.004$), and occipital ($p = 0.005$) regions. In addition, a significant stimuli type* ROI *electrode interaction was observed [$F(5, 60) = 4.68$, $p = 0.004$, $\eta_p^2 = 0.281$], with post-hoc tests revealing audiovisual integration at electrodes C3, P3, P4, O1, O2, and T8 (all $p < 0.05$). For SF 1.86 c/d, ANOVA revealed a significant main effect of ROI [$F(5, 60) = 12.67$, $p = 0.001$, $\eta_p^2 = 0.513$] and a significant ROI * electrode interaction [$F(5, 60) = 3.27$, $p = 0.046$, $\eta_p^2 = 0.214$]. Post-hoc analyses showed larger amplitudes in right electrodes than in left electrodes in parietal

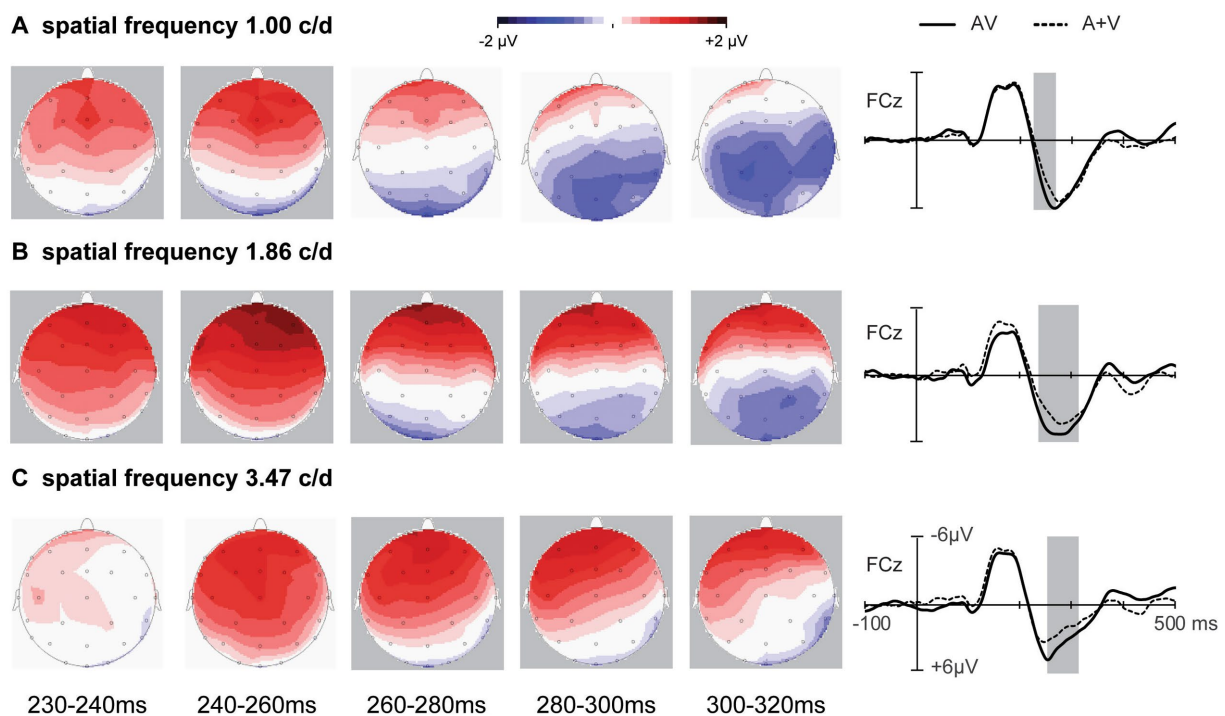


FIGURE 5

Topography of the different significant spatiotemporal patterns of integration in the fronto-central regions. Right sides: event-related potentials of the sum of the AV and A+V stimuli at electrode FCz are shown from 100 ms before the stimulus to 500 ms after the stimulus. The shaded areas indicate the time periods when the AV response significantly differs from the A+V responses ($p < 0.05$).

(3.69 μ V vs. 5.13 μ V, $p = 0.050$) and occipital (3.93 μ V vs. 4.70 μ V, $p = 0.015$) regions. Furthermore, a significant ROI * stimuli type interaction was also observed [$F(5, 60) = 5.16$, $p = 0.011$, $\eta_p^2 = 0.301$], with AV amplitudes smaller than A+V amplitudes in parietal ($p = 0.039$) and occipital ($p = 0.011$) regions. However, there was no significant main effect of stimuli type or stimuli type * ROI interaction for SF 3.47 c/d (all $p > 0.05$), with only a significant main effect of ROI [$F(5, 60) = 12.98$, $p = 0.001$, $\eta_p^2 = 0.520$] and ROI * electrode interaction [$F(5, 60) = 4.11$, $p = 0.023$, $\eta_p^2 = 0.255$]. Post-hoc tests confirmed larger amplitudes in right electrodes than in left electrodes in parietal ($p = 0.019$) and occipital ($p = 0.009$) regions. These results indicate that audiovisual integration over parieto-occipital regions is decreased with increasing visual SF.

4 Discussion

In the present study, we aimed to investigate the neural mechanism by which visual SF modulates audiovisual integration using a visual orientation discrimination task. Our results clearly revealed that SF influences audiovisual integration and that different patterns of SF modulation occur in the early perceptual and late cognitive stages.

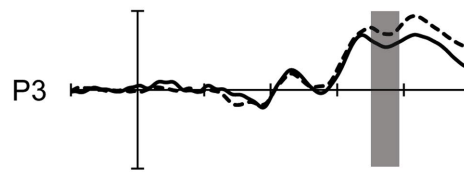
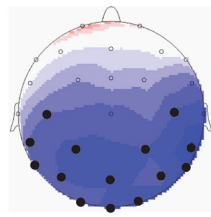
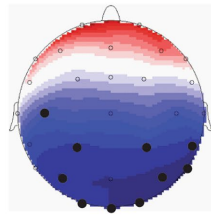
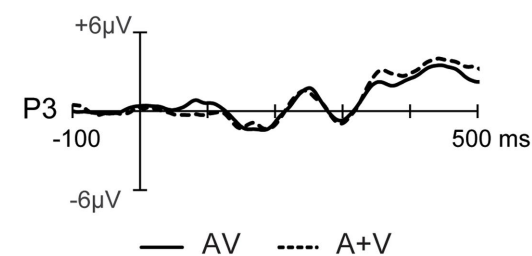
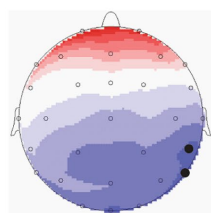
4.1 SF modulates audiovisual integration in a visual orientation discrimination task

At the behavioral level, our results showed that responses to audiovisual stimuli were faster and more accurate than responses to

visual stimuli, suggesting that the presence of a synchronous auditory stimulus facilitates visual orientation discrimination (Busse et al., 2005; Frassinetti et al., 2002; Li et al., 2015; Lippert et al., 2007). This facilitating effect on RTs significantly increased as the SF increased from 1.00 to 1.86 c/d, whereas it disappeared at 3.47 c/d. It seems that part of the attention necessary for cross-modal processing (Busse et al., 2005; Donohue et al., 2011) shifted to identify visual orientation as the SF increased, resulting in the disappearance of audiovisual facilitation. This explanation is consistent with sensitivity (d') results, which decreased with increasing SF for both audiovisual and visual stimuli (1.00 > 1.86 > 3.47, all $p < 0.05$), suggesting that the participants' orientation discrimination ability decreased as the SF increased from 1.00 to 3.47 c/d (Musselwhite and Jeffreys, 1985; Pérez-Bellido et al., 2013). However, the facilitating effect was significantly higher with increasing SF in d' . This observation is in line with those of previous studies (Bolognini et al., 2010; Corneil et al., 2002; Noesselt et al., 2010), which demonstrated an inverse relationship between audiovisual benefits and stimulus intensity. In addition, behavioral results revealed that there may be differences in the effects of SFs on audiovisual integration during different stages.

4.2 Audiovisual integration at the early sensory stage

As shown in Figures 2, 3, our results revealed that audiovisual integration occurred as early as 60–90 ms over temporal-occipital regions. This early latency was in line with previous studies that reported low-level sensory interactions, which are considered the

A spatial frequency 1.00 c/d**B spatial frequency 1.86 c/d****C spatial frequency 3.47 c/d**

350 - 380 ms

FIGURE 6

Topography of the different significant spatiotemporal patterns of integration in the parieto-occipital regions. Right sides: event-related potentials of the sum of the AV and A+V stimuli at electrode P3 are shown from 100 ms before the stimulus to 500 ms after the stimulus. The shaded areas indicate the time periods when the AV response significantly differs from the A+V responses ($p < 0.05$).

earliest stage of multisensory processing within 100-ms post-stimulus onset, allowing the brain to automatically select and encode external inputs that can facilitate simultaneous stimulus encoding (Cappe et al., 2010; Giard and Peronnet, 1999; Meo et al., 2015; Molholm et al., 2002; Senkowski et al., 2011; Talsma et al., 2007; Van der Burg et al., 2011). Therefore, the task-irrelevant auditory stimulus in the present study can interact with the simultaneous visual stimulus during the early visual sensory processing stage, thereby enhancing the perceptual salience of the visual stimulus. Importantly, our results revealed a left lateralization effect over temporal-occipital regions. Some studies have reported ERPs similar to the left lateralization effect over posterior regions under visual or auditory selective attention (Starke et al., 2017; Van der Burg et al., 2011). For example, in the study by Van der Burg et al. (2011), participants were asked to perform a visual search task to investigate early audiovisual stimuli and were required to report the orientation of the target visual stimulus that was present or not present with the auditory stimulus (Van der Burg et al., 2011). Their results revealed early audiovisual integration at 50–60 ms over the left parieto-occipital region. Furthermore, Starke et al. (2017) used combined functional magnetic resonance imaging and EEG methods to investigate the neural basis of the visually induced enhancement of auditory detection via auditory detection tasks (Starke et al., 2017). They reported that visual-induced auditory enhancement involved left lateralization for

low-intensity sounds over the superior temporal sulcus. However, Senkowski et al. (2011) reported that even if attention is directed to both modalities simultaneously, the left lateralization effect occurs during the earliest integration (Senkowski et al., 2011). Their results revealed an ERP component at 40–60 ms over the left posterior and right anterior regions for the low-intensity condition. Therefore, both attention and stimulus intensity may influence early audiovisual stimuli integration over occipital-temporal regions, and further electrophysiological studies are required to investigate this observation in detail.

Notably, the earliest audiovisual integration was found in the 3.47 c/d condition but was absent in the 1.00 and 1.86 c/d conditions (Figure 4). This phenomenon may be related to the intensity of the visual stimulus; a high-SF visual signal tends to be perceived as having a lower intensity than low-SF visual signals when contrast is constant (Georgeson and Sullivan, 1975). Our behavioral results confirmed this finding, showing that visual perceptual ability (d') decreased with increasing SF from 1.00 c/d to 3.47 c/d (Table 1). Some studies have shown that stimulus intensity can modulate audiovisual integration (Fort et al., 2002; Senkowski et al., 2011; Stevenson and James, 2009). For instance, Fort et al. (2002) manipulated the orientation of visual stimuli (horizontal and vertical) and frequency of sounds (540 Hz and 560 Hz with a low intensity of 50 dB) to investigate the neural mechanism of audiovisual integration in simple detection tasks (Fort

et al., 2002). Their results revealed that early integration occurred at 45–85 ms over the occipital-parietal regions when their participants were presented with a low-intensity auditory stimulus. Furthermore, Senkowski et al. (2011) manipulated the intensity of auditory, visual, and audiovisual stimuli of low, middle, and high levels to investigate the effects of stimulus intensity on multisensory audiovisual processing. Their results also revealed an early audiovisual interaction (40–60 ms), showing that the integration effect occurred particularly for low-intensity inputs but not for stimuli with middle and high intensities. Overall, in these studies, the earliest integration occurred when at least one of the presented input modalities (auditory and/or visual) was relatively low in stimulus intensity, which follows the principle of inverse effectiveness. Therefore, we speculated that a high-SF-evoked audiovisual integration at the early sensory stage was dependent on stimulus intensity. However, in the present study, only SFs ranging from 1.00 to 3.47 c/d were presented; thus, our study does not allow us to draw conclusions about how high an SF needs to be to evoke an early integration effect. Further electrophysiological studies are needed to elucidate the neural mechanisms of integration under more detailed visual SF conditions.

4.3 Audiovisual integration at the late cognitive stage

Audiovisual integration was significantly delayed with increased SFs over the frontal and fronto-central regions (Figure 5). Audiovisual integration was observed at 230–260 ms, 230–320 ms, and 260–320 ms at 1.00 c/d, 1.86 c/d, and 3.47 c/d, respectively. This phenomenon may be related to the two visual processing pathways of the dorsal and ventral streams (Fang and He, 2005; Haxby et al., 1991). A visual stimulus with low-SF information is primarily processed through the dorsal stream, which responds relatively faster, whereas high-SF information is projected chiefly to the ventral stream, with fine resolution but slow responses (Parker, 1980; Tootell and Nasr, 2017; Zhang et al., 2015). Consistent with our findings, previous behavioral investigations revealed that audiovisual integration occurs through both the dorsal and ventral pathways by processing low SFs (Jaekl and Soto-Paraco, 2010) and high SFs (Jaekl and Harris, 2009), respectively. Thus, audiovisual stimuli of 1.00 c/d allow the stimulus to reach high-order areas rapidly, primarily via the dorsal visual stream, and integrate with the auditory stimulus, whereas audiovisual stimuli of 3.47 c/d require more time to reach high-order areas, primarily via the ventral visual stream, and integrate with the auditory stimulus, resulting in delayed audiovisual integration. Importantly, no stimulus is processed exclusively through the ventral or the dorsal pathway. Both visual and auditory stimuli have been shown to be processed in parallel processing streams (Merigan and Maunsell, 1993; Nassi and Callaway, 2009). This parallel processing has subsequently been confirmed in audiovisual integration (Ahveninen et al., 2016; Kaposvári et al., 2015). Therefore, audiovisual stimuli of 1.86 c/d allow parallel processing in two pathways, leading to a wider integration time interval (230–320 ms), which combines 1.00 c/d with 3.47 c/d. Overall, we speculate that integration over frontal and fronto-central regions was influenced by the visual processing pathway and that a high SF delayed audiovisual integration.

In addition, our results revealed another instance of audiovisual integration at 350–380 ms over the parietal and occipital regions. Similar to our observations, audiovisual integration activity over the parietal and occipital regions has also been reported in some previous

studies in which participants were asked to perform visual-direction-related tasks (Kayser et al., 2017; Yang et al., 2013). Yang et al. (2013), using the same visual orientation discrimination task to investigate the influence of sound location on audiovisual integration, reported significant integration in the parietal and occipital regions at 360–400 ms (Yang et al., 2013). More recently, Kayser et al. (2017) used the visual motion direction discrimination task and reported that sound facilitates visual motion discrimination by enhancing occipital visual representations at approximately 350 ms after stimulus onset. However, integration in these regions was absent for 3.47 c/d. This absence may be related to visual perceptual load, which has been elucidated to significantly influence audiovisual processing (De Nier et al., 2016; Macdonald and Lavie, 2011). Macdonald and Lavie (2011) reported that participants were less able to notice the presence of a simple auditory tone in the last trial while they were performing a high-visual-load task than when they were performing a low-visual-load task. Furthermore, Gibney et al. (2017) provided further evidence for the effect of visual perceptual load on audiovisual integration using audiovisual speed detection tasks via dual-task paradigms. Their results revealed that audiovisual integration occurred under no and low perceptual load conditions but was absent under high perceptual load conditions. Indeed, in the present study, discriminating visual orientation with under the 3.47 c/d condition was the most difficult task (Musselwhite and Jeffreys, 1985; Pérez-Bellido et al., 2013), and participants needed to pay more attention to this orientation, which was also necessary for cross-modal audiovisual processing to identify the orientation (Busse et al., 2005; Donohue et al., 2011), resulting in the absence of audiovisual integration. Specifically, our results revealed that the activity in the parietal and occipital regions was particularly relevant to the enhancement of behavioral performance (the absence of audiovisual benefits in RTs). It was previously noted that the activity over the parietal and occipital regions results in task-relevant representations. Therefore, we speculated that modulations in the parietal and occipital regions may be dependent on feedback from higher association areas, which guide audiovisual influences based on task requirements.

5 Conclusion

In summary, the present study investigated the neural mechanism by which visual SFs modulate audiovisual integration during a visual orientation discrimination task. Our results showed that the modulatory effect in the brain was a dynamic process. In the early sensory stage (60–90 ms), audiovisual integration occurred in temporal-occipital regions as the SF increased, which may reflect an automatic, bottom-up intersensory mechanism that can increase perception depending on stimulus intensity. In the late cognitive stage, audiovisual integration was delayed (230–320 ms) over fronto-central regions and attenuated (350–380 ms) over parieto-occipital regions with increasing SFs, which may reflect a top-down mechanism that is influenced by the signal processing pathway and task requirements. Taken together, our findings can be useful for further studies that investigate the integration of complex stimuli, especially emotional and semantic integration.

Data availability statement

The datasets and materials generated during the current study are available from the corresponding author upon reasonable request.

Ethics statement

The studies involving humans were approved by Ethics Committee of Okayama University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FW: Visualization, Formal analysis, Funding acquisition, Data curation, Validation, Resources, Writing – review & editing, Methodology, Writing – original draft, Conceptualization. YR: Writing – review & editing, Formal analysis. TH: Software, Writing – original draft. JinY: Methodology, Writing – original draft. QW: Methodology, Writing – original draft. JiaY: Data curation, Writing – original draft. MW: Writing – original draft, Methodology, Supervision, Writing – review & editing.

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Neural basis of self-esteem: social cognitive and emotional regulation insights

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Introduction: Self-esteem (SE) can significantly affect individual well-being and has been linked to various psychiatric conditions. SE involves cognitive and emotional regulation within a social context. Prior research focusing on young adults has indicated neural correlations in prefrontal cortex areas but presented inconsistent findings. Our study expanded this to a broader age range and covariates, and examined the influence of subthreshold depression, emphasizing the functional role of the dorsolateral (dlPFC), ventrolateral prefrontal cortices (vlPFC) and cerebellum in social cognition and emotional regulation of social exclusion.

Methods: We conducted resting-state functional magnetic resonance imaging analyses on 114 participants to investigate the neural correlates of self-esteem.

Results: We found that high SE correlated with robust functional connectivity between the left dlPFC and posterior cerebellum. Associations between the left dlPFC and right lingual gyrus, the right vlPFC and insula were FDR-survived, along with diminished connectivity between the left vlPFC, angular gyri, and thalamus.

Discussion: These results not only support our hypothesis regarding the dual role of SE—which includes its social cognitive role in avoiding social exclusion and its emotional resilience in enduring such exclusion—but also suggest a potential link with rumination.

KEYWORDS

self-esteem, resting state functional magnetic resonance imaging, cerebellum, dorsolateral prefrontal cortices, ventrolateral prefrontal cortices

1 Introduction

Global self-esteem (SE), subjective appraisal of self-worth or value (Tafarodi and Swann, 1995) profoundly influences our patterns of social interactions, decision-making processes and social capabilities and mental well-being (Baumeister et al., 2003; Kuster et al., 2013). Recent meta-analysis strengthen the significance of high SE for adaptive social behaviors and mental health (Orth and Robins, 2022). In contrast, insufficient SE is implicated in a multitude of psychiatric conditions or symptoms, such as anxiety (Rosenberg and Owens, 2009; Sowislo and Orth, 2013; Nguyen et al., 2019), eating disorders (Heatherton and Baumeister, 1991; Pelc et al., 2023), self-stigma, suicide (Corrigan et al., 2009; Oexle et al., 2017), and depression (Cheng and Furnham, 2003; Orth and Robins, 2013; Huang, 2021). From a neuroscientific perspective, these psychological phenomena suggest some underlying neural frameworks that SE may modulate, thus warranting the importance of exploration of associated neural mechanisms.

The complex etiology of SE has led to the development of various hypotheses. One influential perspective is the social-cognitive aspect, which highlights how we evaluate ourselves within social contexts. Leary et al. proposed the sociometer theory (Leary et al., 1995a,b), in which SE plays as a psychological “sociometer” or gauge that monitors the risk of social exclusion. A decrease in SE can indicate a potential disruption in social relationships, promoting actions in individuals to avoid social pain or rejection. Conversely, people with high SE are resilient against negative self-related emotions arising from social rejection and reputational concerns. Specifically, individuals with high SE can effectively maintain self-worth and a positive self-image despite experiencing social rejection or failure (Brown and Marshall, 2001).

These contrasting characteristics of SE raised the following important question: “How can brain reconcile SE’s role as a guardian of social inclusion with its ability to mitigate the emotional impact of social setbacks?” From a neurobiological standpoint, social exclusion and inclusion signals may involve neural circuits in prefrontal area. Especially dorsolateral prefrontal cortex (dlPFC) and ventrolateral prefrontal cortex (vlPFC) could be key neural substrates in emotion regulation and responses to social exclusions, because studies have highlighted the involvement of the dlPFC with distraction strategies and the vlPFC in reappraisal strategies during social pain regulation and modulating emotional responses to social exclusion (He et al., 2018; Zhao et al., 2021). Cerebellar regions are also candidates of SE neural basis associated with social cognition (crus 1) and emotional regulation (crus 2) (Sokolov, 2018; Van Overwalle et al., 2020a), and cortico-cerebellar circuit is reported to be altered in people with social anxiety disorder (Zhang et al., 2022), which also validate our focus on the cerebellum. Although regions such as the amygdala and cingulate cortex also contribute to emotional processing, we focused on the PFC regions for their direct involvement in higher-order self-evaluation and regulatory mechanisms central to SE. So as the neural basis of sociometer theory and social setback buffer of SE, we hypothesized dlPFC and cerebellum’s activity mediates social and emotional monitoring.

Neuroimaging research was conducted to clarify the relationship between SE and brain structure and function. Previous voxel-based morphometry (VBM) studies reported a positive correlation between SE and regional volume in areas linked to adaptive stress responses (McEwen and Gianaros, 2010;

Agroskin et al., 2014). According to these studies, individuals with lower SE showed decreased gray matter volume in these areas, possibly suggesting difficulties in emotional self-regulation during stress.

Several task-based functional magnetic resonance imaging (fMRI) studies identified increased activity in the medial prefrontal cortex (mPFC), which was correlated with higher SE during self-related social feedback (van der Meer et al., 2010; Chavez and Heatherton, 2015; Yang et al., 2016). Further, two studies reported correlations between SE and activity in the prefrontal cortices of young participants using fractional amplitude of low-frequency fluctuations and resting-state fMRI (rsfMRI) (Pan et al., 2016; Chen et al., 2021). However, the regions of interest and results were inconsistent across studies; one found correlations in the ventromedial prefrontal cortex whereas the other in the right dorsolateral prefrontal cortex (dlPFC).

The inconsistent findings from rsfMRI studies in the PFC and the unexplored influence of age and subthreshold depression on SE require closer attention. Therefore, the present study aimed to bridge these knowledge gaps and provide a clearer understanding of the neural substrates underlying SE.

To explore the neural basis of SE, this study incorporated two important perspectives. First, SE fluctuates and develops across age due to cumulative life events (Erol and Orth, 2011). Thus, a broader age range should be included and covariates to understand SE-related brain connectivity without specific age-range effect (like connectivity trait in adolescent SE). Second, subthreshold depression, which is characterized by mild depressive symptoms that do not meet full diagnostic criteria (Pincus et al., 1999), is frequently associated with lower SE and altered neural functioning. Global SE, measured with the Rosenberg Self-Esteem Scale (RSES), is generally considered a relatively stable trait in healthy individuals (Donnellan et al., 2012). However, previous research reported a correlation between depressive symptoms in healthy participants and SE; for example, in individuals with a negative self-image (interpreted as individuals with lower SE) exhibited depressive symptoms but were not diagnosed with depression (Savilahti et al., 2018). Similarly, SE was found to correlate with depression scales even in healthy participants (Nguyen et al., 2019; Jafari et al., 2021). In a VBM study, similar changes in depression scales were found in individuals with subthreshold depression (Li et al., 2017), while functional changes in the prefrontal regions, such as the right orbitofrontal cortex (OFC) and left dlPFC (Ma Q. et al., 2013; Ma Z. et al., 2013; Wu et al., 2025), along with changes in large-scale networks (Hwang et al., 2015), were also reported in older individuals with subthreshold depression. Overall, these findings highlight the need to exclude the effects of subthreshold depression in a study on the neural basis of SE. However, to the best of our knowledge, SE fMRI studies considering subthreshold depression have not yet been conducted.

Given these theoretical and empirical backgrounds, the present study aimed to elucidate how individual differences in SE are associated with resting-state functional connectivity (rsFC) within networks including prefrontal areas, controlling for age, sex, and subthreshold depressive symptoms. We hypothesized that higher SE would correlate with increased functional connectivity between prefrontal regions (particularly dlPFC and vlPFC) and cerebellar regions involved in social cognition and emotional regulation, reflecting more efficient neural integration supporting positive self-evaluation and emotional resilience.

2 Materials and methods

2.1 Participants

Overall, 128 healthy adults (mean age = 29.07, 82 males), recruited through advertisements and personal contact, underwent mental health screening by experienced psychiatrists using the Structured Clinical Interview for DSM-IV Disorders (SCID-IV-TR). The exclusion criteria were 1. psychiatric disorders or severe medical or neurological illnesses, 2. claustrophobia or any other reason for unavailability of MRI scan, 3. Abnormal brain structures such as arachnoid cysts and cavum vergae, 4. Incomplete psychological scale, and 5. excessive head motion during scans (details in 2.5 image preprocessing section). After exclusions (see 3.1 Demographic information), 114 participants remained. All participants provided written informed consent. This study was approved by the Ethics Committee of the Faculty of Medicine, Kyoto University Graduate School, and was performed in accordance with the tenets of the Declaration of Helsinki.

2.2 Psychological questionnaires

The RSES (Rosenberg, 1965), which measures global SE, encompasses 10 items, each with a 4-point Likert scale, yielding a total score between 10 and 40. Higher scores indicate higher SE. The validated Japanese version was used for the study (Mimura and Griffiths, 2007; Uchida and Ueno, 2010). The internal consistency (Cronbach's alpha) is = 0.81.

The Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) is a 21-item scale that assesses the severity of depressive states. Scores range from 0 to 63, with higher scores denoting more severe depressive tendencies. The Japanese version has been previously validated and exhibits internal consistency (alpha = 0.87) (Kojima et al., 2002).

2.3 Statistical analyses

We performed statistical analyses using SPSS Statistics (version 26.0; IBM, Armonk, NY). Bivariate correlations among key variables (gender, age, SE, depression symptoms, and head motion) were calculated. Spearman's rank correlation was used for correlation analysis. The correlation was considered statistically significant at $p < 0.05$. Seed-to-voxel FC analysis were conducted to search for the FC correlating SE, using General Linear Model (GLM), with BDI-II scores, age, and gender as covariates. We did not use framewise displacement (FD) as covariates because in the ART-scrubbing procedure FD threshold was set on 0.5 mm and identified and regressed out high-motion frames based on FD values (see 2.5 preprocessing), and subjects with large movement is excluded from the analysis. Therefore, additional inclusion of mean FD as a covariate in FC analyses was considered redundant and not applied. Statistical significance was set as following: an initial voxel-level threshold was set at $p < 0.001$ (uncorrected), followed by a cluster-level threshold corrected using false discovery rate (FDR) at $p < 0.05$. Additionally, a Bonferroni corrected threshold was set at $p < 0.0041$, for multiple comparisons for the 12 ROIs, so it means that results surviving

Bonferroni correction ($p < 0.0041$) are considered statistically robust, while result significant only after FDR are exploratory.

2.4 Neuroimaging acquisition

MRI was performed using a 3-T MRI scanner (Tim-Trio; Siemens, Erlangen, Germany) with a 40-mT/m gradient and a receiver-only 32-channel phased-array head coil. To acquire a 360-s (6-min) rsfMRI scan, a single-shot gradient-echo planar imaging (EPI) pulse sequence was used. The participants were instructed to look at a fixation cross in the center of the screen and avoid thinking about anything during the resting-state data acquisition. Head movement was minimized by placing rubber pads within the head coil. For B0 field-mapping distortion correction, a dual-gradient echo dataset was also acquired. Magnetization-prepared rapid gradient-echo (MPRAGE) sequences were used to acquire T1-weighted three-dimensional structural images. Data were excluded from the analysis if structural abnormalities, such as arachnoid cysts or cavum vergae, were detected.

The parameters used were as follows: MPRAGE: echo time (TE), 3.4 ms; repetition time (TR), 2,000 ms; inversion time, 990 ms; field of view (FOV), 225×240 mm; matrix size, 240×256 ; resolution, $0.9375 \times 0.9375 \times 1.0$ mm³; and 208 total axial sections without intersection gaps; rsfMRI: TE, 30 ms; TR, 2,500 ms; flip angle, 80°; FOV, 212×212 mm; matrix size, 64×64 ; in-plane spatial resolution, 3.3125×3.3125 mm²; 40 total axial slices; slice thickness, 3.2 mm with 0.8-mm gaps in ascending order.

2.5 Image preprocessing

To rectify EPI distortions in the rsfMRI dataset, FMRIB's Utility for Geometrically Unwarping EPIs was employed, a component of the FSL software suite (FMRIB's software library version 5.0.9). This process included alignment adjustments using FMRIB's Linear Image Registration Tool (FLIRT). We removed artifactual components and movement-related fluctuations using the FMRIB ICA-based x-noiser (Griffanti et al., 2014). FD was calculated to assess head motion during rsfMRI (Power et al., 2012), using the ART-based scrubbing procedure implemented in CONN toolbox. The following two exclusion criteria were applied based on past rsfMRI studies: (exclusion criteria 5–1) when the count of scans showing a head position variance of 0.5 mm from neighboring scans surpassed 25% and (5–2) when the peak head motion exceeded 3.0 mm or a 3.0° angle (Nilsson et al., 2017; Zhang et al., 2015).

The CONN-fMRI Functional Connectivity toolbox (version 22.a) (Whitfield-Gabrieli and Nieto-Castanon, 2012), and the statistical parametric mapping software package SPM12 (Wellcome Trust Centre for Neuroimaging) were employed for the processing of the preprocessed rsfMRI and structural MRI data. Using a bespoke preprocessing pipeline of the CONN toolbox, all functional images were entailed with spatial normalization into the standard Montreal Neurological Institute (MNI) space, resampled to 2 mm isotropic voxels, underwent outlier detection through ART-based scrubbing, and were smoothed utilizing a Gaussian kernel having a full-width-at-half maximum of 8 mm. A standard preprocessing pipeline for volume-based analysis was used for all preprocessing steps. The same pipeline was used to segment and normalize the structural data into gray matter,

white matter (WM), and cerebrospinal fluid (CSF). The principal components of the WM and CSF signals, along with translational and rotational motion parameters (including six additional parameters signifying their first-order temporal derivatives) obtained from realignment using FLIRT, were eliminated using the CONN covariate regression analysis. Standard denoising pipeline was used to minimize the impact of confounding covariates, including the CompCor strategy (Behzadi et al., 2007), which extracted fluctuations in the rsfMRI signals originating from the WM and CSF, along with their derivatives, and noise stemming from realignment parameters. Additionally, bandpass filtering was executed. The frequency window was 0.008–0.09 Hz. This processing step resulted in an increase in retest reliability.

2.6 FC analysis

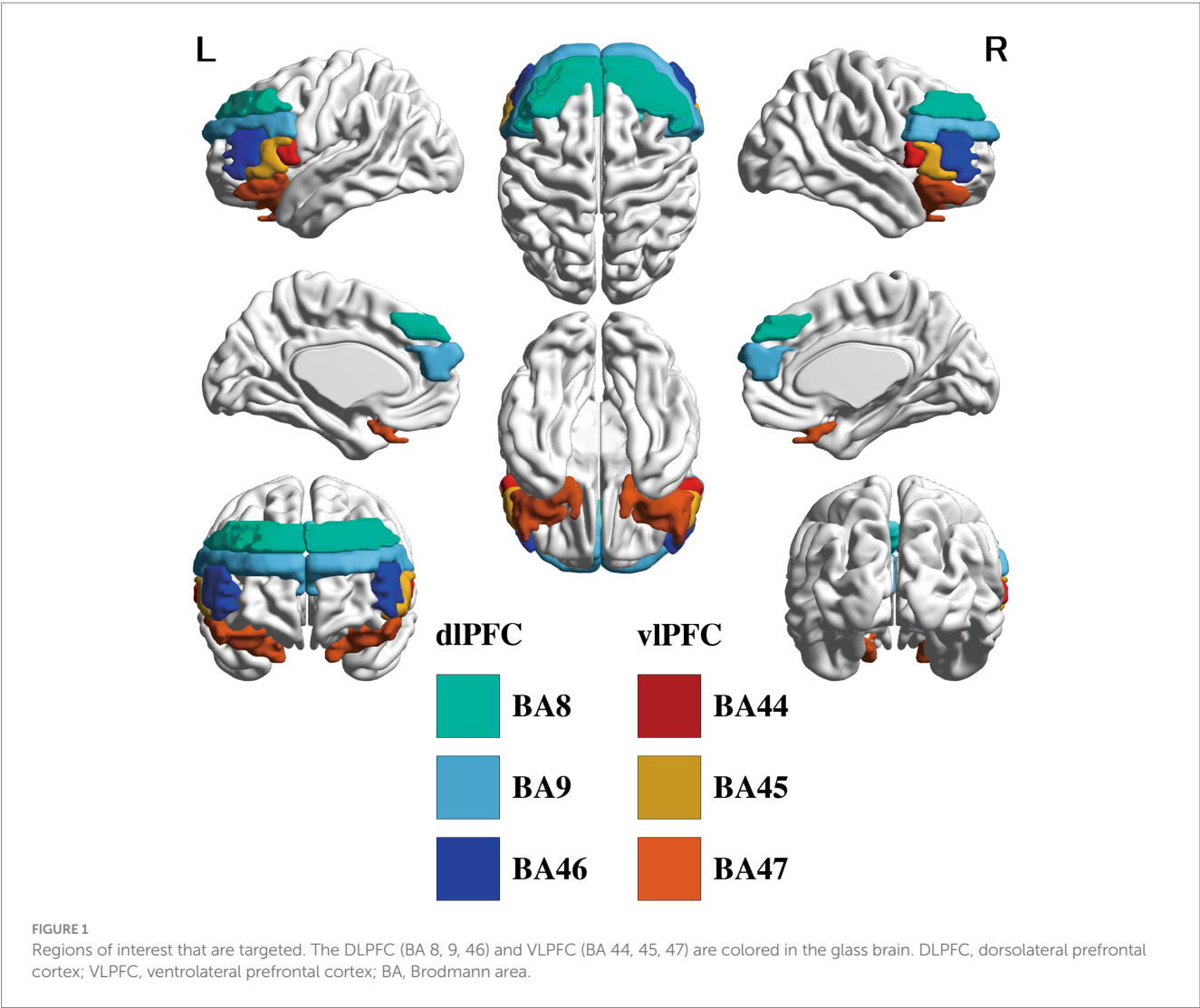
Seed-to-voxel rsFC analyses were conducted to examine FCs correlating with SE. The regions of interest (ROIs) were the dlPFC and vlPFC. We used the Brodmann area (BA) atlas to define these areas anatomically. Employing the BA atlas in CONN (path: util/otherrois/BA.img), which was transformed into the MNI space via a Lancaster

transformation from the Talairach atlas, we established seeds on bilateral BA 8 (frontal eye fields), 9 (dorsolateral and medial prefrontal cortex), and 46 (anterior middle frontal gyrus and middle frontal area) for the dlPFC (Sallet et al., 2013) and 44 (opercular part of inferior frontal gyrus: IFG), 45 (triangular part of IFG), and 47 (orbital part of IFG) for the vlPFC (Levy and Wagner, 2011), totaling 12 seeds for analysis (Figure 1). Based on the initial FC analysis results, we conducted a post-hoc seed-to-voxel analysis using cerebellar seeds (bilateral crus 1, 2, and lobule 6, which were included in the Bonferroni-survived cluster, and were reported regions to be involved in social or emotional recognition: Van Overwalle et al., 2020b) from the the Automated Anatomical Labeling atlas provided in CONN toolbox. This post-hoc analysis is to specify the functional meaning and region of the results of the main analysis.

3 Results

3.1 Demographic information

After completing all psychological tests and MRI examinations, 14 participants were excluded from the analysis. No participants were



excluded by the psychiatric diseases (criteria 1) and claustrophobia (criteria 2), but six participants had minor organic brain abnormalities (arachnoid cysts and cavum vergae; criteria 3), four of them did not fully answer the psychological tests(criteria 4), and MRI images of four participants had a maximum motion of more than 3 mm or 3°(criteria 5). Consequently, 114 participants' data were included in the analysis.

Their demographic data are summarized in [Table 1](#). The RSES seems low in average, but the score is not so different from the past research (e.g., [Schmitt and Allik, 2005](#)). Regarding the BDI-II scores, 16 participants had a score of 14 or more, which is the threshold for mild depression, as defined by Beck and the Japanese version of the BDI-II ([Hiroe et al., 2005](#)), indicating that these participants were considered healthy on the SCID-IV-TR but had values above the threshold for mild depression on the BDI-II. Their average of FD was 0.12 mm(SD = 0.05), which is in a normal range([Power et al., 2012](#)).

3.2 Analysis of psychological data

We conducted Spearman's correlations among age, gender, RSES scores, BDI-II scores, and mean FD. Significant correlations were observed between age and FD ($\rho = 0.24$, $p = 0.01$), indicating that older participants had more head motion. Additionally, BDI-II score was negatively correlated with the RSES score ($\rho = -0.45$, $p < 0.001$), suggesting that the participants with higher SE scores have lower depressive symptoms. There were no significant correlations between gender and other variables, nor between FD and psychological measures(all $p > 0.05$). The whole result is shown in [Supplementary Table 1](#).

3.3 Main result of functional connectivity related to SE

We performed a correlation analysis of the functional connectivity (FC) strength to explore the neural correlates of SE. We found four seeds (BA 8 left, BA 9 left, BA 44 left, and BA 45 right) that had statistically significant FC values correlating with RSES scores in seed-to-voxel analyses; however, significant correlations were observed only in the left BA 9 after correcting for multiple comparisons ([Table 2](#)).

The left BA 8 seed yielded a significant positive correlation with the RSES score in the rsFC with the right lingual gyrus (BA 18, 19) and right cerebellar lobule 6 ($p = 0.0061$) ([Figure 2](#)).

The FC strength between the left BA 9 and bilateral cerebellum was significantly positively correlated with the RSES scores (left: $p = 0.0008$, right: $p = 0.0209$) ([Figure 3](#)). Both clusters primarily covered crus 1 and 2 and lobule 6 of each cerebellar hemisphere. Cluster 1 on the left

cerebellum was the largest and was the only cluster that was significantly correlated after multiple corrections were applied. Notably, the right side of dlPFC showed no significant FC ([Table 2](#)).

The left BA 44 yielded four clusters ([Figure 4](#)). Three of them were located on the thalamus, brainstem, and both sides of the angular gyrus, which were negatively correlated with the RSES score, while the other one was located on the right frontal pole (BA 10) and was positively correlated with the RSES. The right BA 45 seed yielded a positive correlation with the RSES, including the right frontal orbital cortex (BA 47) and right insular cortex (BA 13) ([Figure 5](#)).

3.4 Post-hoc analysis to understand the part of significant FC, seeding on the cerebellum

We got the result on BA8 and 9 on the main analysis, but that seed is spatially widely spread from medial to lateral (see [Figure 1](#)).To understand which side of (medial or lateral) BA 8 and 9 had connectivity with the cerebellum and to consider the functional significance, we performed a post-hoc seed-to-voxel analysis with the cerebellar seeds (according to the result in BA8 and 9, we set the ROI in both side of Crus 1, 2, and lobule 6). Both sides of the cerebellum crus 1 had a significant connection with the lateral prefrontal area. The left cerebellum crus 1 yielded a cluster correlating with the RSES, including the frontal pole cortex (BA 10) and dlPFC (BA 9) ([Supplementary Figure S1](#)). The right side of crus 1 showed significant connectivity with both sides of the lateral anterior prefrontal area. The two clusters were both mainly included BA 9 and 10 ([Supplementary Figure S2](#)). The detailed results of clusters are shown in [Supplementary Table 2](#).

4 Discussion

4.1 Summary of main findings

This pioneering rsfMRI study probed the neural underpinnings of SE in 114 healthy adults, meticulously considering and covarying out the potential influence of age, sex, and depressive symptoms. These factors can subtly vary within a healthy population and could confound the interpretation of the FC between brain regions related to social cognition and emotional regulation.

Before discussing the main FC findings, our bivariate analyses revealed a negative correlation between the RSES and BDI-II scores, which underscores the close link between SE and depressive symptoms, even among non-clinical populations. This correlation aligns with previous research demonstrating that individuals with higher BDI-II scores harbor a more potent negative self-image, even without major depression ([Vaccaro et al., 2017](#)). Importantly, this result substantiates the validity of our decision to statistically control for depressive symptoms. Additionally, a negative correlation between age and mean FD was observed, consistent with the previous reports ([Hausman et al., 2022](#); [Kato et al., 2021](#)), further supporting covarying age in our rsfMRI analyses.

SE is postulated to relate closely to the sociometer theory, implicating brain regions responsible for social cognition and emotional regulation. Our findings support this hypothesis, particularly emphasizing the robust increase in FC between the left

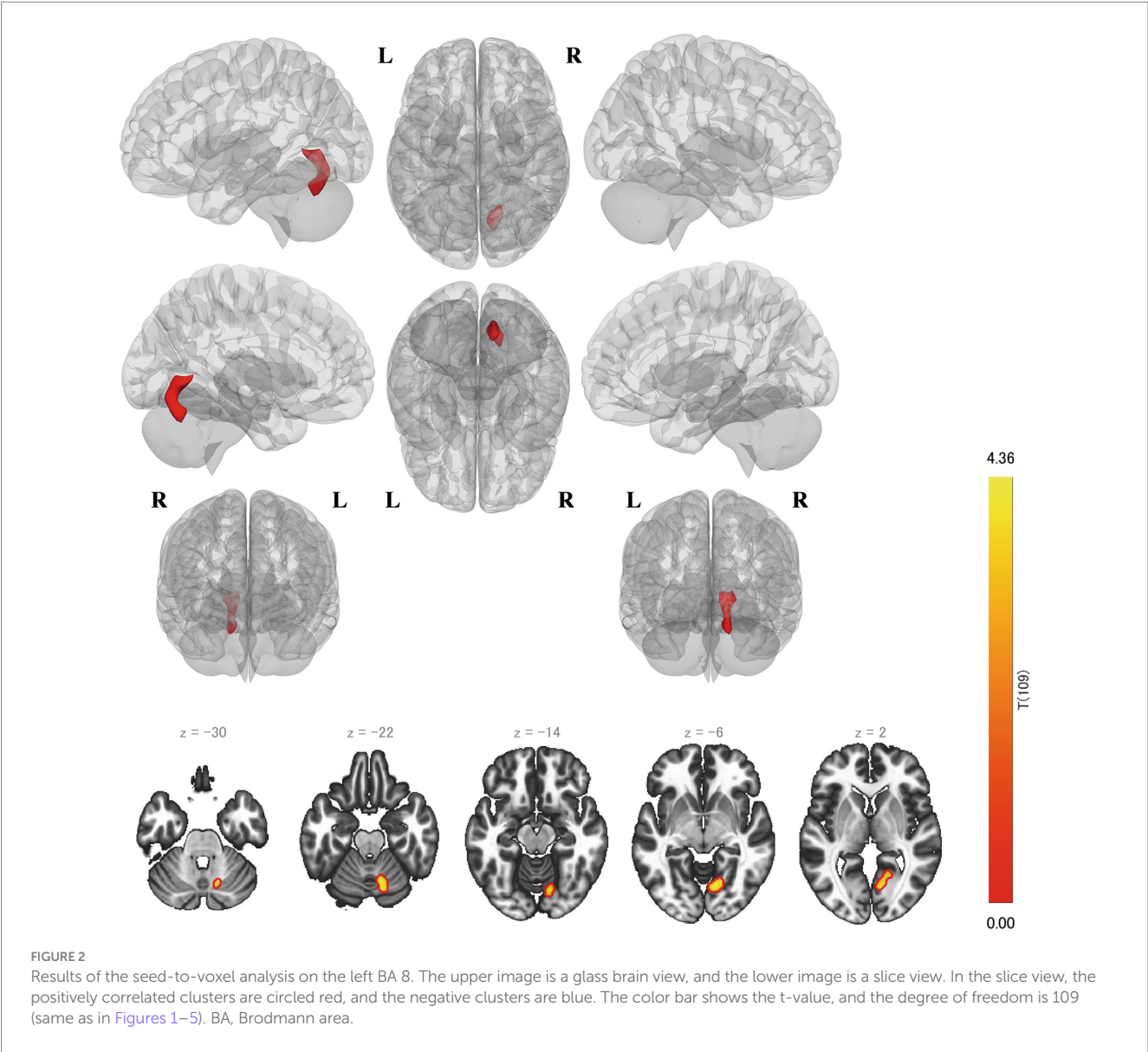
TABLE 1 Demographic and clinical characteristics.

Baseline characteristics	Mean $\pm$ SD
Mean age (in years)	29.66 $\pm$ 12.56
Sex (female/male)	42/72
Rosenberg's self-esteem scale (mean)	26.9 $\pm$ 4.7
Beck depression inventory - II (mean)	7.0 $\pm$ 6.7
Framewise displacement (mean)	0.12 $\pm$ 0.05

TABLE 2 Summary of seed-to-voxel analyses.

Seed	Anatomical location (BA) of cluster	L/R	Cluster MNI space, x,y,z	Cluster size	Size ρ (FDR-corrected)
BA8 left	Lingual gyrus (BA18,19) and cerebellum lobule 6	Right	+12, -62, -24	471	0.00605
BA9 left	Cerebellum crus I, II and lobule 6	Left	-22, -70, -30	634	0.000834*
	Cerebellum crus I, II, and lobule 6	Right	+18, -70, -26	322	0.0209
BA44 left	Thalamus and brain stem	Left	+12, -32, -04	365	0.0344
	Angular gyrus (BA40)	Left	-32, -74, +34	235	0.05
	Angular gyrus (BA40)	Right	+32, -54, +34	228	0.05
	Frontal pole (BA10)	Right	+26, +54, -14	305	0.0358
BA45 right	Frontal orbital cortex (BA47) and insular cortex (BA13)	Right	+40, +20, -10	396	0.0165

* Survived Bonferroni multiple comparison ($\rho < 0.0041$); the other clusters are only FDR-survived and exploratory results. BA, Brodmann area; FDR, false discovery rate, MNI, Montreal Neurological Institution.



dIPFC and the posterior cerebellum. This result survived strict multiple comparison corrections, and suggests a significant neural link potentially involved in the integration of social cognitive inputs and emotional processing with the cerebellum. In addition to this central finding, exploratory results indicated that enhanced FC between the left dIPFC and the lingual gyrus might reflect integrated

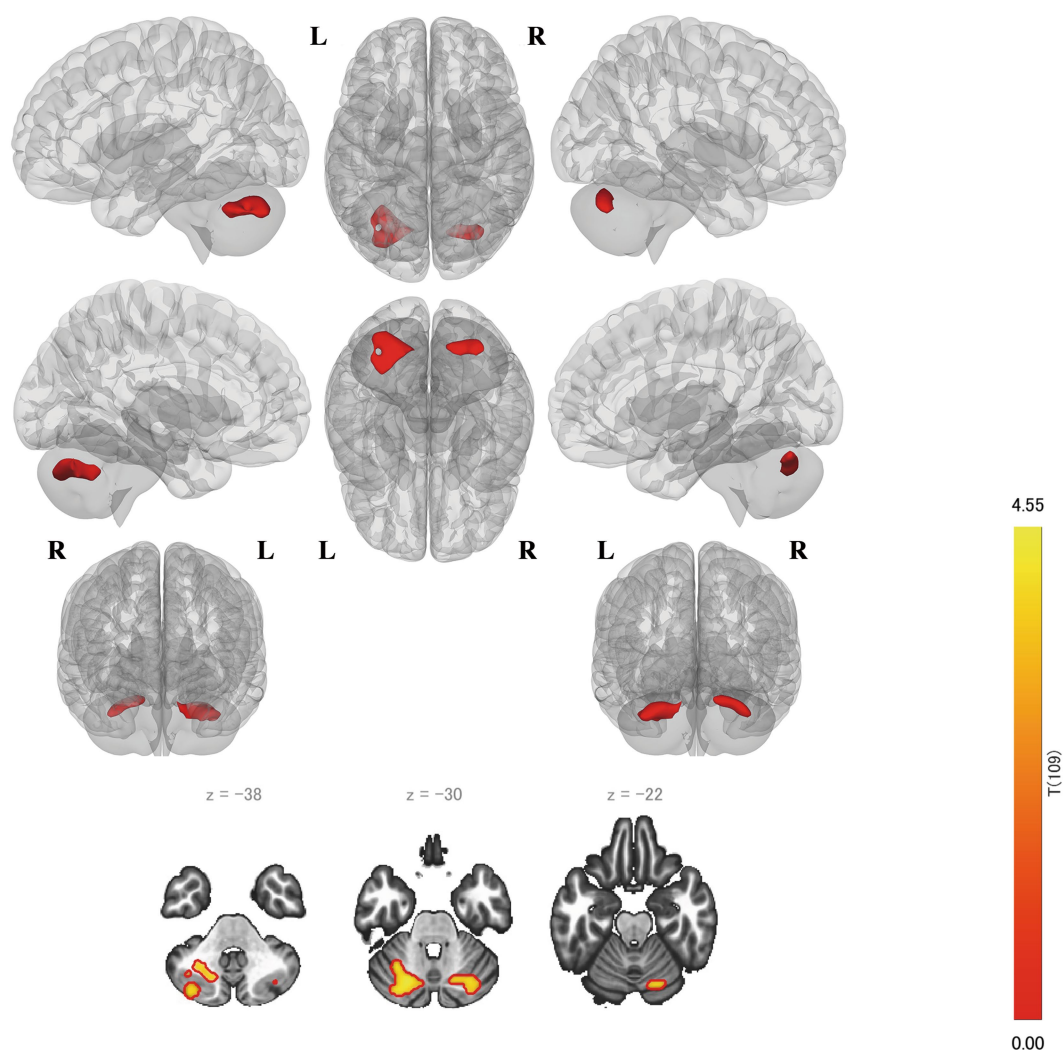


FIGURE 3

Results of the seed-to-voxel analysis on the left BA 9. The left cluster remains even after Bonferroni multiple correction is considered. BA, Brodmann area.

self-referential emotional and cognitive processing, whereas increased FC within the right vIPFC could relate to emotional regulation. Among these, the robust FC between the dlPFC and posterior cerebellum merits particular attention regarding the neural basis of SE.

4.2 FC between dlPFC and cerebellum positively correlated with SE: implications for social cognition and emotional regulation

Enhanced FC was observed primarily between the dlPFC regions (BA8 and 9) and posterior cerebellum (crus 1 and 2, lobule 6). Post-hoc analyses further supported increased FC between cerebellar crus 1 and lateral, not medial, part of prefrontal cortexes including dlPFC and anterior prefrontal cortex (aPFC). Here we review the role of each region and interpret this FC correlation with SE.

4.2.1 dlPFC

The dlPFC is critically involved in higher-level cognition functions (O'Reilly, 2006), coordination of responses to environmental stimuli (O'Reilly, 2010), attention control (Lai, 2021), emotional evaluation (Hutcherson et al., 2005), cost-sensitive decision-making (Botvinick and Braver, 2015), social cognitive processing (Weissman et al., 2008), and volition (Nitschke and Mackiewicz, 2005). This region exhibits hemispheric imbalance in depression (Mayberg, 2003; Phillips et al., 2003), with decreased left-side activity associated with depressive symptoms (Dutta et al., 2014) and increased ruminative thought process (Cooney et al., 2010; Wang et al., 2015; Lefaucheur et al., 2020; Baeken et al., 2021).

4.2.2 aPFC

The aPFC (BA 10), or frontal pole, contributes to introspection, self-related processes and social relationships, recording actions, distinguishing real from imaginary events (Tsujimoto et al., 2011), confidence in judgments (Miyamoto et al., 2018), metacognition (Baird et al., 2013), emotional action control (Koch et al., 2018) and executing

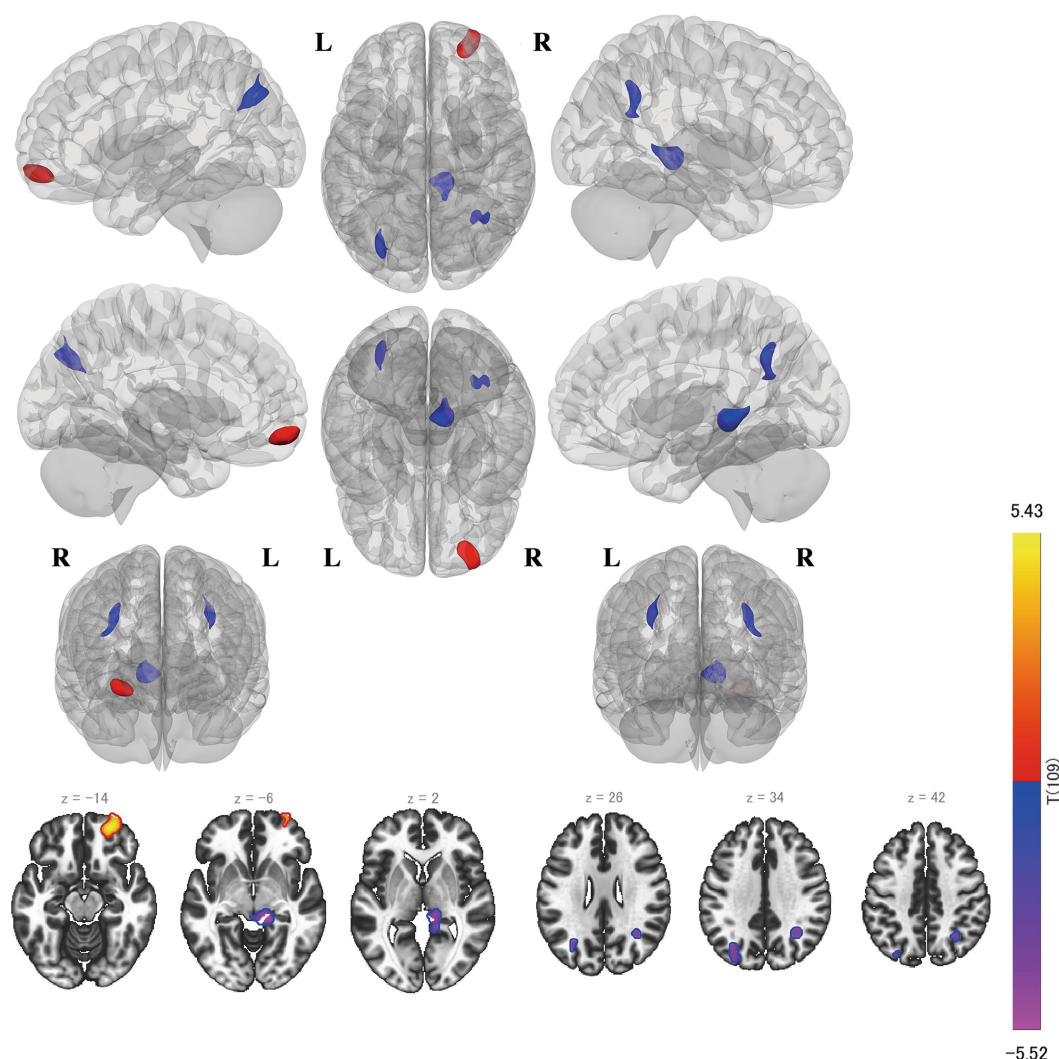


FIGURE 4

Results of the seed-to-voxel analysis on the left BA 44. The blue clusters are negatively correlated with SE, and the red clusters are positively correlated with SE. BA, Brodmann area; SE, self-esteem.

control beyond automatic behaviors (Volman et al., 2011; Bramson et al., 2020). One study showed that a higher aPFC baseline activity correlated with lower post-traumatic stress disorder symptoms (Kaldewaij et al., 2021), highlighting its role in adaptive emotional and cognitive control.

4.2.3 Cerebellum

Anatomical tracing studies have demonstrated closed-loop circuits between the lateral prefrontal cortex and cerebellar Crus 1 and 2. These circuits are segregated from motor loops, indicating that a substantial portion of the cerebellum is dedicated to cognitive-affective networks rather than sensorimotor control (Habas et al., 2009; Buckner et al., 2011; Habas, 2021). Crus 1 predominantly supports social cognitive processes such as mentalizing and predicting social sequences, whereas Crus 2 is more strongly involved in emotional regulation processes (Guell et al., 2018; Van Overwalle et al., 2020b). These cerebellar regions activate in conjunction with medial prefrontal and temporoparietal areas during theory-of-mind tasks, reflecting their role in internal models of social dynamics and

predictive coding of social behaviors (Van Overwalle et al., 2014; Olivito et al., 2023).

Schmahmann (1998) observed psychiatric symptoms in patients with cerebellar damage, proposing the “dysmetria of thought” hypothesis, linking cerebellar impairments in emotional and social cognitive control to psychiatric symptoms such as anxiety, depression, aggression, and passivity (Schmahmann et al., 2007; Hoche et al., 2016). Subsequent research supports cerebellar involvement in emotional processing, predictive coding, and internal modeling of cognitive-affective processes (Alalade et al., 2011; Liu et al., 2012; Guo et al., 2013; Ma Q. et al., 2013; Ma Z. et al., 2013; Baetens et al., 2014; Van Overwalle et al., 2014; Van Overwalle et al., 2015; Depping et al., 2018; Guell et al., 2018; Guell and Schmahmann, 2020).

4.2.4 Interpretation of the positive correlation of FC with SE

Our results showed that higher SE is associated with stronger FC between the dlPFC-aPFC and cerebellar regions. This connectivity

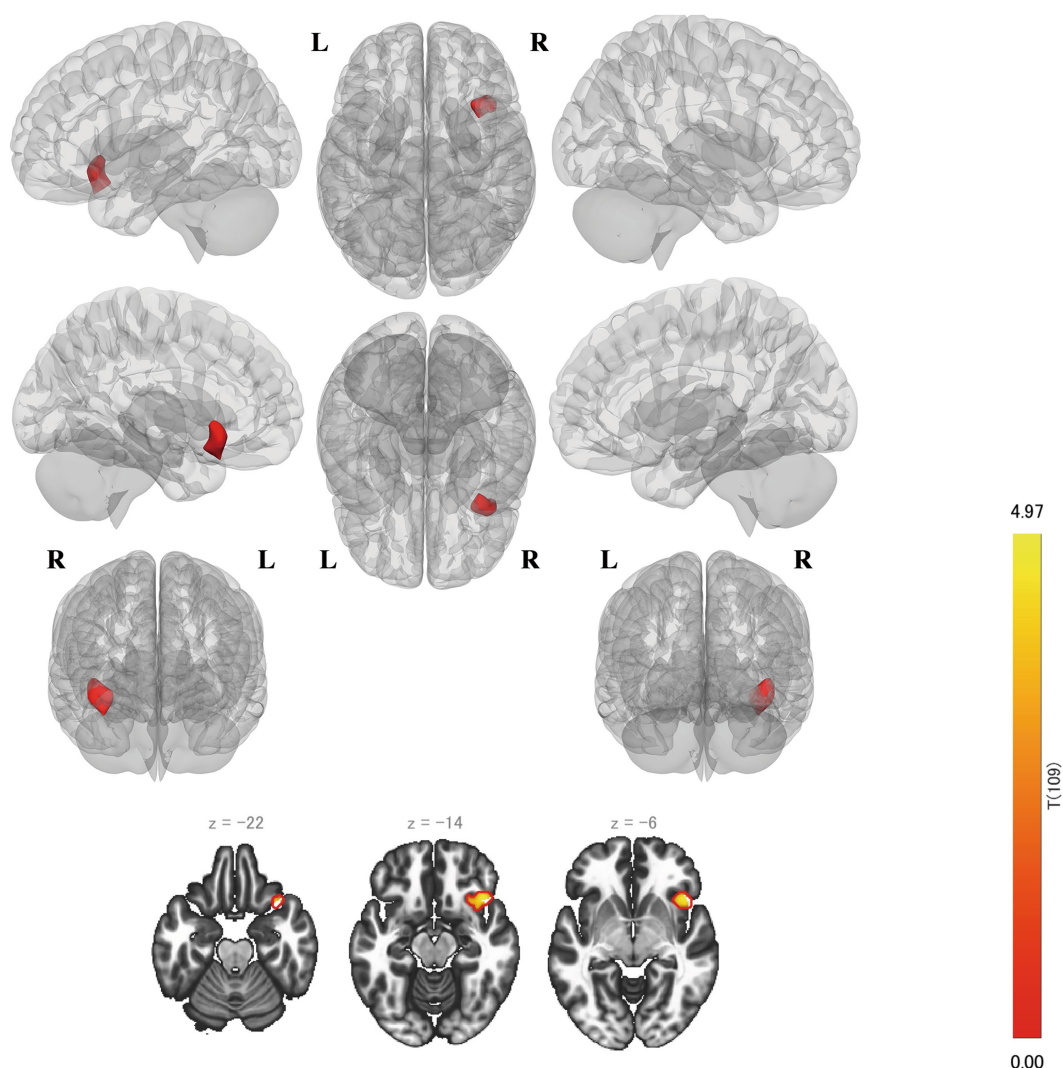


FIGURE 5
Results of the seed-to-voxel analysis on the right BA 45. BA, Brodmann area.

likely underpins effective predictive coding and emotional regulation through fronto-cerebellar loops. The dlPFC conveys contextual social information to the cerebellum, which generates prediction regarding cognitive and emotional outcomes. Any mismatch between predicted and actual outcomes results in feedback signals that update and optimize prefrontal processing (Ito, 2008; Sokolov et al., 2017). Weakened connectivity between gradual τ dlPFC-aPFC and cerebellar areas could decrease the ability to predict and regulate emotional and social outcomes effectively, thus increasing vulnerability to maladaptive emotional reactions and ruminations (Cooney et al., 2010; Wang et al., 2015).

Conversely, individuals with higher SE may have increased dlPFC-cerebellar interactions that enables efficient monitoring of social feedback, prediction of emotional states, and rapid error correction when social outcomes deviate from expectations. Such adaptive fronto-cerebellar coupling, potentially mediated by interactions with large-scale networks such as the DMN, supports resilience against negative self-evaluations and facilitates stable self-esteem by continuously adjusting social-cognitive strategies and

emotional responses (Brown and Mankowski, 1993; Campbell et al., 1991). Thus, this dlPFC-cerebellar network is important not merely for cognitive and affective adjustment but also for sustaining psychological well-being through predictive control in social and emotional dynamics.

4.3 Other FC changes which could not survive multiple comparisons (exploratory results)

4.3.1 FC increase between the left BA 8 and right lingual gyrus

We observed a positive correlation between the SE and FC involving the left BA 8 and the right lingual gyrus. The lingual gyrus plays a pivotal role in visual perception, visual agnosia (Hirayama, 2017), facial emotion recognition (Kitada et al., 2010), and self-referential processes (Kircher et al., 2000; Makino and Ikoma, 2022). A reduction in the surface area of the right lingual gyrus has

been associated with anxiety, depression (Couvry-Duchesne et al., 2018), and adolescent major depressive disorder (Schmaal et al., 2016), which may influence adult psychiatric outcomes. Based on sociometer theory, cooperation between the lingual gyrus and dlPFC may facilitate integrated processing of self-referential emotional and cognitive information, essential for maintaining positive self-evaluation.

4.3.2 FC increase between the left BA 44 and right frontal pole as well as between the right BA 45, BA 47, and insula

Our analysis identified positive correlations between the left BA 44 and the right frontal pole (right BA 10), as well as between the right BA 45 and a cluster including the right OFC (right BA 47 right) and insular cortex (BA 13).

BA 44, 45, and 47 collectively form the inferior frontal gyrus (IFG), crucial for verbal motor function, working memory (Osaka, 2007), and behavioral regulation (Forstmann et al., 2008; Sundby et al., 2021). The right vlPFC is linked to social exclusion (Riva et al., 2012) and the cognitive reappraisal and suppression of amygdalar activity associated with fear and anger (Lieberman et al., 2007). Previous research detected diminished right IFG activity in depressed individuals experiencing pronounced rumination (Kühn et al., 2012) and increased vlPFC-amygdala FC in individuals with high SE during mortality threat tasks (Yanagisawa et al., 2016), highlighting its importance in emotional and cognitive regulation relevant to SE. One study (Kim G. W. et al., 2022; Kim H. et al., 2022) revealed reduced FC between the bilateral IFG regions in young adults with pronounced suicidality, which is consistent with our findings. The insular cortex is also instrumental in emotional judgment (Zaki et al., 2012). Given the amplified FC among vlPFC, frontal pole, and insula, individuals with high SE may exhibit superior skills in effectively monitoring and regulating emotional states, using the frontal pole as a protective buffer against intense negative emotions.

4.3.3 FC decrease between the BA 44, angular gyri, and thalamus

Seeding on the BA 44 left, a negative correlation with SE was observed in FC involving clusters within bilateral the angular gyri and the thalamus. The left BA 44 (Broca's area) contributes to the production of language, grammar, fluency, and processing of sentences (Grewe et al., 2005; Ardila, 2012). These are known to work as networks with Wernicke's area and extended area, including the thalamus (Bohsali et al., 2015; Kim G. W. et al., 2022; Kim H. et al., 2022; Junker et al., 2023). Previous studies have suggested that rumination is negatively associated with SE and is often experienced as inner speech (Moffatt et al., 2020; Bugay-Sökmez et al., 2023), indicating that people with low SE tend to engage in excessive internal verbalization and cognitive rumination during the resting state.

4.3.4 Null findings in right dlPFC seeds

Interestingly, we did not find significant FC correlations with SE involving the right dlPFC (BA8,9,46). The null significant results in the right dlPFC might indicate a left-lateralized neural substrate for SE processing. Prior neuroimaging studies showed greater left-hemispheric prefrontal activation during positive emotional experiences and self-referential cognition (Weissman et al., 2008). Future research should explicitly examine lateralization patterns in

neural mechanisms underpinning SE to further validate this hemispheric distinction.

4.4 Neural correlates of SE

With multiple comparisons corrections, only FC between the dlPFC and cerebellum remained significant. This robust result suggests the dlPFC's coordinating role in cognitive process and reciprocal interactions with the cerebellum during SE establishment. Additionally, observed the FC with the lingual gyrus is associated with self-perception and social interaction, while FC among the vlPFC, frontal pole, and insula contributes to emotion regulation. Consequently, our findings suggest the potential for the language network (BA44-angular gyrus-thalamus) to become less active, achieving a state close to true resting conditions without inner speech.

The relationship between SE and FC could serve as a surrogate marker for predicting the risk of mental illnesses onset. Considering that established psychiatric interventions like cognitive-behavioral therapy impact SE (Mann et al., 2004; Roberts, 2006; Niveau et al., 2021), the FC-SE relationship may offer valuable insights for evaluating the effectiveness of these interventions.

4.5 Limitations and future prospects

This study has some limitations. First, we only used data from the Japanese population. Previous research indicates that SE varies across countries (Schmitt and Allik, 2005). Despite this, we believe our findings reflect universal aspects of SE. Future research involving international participants for studying SE and brain function is necessary for generalizing present results.

Second, we identified associations between SE and FC in regions involved in social cognition and emotional regulation, but this does not confirm that social cognition or emotional regulation directly mediate or causally influence the neural relationship with SE. Although interpretations were provided regarding these processes, we did not empirically test their direct functional roles. Future studies should explicitly examine the mediating or moderating effects of social cognitive and emotional regulation factors using task-based fMRI paradigms and mediation or moderation analyses (e.g., see Zhang et al., 2023).

Third, this was a cross-sectional study. While SE is relatively stable, it is also known to change gradually over the course of a person's life. Future studies should observe the correlation between intra-individual changes in SE and changes in FC.

Lastly, we focused on specific seeds to identify SE neural correlates. Although we found some FCs potentially related to large-scale networks like default-mode, these networks were not directly analyzed. Further research should explore the relationship between intra-network and inter-network FC and SE, which might have implications for psychological traits and brain changes.

In conclusion, our study examined the neural correlates of SE, excluding associations with subthreshold depressive symptoms. As hypothesized, FC in social cognition and emotional regulation areas, especially the dlPFC and the posterior cerebellum, was

associated with SE. Based on these findings, we propose the possibility of SE as a surrogate marker of mental health management, and the viability of FC as a neurobiological index for evaluating mental health interventions.

Data availability statement

The datasets generated during this study are available from the corresponding author, HF, upon reasonable request.

Ethics statement

The studies involving humans were approved by Ethics Committee, Kyoto University Graduate School and Faculty of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MA: Formal analysis, Investigation, Visualization, Writing – original draft. MaS: Writing – review & editing. YF: Writing – review & editing. MiS: Writing – review & editing. KK: Writing – review & editing. TU: Writing – review & editing. TaM: Writing – review & editing. SY: Writing – review & editing. NO: Data curation, Resources, Software, Writing – review & editing. ToM: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing. HF: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The authors declare that Gen AI was used in the creation of this manuscript. Used ChatGPTs for the translation of Japanese into English partially, which was proofread by the authors, and after that we asked the translation company (Editage.inc) to modify the expressions and grammars.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnins.2025.1588567/full#supplementary-material>

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Alterations of the default mode network, salience network, and frontoparietal network in non-problematic Internet use and their association with mood regulation: from an internet literacy perspective

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Introduction: Although a number of neuroimaging studies on problematic internet use (PIU) have been conducted, few studies on non-problematic internet use (non-PIU) are available; therefore, the influences of non-PIU on brain function are unclear. Resting-state functional connectivity (rsFC) could be an appropriate tool to investigate subclinical samples, such as non-PIU, to capture the potentially subtle changes compared to clinical samples. In the context of rsFC, the default mode network (DMN), the central executive network (CEN), and the salience network (SN) are representative of the brain networks. Because accumulating studies have investigated rsFC between these networks in PIU samples, investigating rsFC between these networks in non-PIU samples could give us a clue to elucidate the neural basis of non-PIU in relation to those of PIU.

Methods: We recruited 119 healthy volunteers and used the General Problematic Internet Use Scale-2 (GPIUS-2) to measure their propensity to use the Internet. The GPIUS-2 consists of four subscales. We analyzed the correlation between the degree of Internet use assessed by the GPIUS-2 and the rsFC of the regions comprising DMN, CEN, and SN using resting-state functional magnetic resonance imaging in non-PIU samples.

Results: There was a positive correlation between the mood regulation subscale score and SN (bilateral anterior insula) – CEN (left lateral prefrontal cortex: LPFC), SN (left anterior insula) – DMN (medial prefrontal cortex: MPFC), and DMN (MPFC) – CEN (right LPFC) rsFC. Additionally, there was a negative correlation between the mood regulation subscale score and DMN – FPN rsFC.

Discussion: The correlations between rsFC and non-PIU suggest that non-PIU and PIU could influence rsFC in opposite directions. Furthermore, the hub regions comprising connections correlated with non-PIU in this study are involved in cognitive and emotional processes. One possible interpretation would be that the bilateral insula and synchronized LPFC activity in individuals with non-PIU results in well-functioning emotion regulation as an appropriate coping strategy, in contrast to PIU. These findings suggest that non-PIU might contribute to health promotion through mood regulation with alterations in the functional connectivity between the regions involved in mood regulation.

KEYWORDS

non-problematic internet use, magnetic resonance imaging, mood regulation, functional connectivity, triple-network model, behavioral addiction

1 Introduction

The Internet has been established as a necessary tool for addressing many social issues. However, its risks include behavioral addiction (Billieux et al., 2015; Müller et al., 2022; Pontes, 2022), with problematic Internet use (PIU) being a notable concern. PIU encompasses gaming disorders, problematic pornography, social network addiction, and compulsive browsing (Pawlikowski et al., 2014; Pontes, 2022; Rendi et al., 2007). One meta-analysis reported that 85% of magnetic resonance imaging (MRI) studies on PIU were conducted in patients with gaming disorders (Sepede et al., 2016). In these studies, PIU was associated with poor performance in attention-demanding tasks (Park et al., 2011), impaired decision-making skills (Sun et al., 2009), and daily cognitive failures (Hadlington, 2015).

Research using structural and functional imaging is accumulating knowledge on the neural basis of PIU. Structural neuroimaging studies have revealed alterations related to PIU, such as volume reduction in the prefrontal cortex (PFC) (Jin et al., 2016; Wang et al., 2018; Yuan et al., 2011). In functional neuroimaging studies, PIU participants showed altered brain activity in a variety of brain regions, including the insula, anterior cingulate cortex, and caudate during a monetary task (Dong et al., 2013); the inferior parietal lobule and PFC during an Addiction Stroop Task (Zhang et al., 2016); and the sensorimotor area during a Go/No-go task (Chen et al., 2015).

Recently, functional connectivity (FC), defined as the temporal correlation between neural activity patterns in different brain regions (Aerts et al., 1989; Friston, 1994), has been investigated. Human brain activity is topologically organized into a set of spatiotemporal networks with phase relationships, often referred to as large-scale brain networks, which orchestrate disparate cognitive processes. The “triple-network model” hypothesizes that three core intrinsic neurocognitive networks—the frontoparietal network (FPN), the default mode network (DMN), and the salience network (SN)—interact with each other within the framework of large-scale networks (Menon, 2011). The FPN and SN typically show increased activation during cognitive tasks. In contrast, the DMN is deactivated during cognitively demanding tasks, and activated during rest (Kamp et al., 2018). The SN plays a pivotal role

in switching between the FPN and DMN by allocating attention, resulting in a negative correlation between the FPN and DMN activity (Fox et al., 2005). In the triple-network model, an increase in functional connectivity between the SN and DMN has been observed in patients with depression, which is often comorbid with PIU (Jiang et al., 2017; Posner et al., 2017; Stern et al., 2012). Several studies have revealed increased SN-DMN connectivity in patients with PIU (Hong et al., 2018; Zhang et al., 2017), although a few have reported decreased SN-DMN connectivity (Wang et al., 2017). One study has reported decreased DMN-FPN connectivity in patients with PIU (Siste et al., 2022).

From the perspective of therapeutic intervention for PIU, unlike other addictions, abstaining from internet use is not always realistic because of its social importance. Moreover, non-PIU could benefit mental health and cognitive abilities (Fujiwara et al., 2018; Huang et al., 2021; US Food and Drug Administration, 2020). Furthermore, adequate Internet literacy has been reported to be associated with self-efficacy in Internet use, including exchanging e-mails or browsing (Huang et al., 2021). Notably, the Internet, presumably under adequate regulation by users, could be applied for cognitive control training for instituting preventive intervention for depression (Hoorelbeke and Koster, 2017) and improving attention and motivation in neurocognitive disorders (Miller et al., 2013; Robert et al., 2020). Game-based devices have been approved by the U.S. Food and Drug Administration as interventions for symptoms of attention deficit hyperactivity disorder (2020).

However, the neural basis of non-PIU remains unclear because neuroimaging studies of non-PIU are scarce. In one of the few reports where moderate use of the Internet could have a positive effect on neural connectivity, video game experts showed higher FC between the SN and FPN than amateur players, presumably resulting from trained attention and working memory, which are needed to play video games (Gong et al., 2016). In another study, the tendency for Internet use was positively correlated with FC in the resting state in reward/motivation networks, indicating that subclinical levels of the Internet use might act to maintain reward/motivation-network integrity (Fujiwara et al., 2018).

It is possible that the degree of change in neural connectivity in non-PIU groups is not as drastic as that in PIU groups, which

may be why there are very few reports on non-PIU. Resting-state FC could be an appropriate tool for studying non-PIU samples to capture potentially subtle changes compared to PIU samples. The purpose of this study is to investigate the relationship between Internet use and resting-state FC within the framework of the triple-network model in healthy participants, and compare it with previously reported alterations of the triple-network in PIU. We hypothesized that resting-state FC between the SN and FPN would be increased in the non-PIU group compared to the PIU group, based on studies showing positive effects on mental state.

2 Materials and methods

2.1 Participants

In the current study, we set the effect size to 0.3, referring to previous studies (Schmitgen et al., 2022; Mizumoto and Takeuchi, 2011). If we set the effect size to moderate ($r = 0.30$), the significance level to 5%, and the power to test to 80%, the sample size would be 84 participants. However, in this study, it was necessary to take into account the possibility of incomplete data collection and dropout cases, and we considered it appropriate to set the sample size at 100 cases. Furthermore, we referred to a previous, similar study that examined the association between the Internet and FC (Vergara et al., 2022). Given these considerations, we targeted a sample size of about 100 individuals. We recruited 119 healthy right-handed volunteers (73 [62.9%] men) from May 2017 to January 2019 with a mean age of 36.20 (standard distribution [SD] = 14.31) years. We included native speakers of Japanese aged 18–70 years at the time of registration. The Structured Interview for Diagnostic and Statistical Manual of Mental Disorders (SCID; American Psychiatric Association [APA], 2013) was performed by well-trained psychiatrists to exclude psychiatric and neurological disorders and diseases such as mood, anxiety, and alcohol use disorders. The concurrent judgment of two well-trained psychiatrists was used to determine that none of the participants had any psychiatric or neurological illnesses. The Japanese version of the Adult Reading Test (Matsuoka et al., 2002) was used to confirm that all participants fell within the normal range of intelligence. After the experimental procedures were fully explained, all participants provided written informed consent before study participation. The Ethics Committee of the Kyoto University Graduate School and Faculty of Medicine reviewed and approved this study (R0879, January 17th, 2017), which was conducted in accordance with the Declaration of Helsinki. We did not have access to information that could identify the individual participants during or after data collection.

2.2 Psychological questionnaire

The General Problematic Internet Use Scale-2 (GPIUS-2) was used to measure PUI. The GPIUS-2 is a self-rating questionnaire containing 15 items, responses are scored on an 8-point Likert scale (1, strongly disagree; 8, strongly agree). The GPIUS-2 scores ranged from 15 to 120. Higher GPIUS-2 scores indicate a more severe tendency toward Internet addiction. Thus, the original GPIUS-2

was validated. The internal consistency reliability of the GPIUS-2 (Cronbach's alpha, 0.78–0.85) indicated a high level of reliability (Caplan, 2002). GPIUS-2 is a multidimensional scale composed of four subscales: preference for online social interaction (POSI), use of the Internet for mood regulation (MOOD), deficient self-regulation (SELF, further divided into cognitive preoccupation and compulsive Internet use), and negative outcomes (NEGA).

The POSI assesses the preference for Internet-based communication over face-to-face interaction. The MOOD assesses the tendency to use the Internet to regulate unpleasant emotional states (e.g., “I have used the Internet to make myself feel better when I've felt upset/lonely/depressed”).

Deficient self-regulation indicates a tendency toward a decreased self-monitoring state in which conscious self-control is consciously diminished because of mechanisms such as a growing habit of using the Internet. Deficient self-regulation, in some cases, can be categorized into “cognitive preoccupation” (e.g., “When I haven't been online for some time, I become preoccupied with the thought of going online”) and “compulsive internet use” (e.g., “I find it difficult to control my Internet use”). Furthermore, deficient self-regulation assesses difficulty in appropriately monitoring and judging an individual's Internet usage patterns and adjusting Internet-related behaviors (Caplan, 2010). Negative outcomes evaluated the adverse consequences of excessive Internet use. We used the Japanese version of the GPIUS-2, the reliability and validity of which have been previously confirmed (Yoshimura et al., 2022). The internal consistency reliability of the Japanese version of the GPIUS-2 total scores and its subscales (Cronbach's alpha, 0.75–0.79) showed high reliability. The correlation coefficient between the Japanese version of the GPIUS-2 and the Internet Addiction Test was 0.75 ($p < 0.001$), indicating satisfactory validity (Yoshimura et al., 2022).

The Beck Depression Inventory-II (BDI-II) assesses the severity of depressive symptoms (Beck et al., 1996). This scale comprises 21 items with scores ranging from 0 to 63. Higher BDI-II scores indicate more severe depressive tendencies. We used the Japanese version of the BDI-II, the validity of which has been previously confirmed by the Center for Epidemiologic Studies Depression Scale. Internal consistency reliability (Cronbach's alpha, 0.87) and item homogeneity (mean inter-item correlation coefficient, 0.24) were also confirmed (Griffanti et al., 2014). We used the BDI-II as a screening tool for depression at the clinical level.

2.3 MRI acquisition

MRI acquisition was performed with a 40-mT/m gradient and a receiver-only 32-channel phased-array head coil on a 3-Tesla MRI unit (Tim-Trio; Siemens, Erlangen, Germany). A rsfMRI was performed. A 360-s rsfMRI scan was obtained using a single-shot gradient-echo planar imaging (EPI) pulse sequence. The imaging time of rsfMRI was determined based on previous studies in the field of behavioral addiction (Tsurumi et al., 2020; Bellmunt-Gil et al., 2023; Wang et al., 2022; Bordier et al., 2022). The participants were instructed to keep looking at the cross displayed on the monitor without thinking about anything specific during the resting-state condition. Structural MRI data were acquired using three-dimensional magnetization-prepared rapid gradient-echo sequences. The parameters for resting-state data were as

follows: echo time, 30 ms; repetition time, 2,500 ms; flip angle, 80°; field of view, 212 × 212 mm; matrix size, 64 × 64; in-plane spatial resolution, 3.3,125 × 3.3,125 mm²; 40 total axial slices; and slice thickness, 3.2 mm with 0.8 mm gaps in ascending order. The parameters for the three-dimensional magnetization-prepared rapid gradient-echo images were as follows: echo time, 3.4 ms; repetition time, 2,000 ms; inversion time, 990 ms; field of view, 225 × 240 mm; matrix size, 240 × 256; resolution, 0.9,375 × 0.9,375 × 1.0 mm³; and 208 total axial sections without intersection gaps. A dual-echo gradient-echo dataset for B0-field mapping was acquired for distortion correction. Head movement was minimized within the head coil using a foam rubber pad.

2.4 Image pre-processing

Using field map data, the rsfMRI dataset was corrected for EPI distortion via the Functional Magnetic Resonance Imaging of the Brain (FMRIB) Utility for Geometrically Unwarping EPIs, which is part of the FMRIB Software Library software package (ver. 5.0.9;³ [Fmrib Analysis Group, 2015](https://www.fmrrib.ox.ac.uk/fsl), Oxford, United Kingdom). Moreover, artifact components and motion-related fluctuations were removed from the images using FMRIB's Independent Component Analysis (ICA)-based Xnoiseifier ([Griffanti et al., 2014](https://www.nitrc.org/projects/conn)). After pre-processing, we processed the structural and functional MRI data using the functional connectivity toolbox (CONN) (ver. 17e;⁴ [Gabrieli Laboratory, Cambridge, MA, United States](https://www.fil.ion.ucl.ac.uk/spm)) and Statistical Parametric Mapping software package (ver. 12;⁵ Wellcome Trust Center for Neuroimaging, 2012, London, United Kingdom) ([Whitfield-Gabrieli and Nieto-Castanon, 2012](https://www.nitrc.org/projects/artifact_detect/)).

The following pre-processing steps were conducted using a default pre-processing pipeline for volume-based analysis in the Montreal Neurological Institute space (Montreal, Canada). All functional images were pre-processed, including realignment, unwarping, slice-timing-corrected, co-registration with structural data, spatial normalization to the standard Montreal Neurological Institute space, outlier detection [Artifact Detection Tools-based scrubbing (ART)],⁶ and smoothing with a Gaussian kernel with a full width at half maximum of 8 mm. Structural data were segmented into gray matter, white matter (WM), and cerebrospinal fluid (CSF) and normalized using the same default pre-processing pipeline. Principal components of signals from the WM and CSF, as well as translational and rotational movement parameters (with another six parameters representing their first-order temporal derivatives), were removed using covariate regression analysis by CONN. Using the implemented CompCor strategy, the effects of nuisance covariates, including fluctuations in fMRI signals from the WM, CSF, and their derivatives, as well as the realignment parameter noise, were reduced. As recommended in a previous study, we performed bandpass filtering with a frequency window of 0.01–0.1 Hz ([Sun et al., 2009](https://doi.org/10.1016/j.neuroimage.2009.06.058)). We observed that this pre-processing

step increased retest reliability. Before running the FMRIB's ICA-based Xnoiseifier, we used frame-wise displacement to evaluate head movement during fMRI, which quantifies the head motion between each volume of functional data. Participants were excluded if the number of volumes in which the head position was 0.5 mm different from the adjacent volumes was more than 15% ([Power et al., 2012](https://doi.org/10.1016/j.neuroimage.2012.07.048)).

2.5 FC analysis

2.5.1 ROI-to-ROI FC analyses

The region of interest (ROI)-to-ROI FC was calculated using the CONN toolbox ([Gabrieli Laboratory, 2017](https://www.fil.ion.ucl.ac.uk/spm)). We adopted the ROIs defined from CONN's ICA of the Human Connectome Project dataset. The ROIs were grouped into several networks, diameters, and peak coordinate bases.

The SN comprises seven areas: the anterior cingulate cortex (0, 22, 35), left and right anterior insula (left: −44, 13, 1; right: 47, 14, 0), left and right rostral PFC (left: −32, 45, 27; right: 32, 46, 27), and the bilateral supramarginal gyrus (left: −60, −39, 31; right: 62, −35, 32). The DMN comprised four areas: the medial PFC (MPFC) (1, 55, −3), left and right lateral parietal lobes (left: −39, −77, 33; right: 47, −67, 29), and the posterior cingulate cortex (1, −61, 38). The FPN comprised four areas: the left and right lateral PFC (LPFC) (left: −43, 33, 28; right: 41, 38, 30), and the left and right posterior parietal cortices (left: −46, −58, 49; right: 52, −52, 45). The preprocessed fMRI time series of all voxels in the 15 ROIs were extracted and averaged for each participant. ROI-to-ROI FC was defined as the Fisher-transformed bivariate correlation coefficient for each pair of 15 regions ($Z_{i,j}$: Z score between the *i*th and *j*th ROI), which resulted in a 15 × 15 correlation matrix (105 FCs) for each participant.

2.5.2 inter-network FC analyses

For each of the three networks, the inter-network FC strength was defined as the mean FC of all of the possible connections, i.e., $Z_{X,Y} = 1/n_X n_Y \sum_{i \in X, j \in Y} |Z_{i,j}|$ where n_X is the number of ROIs within a specific network X. X and Y represent one and another network of the three networks ([Wang et al., 2015](https://doi.org/10.1016/j.neuroimage.2015.07.048)).

2.6 Statistical analyses

Kolmogorov–Smirnov tests were performed to test whether age and total and subscale GPIUS-2 scores were normally distributed. Additionally, to assess the differences in age and scores by sex, the student's *t*-test (two-tailed) was applied for items with a normal distribution, while the Mann–Whitney U test was used unless the items were normally distributed. Correlation analyses among the items were performed using Pearson's correlation coefficient or Spearman's rank correlation coefficient depending on the normality of the data distribution. These tests were performed using SPSS Version 22.0.0 ([International Business Machines Corporation, 2013](https://www.ibm.com/products/spss-statistics)).

2.6.1 ROI-to-ROI FC analyses

We assessed the associations between the GPIUS-2 total score and its subscales and the FC values between each ROI. The

1 www.nitrc.org/projects/conn

2 <https://www.fil.ion.ucl.ac.uk/spm>

3 <https://www.fmrrib.ox.ac.uk/fsl>

4 www.nitrc.org/projects/conn

5 <https://www.fil.ion.ucl.ac.uk/spm>

6 www.nitrc.org/projects/artifact_detect/

associations between the GPIUS-2 scores and FC values of the two ROIs were calculated using *t*-statistics by CONN, with age, sex, and BDI-II scores as covariates. Significant connections were identified by calculating false discovery rate (FDR)-rate-corrected $p < 0.05$. Owing to the exploratory nature of this study, we used FDR correction for multiple comparison correction rather than Bonferroni correction (statistical significance, $p < 0.0033$) based on the number of ROIs in the SN, DMN, and FPN. It is because we considered it more appropriate to prioritize statistical power over strict control of Type I error. When applying FDR correction, a single FDR correction was applied to all comparisons across the three networks (SN-DMN, SN-FPN, and FPN-DMN).

2.6.2 Inter-network FC analyses

We assessed the associations between the GPIUS-2 total score and its subscales and the FC values between the SN and DMN, SN and FPN, and FPN and DMN. The Kolmogorov-Smirnov tests were performed to test whether the inter-network FC strengths were normally distributed. Furthermore, a partial correlation analysis was performed by controlling for age, sex, and BDI-II using SPSS Version 22.0.0.

3 Results

3.1 Demographic information and psychological data

Three participants were excluded because of head motion, and 116 were included in the psychological data analysis. The demographic data are summarized in Table 1. The mean GPIUS-2 score was 36.78 ($SD = 15.91$), which was lower than the mean score (GPIUS-2 = 40.53) from a previous PIU study (Yoshitake, 2018). The mean values were below the BDI-II cut-off points. The Kolmogorov-Smirnov tests revealed that age, POSI, MOOD, SELF, NEGA, and BDI-II were not normally distributed. Therefore, Spearman's ρ was used to analyze the correlation between each GPIUS-2 score and BDI-II.

Correlation analysis revealed that neither the GPIUS-2 total scores nor each subscale, except for the SELF, correlated with the BDI-II scores. However, the SELF subscale scores were positively

TABLE 1 Demographic data.

	<i>N</i> = 116
Men (%)	73 (62.9%)
Mean age	35.78 ± 14.20
Mean GPIUS-2	36.78 ± 15.91
Mean POSI	5.76 ± 2.64
Mean MOOD	5.76 ± 5.00
Mean SELF	15.37 ± 7.27
Mean NEGA	6.64 ± 3.71
Mean BDI-II	6.33 ± 5.96

GPIUS-2, Generalized Problematic Internet Use-2; POSI, preference for online social interaction; MOOD, mood regulation; SELF, self-regulation; NEGA, negative outcome; BDI-II, Beck Depression Inventory-II.

TABLE 2 Correlation between GPIUS-2 and BDI-II.

	BDI-II	
	Spearman's ρ	<i>p</i> -value
GPIUS-2 total score	0.176	0.059
POSI	0.083	0.376
MOOD	0.085	0.362
SELF	0.236*	0.011*
NEGA	0.110	0.239

GPIUS-2, Generalized Problematic Internet Use-2; POSI, preference for online social interaction; MOOD, mood regulation; SELF, self-regulation; NEGA, negative outcome; BDI-II, Beck Depression Inventory-II. *Statistical $p < 0.05$ was considered statistically significant.

correlated with the BDI-II scores (Table 2). The student's *t*-test revealed no difference in the total GPIUS-2 scores between sexes [$t(114) = 0.975$, $p = 0.331$]. The Mann-Whitney U test also revealed no differences in age and each subscale between the sexes (age, $p = 0.527$; POSI, $p = 0.132$; MOOD, $p = 0.567$; SELF, $p = 0.114$; NEGA, $p = 0.153$; and BDI-II score, $p = 0.945$). Since the GPIUS-2 scale has no cut-off point, we excluded patients with GPIUS-2 scores above +2SD (total GPIUS-2 score, 68.60 points). The remaining 110 participants were classified as non-PIUs. The participant recruitment flowchart is summarized in Figure 1.

3.2 Correlation between the GPIUS-2 score and FC

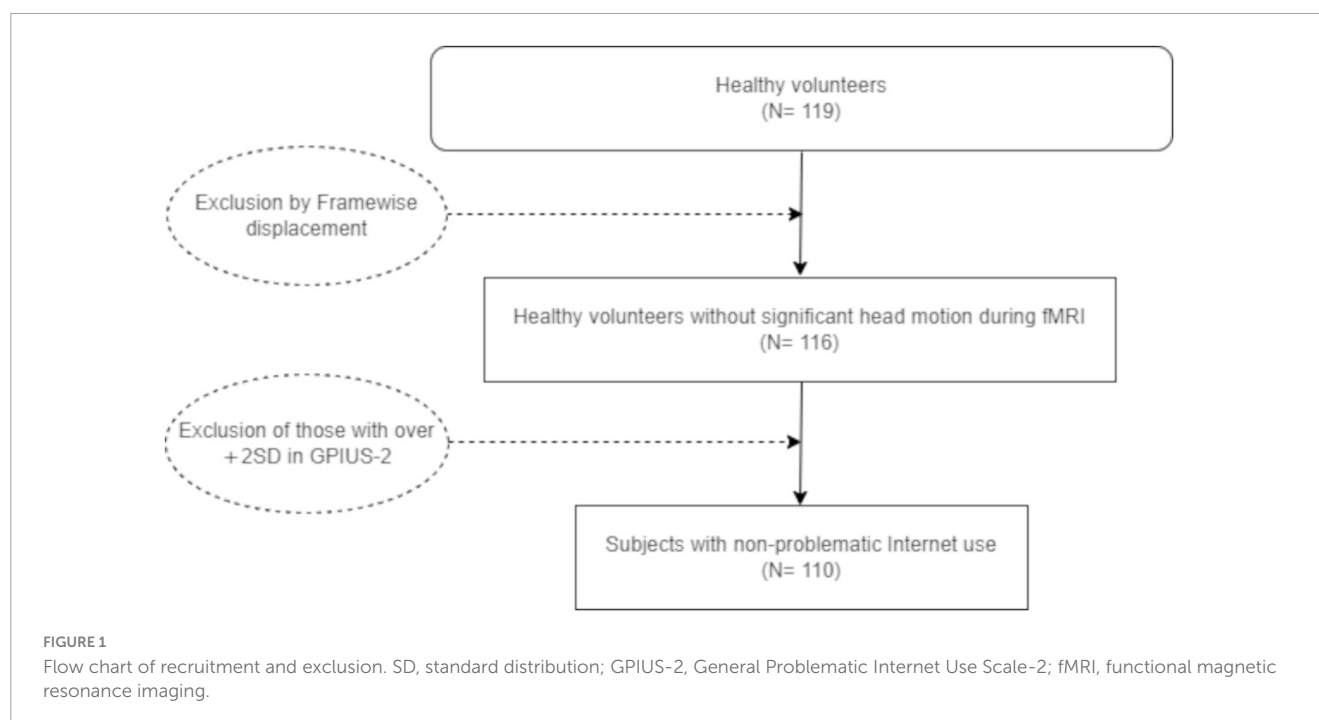
3.2.1 ROI-to-ROI FC analyses

The correlations between the GPIUS-2 scores and each ROI in the three networks are shown in Figure 2. CONN toolbox analysis revealed the following: (1) the MOOD score of the GPIUS-2 showed a significantly positive correlation with FC between the left anterior insula (SN) and left LPFC (FPN) [$T_{(105)} = 3.46$; $r = 0.172$, $p = 0.0109$] (Figure 2a); (2) the MOOD score showed a significantly negative correlation with FC between the left anterior insula and MPFC (DMN) [$T_{(105)} = -2.87$, $r = -0.159$, $p = 0.0351$] (Figure 2a); (3) the MOOD score showed a significantly positive correlation with FC between the right anterior (SN) insula and left LPFC [$T_{(105)} = 3.27$, $r = 0.168$, $p = 0.0204$] (Figure 2b); and (4) the MOOD score showed a significant positive correlation with FC between the MPFC and right LPFC (FPN) [$T_{(105)} = 3.42$, $r = 0.171$, $p = 0.0125$] (Figure 2c). However, there were no significant associations between MOOD scores and intra-network FC values in the DMN, FPN, and SN.

3.2.2 Inter-network FC analyses

The results of inter-network FC analyses are summarized in Table 3. The Kolmogorov-Smirnov tests revealed that each inter-network FC were normally distributed. Therefore, a partial correlation analyses was performed using Pearson's by controlling for age, sex, and BDI-II. There was no significant correlation between the GPIUS-2 scores and inter-network FC among the three large-scale networks.

In summary, statistically significant correlations between Internet Use and FCs were found in ROI-to-ROI FC analyses, i.e., FCs between ROIs that are involved in the DMN, SN, and



FPN were associated with the tendency of Internet use in ROI-to-ROI analysis.

4 Discussion

We analyzed the correlation between Internet use assessed using the GPIUS-2 and FC of inter- and intra-networks of the SN, DMN, and FPN using rsfMRI in non-PIU individuals. The mean GPIUS-2 total score was lower than that previously reported in a study of PIU, and the mean BDI-II score was lower than the cutoff point. It was confirmed that the participants were subclinical Internet users and were not depressed at the clinical level, in contrast to the fact that people with PIU have a high rate of comorbid depression. SELF scores were positively correlated with BDI-II scores, suggesting that internet use with higher but less than moderate levels of self-dysregulation was utilized as a coping strategy, as neither SELF nor depression levels reached a clinical level in this study sample. The results of ROI-to-ROI FC analyses revealed that the MOOD score showed (1) a significantly positive correlation with FC between the left anterior insula (SN) and left LPFC (FPN); (2) a significantly negative correlation with FC between the left anterior insula (SN) and MPFC (DMN); (3) a significantly positive correlation with FC between the right anterior insula (SN) and left LPFC (FPN); and (4) a significantly positive correlation with FC between the MPFC (DMN) and right LPFC (FPN). However, no significant relationship was found between the tendency toward Internet use and FCs in each network, contrary to our hypothesis.

Despite the negative results of the internetwork FC analyses, those of the ROI-to-ROI FC analyses can be discussed in the context of a triple-network model. Results (1)–(3) are inconsistent with those of most previous studies on PIU: increased FC between the SN and DMN and decreased FC between the SN and FPN in

problematic Internet users compared with healthy controls (Chen et al., 2016; Hong et al., 2018; Yuan et al., 2016; Zhang et al., 2017). Results (1)–(3) were also inconsistent with a report on gambling disorder (Tsurumi et al., 2020). In contrast, these results are consistent with previous reports of elevated FC between the SN and FPN in expert video gamers (Caplan, 2010). Internet use is generally discussed in the context of behavioral addiction, and PIU has the same alterations in the internetwork integrity of the triple network as those in other psychiatric disorders, such as depression and schizophrenia (Manoliu et al., 2013; Shao et al., 2018). However, our results allow us to speculate that non-PIU is associated with an opposite modulation of psychiatric disorders in the internetwork FC of the triple network, which is responsible for affect and cognition and that non-PIU is a health-promoting habit. There are reports that cognitive load caused by non-PIU has a promoting effect on various brain functions. Internet users show increased activity in brain regions associated with decision-making and complex reasoning during internet use compared to non-users, and this activity further improves after training using internet search (Small et al., 2020). Additionally, computer-based brain training exercises have been reported to improve delayed memory and working memory abilities (Miller et al. 2013; Halford et al., 2007). Furthermore, groups that underwent multitasking training through video games showed improved abilities in working memory, divided attention, and sustained attention compared to those who did not (Anguera et al., 2013). Brain imaging studies have reported that the tendency of media multitasking, based on the Internet environment in many cases, was associated with higher attention network integrity (Kobayashi et al., 2020). The results of our current study support previous reports that appropriate level of internet use including computer-based brain training exercises improve working memory, attention functions, and multitasking abilities compared to groups that do not use them, from the perspective of FC.

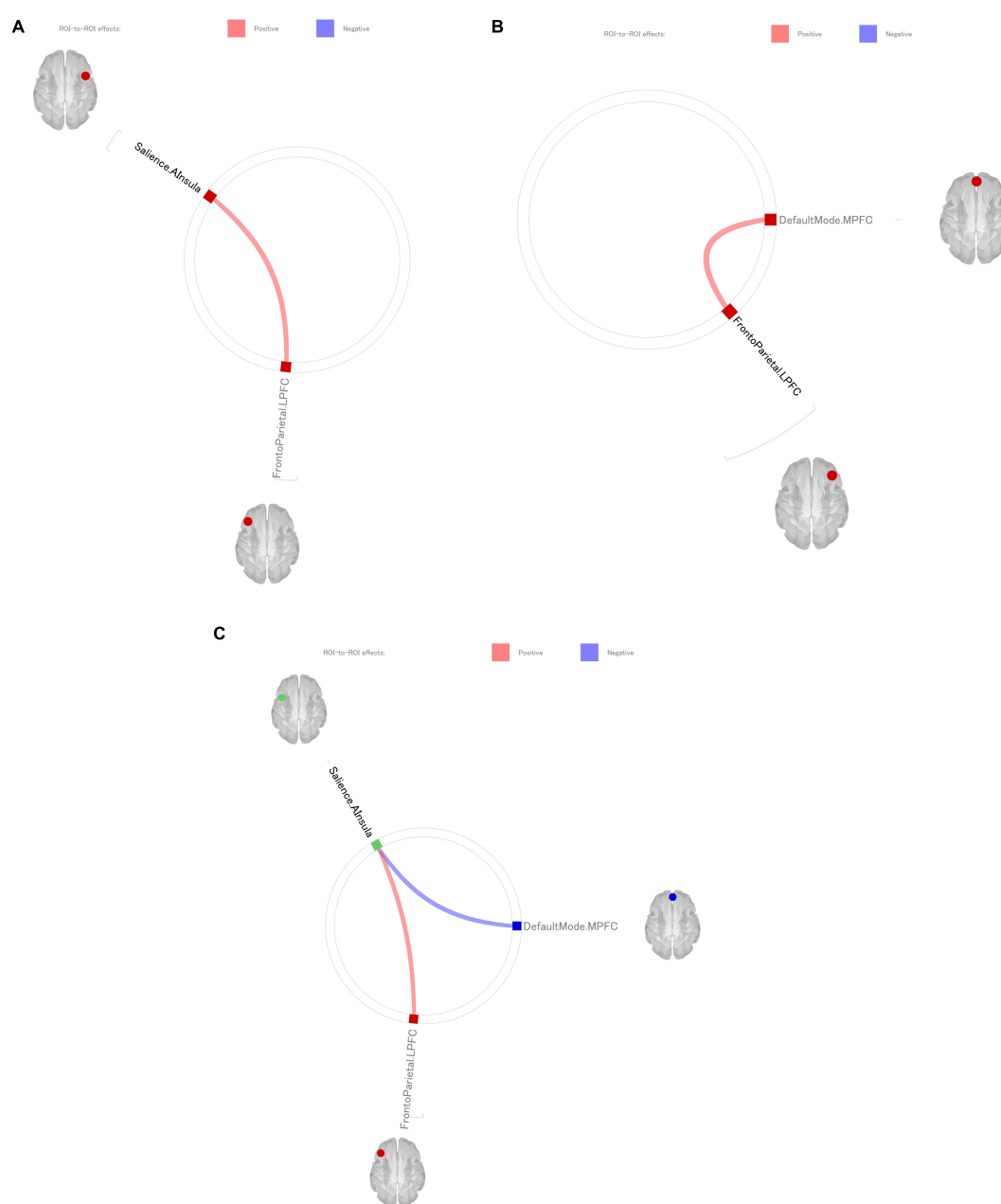


FIGURE 2

Functional connectivity (FC) with a significant correlation between “MOOD” subscale scores of the GPIUS-2 and resting-state connectivity (FDR-corrected, $p < 0.05$). The red line indicates a positive correlation between FC during the resting state and “MOOD” scores. Conversely, the blue line indicates a negative correlation between FC during the resting state and “MOOD” scores. (a) The “MOOD” score of the GPIUS-2 showed a significantly positive correlation with FC between the left anterior insula and the left LPFC. Conversely, the “MOOD” score showed a significantly negative correlation with FC between the left anterior insula and the MPFC. (b) The “MOOD” score showed a significant positive correlation with FC between the right anterior insula and left LPFC [$T_{(105)} = 3.27$, $p = 0.0204$]. (c) The “MOOD” score showed a significantly positive correlation with FC between the MPFC and right LPFC. MOOD, GPIUS-2 subscale of using the Internet for mood regulation; GPIUS-2, General Problematic Internet Use Scale-2; FDR, false discovery rate; ROI, region of interest; MPFC, medial prefrontal cortex; LPFC, lateral prefrontal cortex.

Regarding the FC between the SN and FPN, an increase in FC has been reported to be associated with psychological benefits. In contrast, a decrease in FC has been reported in various psychiatric disorders, including substance dependence (Wilcox et al., 2019). Moreover, expert video gamers showed increased FC between the SN and FPN. This factor is potentially associated with higher cognitive functions including attention and working memory, which are required to play video games (Caplan, 2010).

Furthermore, elevated FC between the SN and the FPN protects against cocaine relapse (McHugh et al., 2017). Regarding mood regulation, lower FC of the SN-FPN is associated with repetitive negative thinking in patients with remitted major depression (Lydon-Staley et al., 2019), presumably because it functions as a hub of cognitive control (Marek and Dosenbach, 2018), and there is an interaction between cognition and mood response, as shown in the Person-Affect-Cognition-Execution model (Brand et al., 2019). Not

TABLE 3 Correlation between each inter-network integrity and GPIUS-2.

	SN-DMN	SN-FPN	DMN-FPN
GPIUS-2 total score (correlation efficient/ <i>p</i> -value)	0.037 0.705	0.085 0.387	0.084 0.392
POSI (correlation efficient/ <i>p</i> -value)	0.010 0.919	0.009 0.927	0.026 0.791
MOOD (correlation efficient/ <i>p</i> -value)	0.059 0.549	0.046 0.639	0.156 0.109
SELF (correlation efficient/ <i>p</i> -value)	0.039 0.691	0.107 0.276	0.037 0.710
NEGA (correlation efficient/ <i>p</i> -value)	−0.064 0.514	0.018 0.853	0.060 0.538

GPIUS-2, Generalized Problematic Internet Use-2; POSI, preference for online social interaction; MOOD, mood regulation; SELF, self-regulation; NEGA, negative outcome; SN, salience network; DMN, default mode network; FPN, frontoparietal network. A *p*-value < 0.05 was considered statistically significant.

only the above interpretation, but FPN has also been reported to be involved in various cognitive processes such as attention control or working memory (Schimmelpfennig et al., 2023; Sridharan et al., 2008). Therefore, it will be necessary to examine specific functions using fMRI tasks related to each cognitive function in the future.

Similarly, when focusing on FPN functions in mood regulation, one possible interpretation is that non-problematic Internet users might have elevated SN-FPN FC due to habitual Internet use, presumably aiming to regulate mood, resulting in successful coping with daily stress through more effective emotion recognition and processing. However, the causality between Internet use and FC remains unclear.

Depression is a common comorbid disorder in PIU, as shown in previous meta-analyses (Bozkurt et al., 2013; Ko et al., 2008). However, our results might be interpreted as a primary care benefit of Internet use below the intermediate level, considering that most Internet users would utilize the Internet at non-problematic levels and can regulate their own mood as a coping strategy against stress throughout their social lives.

The FC between the DMN and FPN was elevated during a divergent thinking task and was associated with creative cognition (Beatty et al., 2015). Moreover, the DMN and FPN cooperate during mind wandering (Andrews-Hanna et al., 2014; Christoff et al., 2009), and sufficient mind wandering can promote high performance during technological use (Sullivan and Davis, 2020). From our results, it can be said that an increase in FC between the DMN and FPN contributes to beneficial mind wandering and may support cognitive performance. Additionally, elevated FC in patients with DMN-FPN has been reported to lower the risk of depression (Mu et al., 2024). Our study results showed that higher DMN-FPN FC in individuals with higher (but non-problematic) levels of Internet use could be explained at a higher level in creative thinking or mind wandering, even in resting-state conditions, although further studies are needed to compare PIU and non-PIU in this context.

In addition to the network, each ROI identified in this study has been reported to be associated with mood regulation. From the

perspective of regional brain function, the results of the ROI-to-ROI FC analyses (section 3.2.1) in relation to the anterior insula, LPFC, and MPFC are consistent with those of previous studies regarding mood regulation. Evidence shows that the anterior insula is involved in mood regulation and plays an important role in controlling and allocating resources to the FPN. In addition, the bilateral insula is a key region of the SN that has been reported to be associated with mood. A meta-analysis of fMRI studies has revealed that the anterior insula is involved in the processing of cognitive and social emotions (Kurth et al., 2010). Moreover, this region is important for dealing with subjective emotional states (Namkung et al., 2017; Uddin, 2015). It has been reported that the mood-improving effects of mindfulness may be associated with increased blood flow in the insular cortex (Sezer et al., 2022; Tang et al., 2015). The LPFC and MPFC are involved in cognitive and emotional processing, and mood regulation (Smith et al., 2018; Tully et al., 2014). The left LPFC has been suggested to be a region of the circuit for emotion regulation (Grabell et al., 2019; Ochsner et al., 2012; Sarkheil et al., 2015). One possible interpretation is that the current study's the bilateral insular and synchronized LPFC activity resulted in well-functioning emotional regulation as an adequate coping strategy for individuals without PIU.

This study had several limitations. First, the causal relationship between non-PIU and FC in the SN and FPN is still unknown because of the cross-sectional nature of this study. Second, we did not consider the purpose of internet use, such as social networking services and gaming. There is still debate about whether online games, gambling, and pornography fall under the category of PIU, because the target behavior itself is addictive. Whether such behaviors are an issue of online use should be clarified in the future by examining individual lifestyle behaviors online. Such information can improve Internet literacy. Third, the GPIUS-2 total scores were not correlated with FC, although a significant relationship was found between mood regulation subscale scores and FC. Therefore, we cannot conclude that subclinical internet use generally facilitates FC. Further studies are warranted to clarify the causal relationship between Internet use and brain function as a representation of mental health using a longitudinal design with a larger sample size for each online behavioral problem. Fourth, the relatively shorter scan time of 360 s for resting fMRI may lead to inadequate capture of low-frequency oscillatory signals (0.01–0.1 Hz) in particular. We believe that future studies should be conducted with longer imaging time. Fifth, the spatial resolution of the functional images obtained in this study not very high. This may cause partial volume effects in some brain regions. However, since the target areas in this study were representative core regions and did not target fine structures, the bias is considered to be relatively small. Sixth, it is necessary for more accurate correction of physiological noise. Although the CompCor used in this study has been shown to be able to reduce physiological noise such as cardiac respiratory related-noise (Behzadi et al., 2007), it is desirable to introduce physiological noise correction by simultaneous measurement of physiological data in our future study. On the other hands, the strength of our study is that it is the first to investigate the alterations in the FC of triple networks in non-PIU patients.

Our findings can be summarized as follows. First, the direction of the correlation of FC among the three core networks with the score of Internet use for mood regulation in non-PIU was

opposite to the change in FCs in PIU. Second, most of the regions comprising the networks that showed a correlation with the Internet use score for mood regulation in non-PIU individuals were regions known to be involved in mood regulation. These results suggest that the resting-state FC of the SN-FPN and DMN-FPN can be used as potential biomarkers for distinguishing the safe use of the Internet from PIU. If the tendency to use the Internet for mood regulation is low to moderate, triple-network FC could be associated with better cognitive processing, potentially resulting in better mental health from the viewpoint of neural connectivity. We believe that these results will provide insight into Internet use, thus establishing ideal Internet literacy with safety and efficacy and appropriate risk assessment of PIU from the perspective of addictive problems. For example, considering FC alterations as a biomarker, and monitoring individuals at risk for PIU for MOOD scores in the appropriate range through periodic GPIUS-2 assessments may have a potential to contribute to mental health management. Furthermore, as reported in substance dependence, interventions involving rTMS targeting areas with impaired functional connectivity may be effective (Amiaz et al., 2009).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Kyoto University Graduate School and the Faculty of Medicine. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MSh: Investigation, Writing – review & editing, Formal Analysis, Data curation, Funding acquisition, Visualization, Conceptualization, Writing – original draft. KT: Conceptualization, Validation, Writing – review & editing, Supervision, Formal Analysis. KK: Data curation, Investigation, Writing – review & editing. SY: Supervision, Conceptualization, Writing – review & editing, Visualization. MSp: Writing – review & editing, Supervision. NO: Methodology, Software, Writing – review & editing, Investigation, Conceptualization, Project

administration, Formal Analysis, Visualization, Resources. TM: Project administration, Supervision, Writing – review & editing, Funding acquisition. HF: Methodology, Conceptualization, Supervision, Project administration, Writing – review & editing, Investigation, Visualization, Funding acquisition.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

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Tactile exploration and imagery elicit distinct neural dynamics in the parietal cortical network

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Background: Tactile imagery involves the reconstruction of sensory experiences without actual tactile input. While tactile perception and imagery exhibit similar spatial patterns of neural activation, the underlying neural dynamics, particularly cortical communications within the parietal network, remain unclear.

Methods: The present study recruited 5 patients with implanted stereo-electroencephalography (sEEG) electrodes and recorded sEEG data during texture scanning and imagery. Local neural representations and interregional communications among parietal cortical regions were analyzed.

Results: Opposing modulation patterns of local time-frequency representations were observed, with inhibited neural synchronization during texture scanning and activated synchronization during texture imagery. Consistently, the directional communication from the somatosensory cortex to the posterior parietal cortex (PPC) was found to be suppressed for scanning but enhanced for imagery. Additionally, bidirectional communication between the supramarginal gyrus and precuneus was activated during imagery but not scanning, suggesting a unique pathway for reconstructing tactile experiences.

Conclusion: Our findings proposed that while texture perception and imagery engage overlapping cortical regions, their mechanisms underlying local encoding and interregional communication are distinct.

KEYWORDS

tactile imagery, somatosensory cortex, posterior parietal cortex, texture scanning, sEEG (stereo-electroencephalography)

1 Introduction

Tactile sensation guides the interaction with the environment by modulating object manipulation in response to sensory feedback. For patients with sensorimotor disorders, artificial tactile sensations can be induced through microstimulation of the somatosensory cortex (Flesher et al., 2016; Greenspon et al., 2024; Hughes et al., 2021), enhancing neuroprosthetic control (Flesher et al., 2021; Valle et al., 2025). While tactile stimulation is encoded in the somatosensory cortex (Delhaye et al., 2018; Jiang et al., 2018; Lieber and Bensmaia, 2019, 2020; Long et al., 2022; Rossi-Pool et al., 2021), the mechanisms underlying its projection to higher-order brain regions for the formation of sensory perception remain unclear. In particular, for patients with impaired sensory inputs, understanding how tactile

experience is generated without real sensory input is crucial for improving the effectiveness of artificial sensation.

Tactile imagery is a top-down process that reconstructs past sensory experiences, recruiting a distributed neural network including the somatosensory cortex and the posterior parietal cortex (Yoo et al., 2003). It provides insights into the formation of tactile experiences, particularly for patients whose sensory input functions are impaired (Bashford et al., 2021; Chivukula et al., 2021). Recent studies have highlighted the potential of tactile imagery in neurorehabilitation. It was demonstrated that tactile imagery achieved classification performance comparable to motor imagery in brain-computer interface (BCI) applications (Sengupta and Lakshminarayanan, 2024; Yao et al., 2018, 2022) and further enhanced motor decoding when integrated with motor imagery (Ahn et al., 2014; Zhong et al., 2023). Furthermore, prolonged training in tactile imagery was shown to enhance both BCI performance (Yao et al., 2019) and cognitive function (Lakshminarayanan et al., 2023), suggesting that tactile imagery would be a promising strategy for cognitive and motor rehabilitation.

There has been a debate of whether perceived and imagined tactile sensation share common neural functions. Neuroimaging studies found that tactile imagery evoked somatotopic activation alike actual perception within the somatosensory cortex, supporting the existence of common neural substrates (Nierhaus et al., 2023; Schmidt et al., 2014; Schmidt and Blankenburg, 2019; Yoo et al., 2003). Similarly, electroencephalography (EEG) studies have demonstrated contralateral event-related desynchronization (ERD) in the somatosensory cortex during tactile imagery, mirroring the neural responses elicited by actual tactile stimuli (Morozova et al., 2024; Wen et al., 2024; Yakovlev et al., 2023). However, some findings suggest that while tactile perception and imagery share common locations of neural activities, the directionality of neural projection is reversed (Dentico et al., 2014). Specifically, tactile perception with actual input involves a bottom-up process storing sensory information in higher-order regions, whereas tactile imagery reinstates past sensory experiences in the somatosensory cortex via top-down processing.

The posterior parietal cortex (PPC) has been recognized for its role in multisensory integration and sensorimotor coordination. Functionally interconnected with multiple brain regions, including the sensory cortex, the PPC integrates multimodal sensory inputs to construct coherent perceptual representations, which are then utilized to regulate motion through sensory feedback (Akrami et al., 2018; Creem-Regehr, 2009; Delhay et al., 2018; Klautke et al., 2023; Whitlock, 2017). PPC has been shown to encode somatotopic tactile perception (Huang et al., 2012; Sereno and Huang, 2014) and respond to tactile properties such as object size and shape during sensorimotor interactions (Michaels et al., 2020; Schaffelhofer et al., 2015). Recent studies suggest that the PPC is also involved in tactile cognitive processes that occur in the absence of real sensory input. In clinical studies involving patients implanted with microelectrode arrays, the supramarginal gyrus (SMG) and the junction of the intraparietal sulcus and postcentral sulcus (PC-IP) have been found to encode tactile information during observation and imagery of touching (Bashford et al., 2021; Chivukula et al., 2021, 2025). It was also found that tactile imagery elicited body-part-specific responses locally in PPC similar to actual touch, supporting the hypothesis of overlapping neural mechanisms within higher-order cognitive centers. However, the neural pathway through which the somatosensory cortex transfers information to the PPC, as well as the internal communication dynamics within the PPC during tactile processing, remain unclear.

Investigating interregional communication of tactile imagery has been challenging, as neuroimaging approaches such as fMRI are constrained by limited temporal resolution, making it difficult to capture frequency-domain features, particularly in high-frequency bands. Stereo-electroencephalography (sEEG), which involves the implantation of electrodes with multiple contacts across different brain regions (Cardinale et al., 2016; Parvizi and Kastner, 2018), enables the simultaneous recording of neural activity across cortical and subcortical areas with both broad spatial coverage and high temporal resolution. It allows for the characterization of network connectivity within the parietal cortex in both the time and frequency domains. sEEG has been employed to decode various sensorimotor functions, including different hand postures, movements, and tactile sensations (Bouton et al., 2021; Breault et al., 2019; Li et al., 2022; Wu et al., 2022, 2023; Wu et al., 2024b), and has been applied in recovery of language disorders (Huang et al., 2021; Wu et al., 2024a). Despite its advantages, no studies to date have comprehensively investigated the parietal neural networks including the somatosensory cortex and PPC during tactile perception and imagery with sEEG.

The current study aimed to identify the local neural representation and interregional communication of the parietal cortical network in clinical patients implanted with sEEG electrodes. As manual texture perception typically involves active hand–environment interaction and can influence object manipulation strategies (Picard and Smith, 1992), an active texture perception task was employed to better capture task-relevant tactile processing. The findings revealed dissociable patterns of local neural synchronization and interregional connectivity within the parietal cortical network between texture scanning and imagery. These results suggested that although both tactile perception and imagery are encoded in somatosensory and posterior parietal cortices, they engage distinct patterns of neural responses and communications.

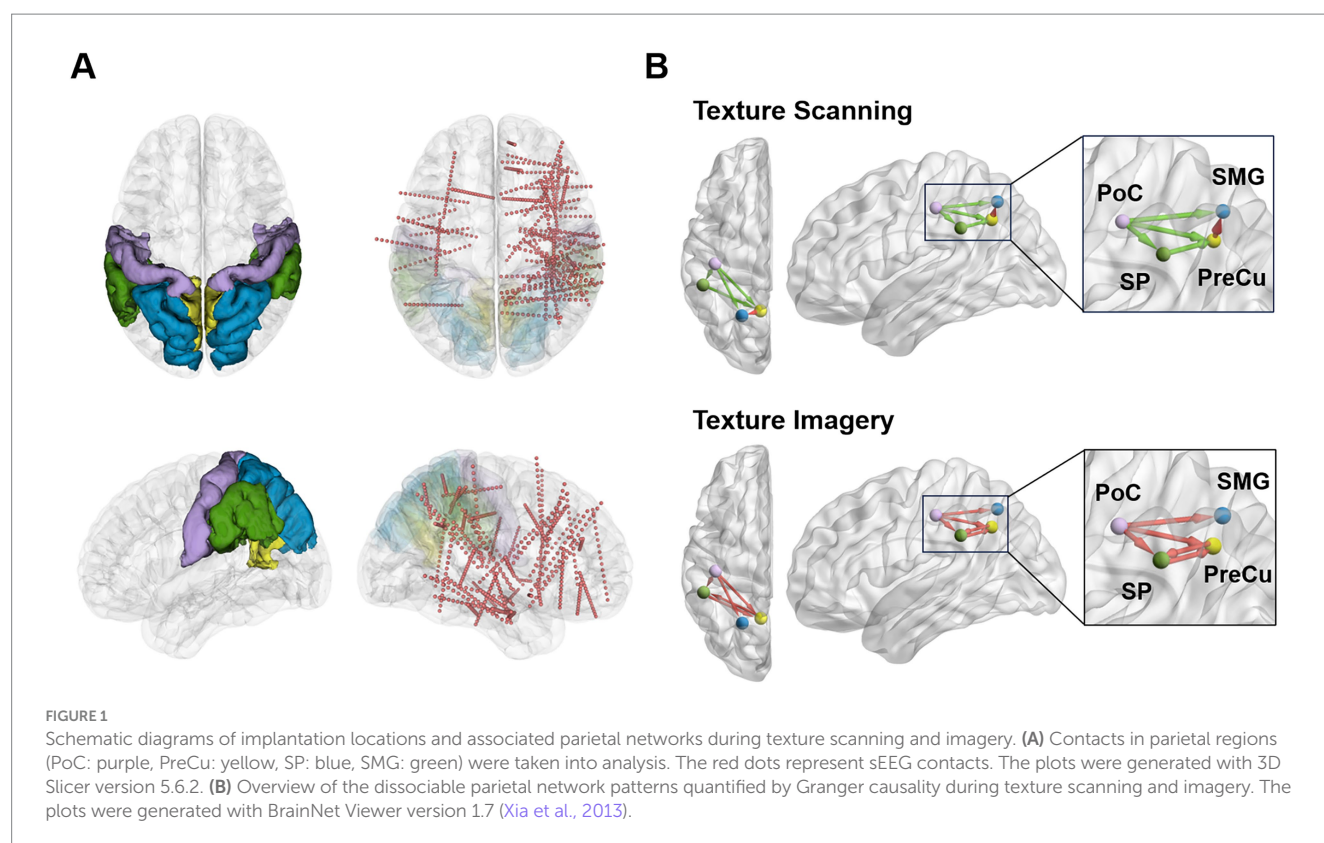
2 Materials and methods

2.1 Participants

Five participants were included in the current study (2 males, 3 females; mean age: 30 ± 8.78 years). All participants were patients with refractory epilepsy and were undergoing presurgical assessment. Participation was entirely voluntary, and all individuals were informed that their involvement in the study would not influence their clinical treatment and that they retained the right to withdraw at any time. Additionally, all experimental procedures were in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University. Notably, all participants remained seizure-free throughout the data collection period.

2.2 Implantations

Electrode placement was determined exclusively based on clinical requirements and was independent of the study's objectives. Each participant was implanted with 6 to 18 semi-rigid platinum/iridium electrodes (shaft diameter: 0.8 mm), with each electrode containing 8 to 16 recording contacts (contact length: 2 mm; inter-contact space: 1.5 mm; Huake Hengsheng, Beijing, China). Two participants received electrode implantation in the left hemisphere, two in the right



hemisphere, and one underwent bilateral implantation. Across all five participants, a total of 850 recording contacts were implanted.

High-resolution pre-operative T1-weighted MPRAGE volumes were processed with FreeSurfer¹ to generate subject-specific cortical segmentations in native space. Centroids of electrode contacts, localized on post-implantation CT scans, were rigidly coregistered to the MPRAGE volumes and projected onto the segmented cortical surface, thereby assigning each recording site an unambiguous neuroanatomical label. For group-level visualization, the resulting electrode coordinates were subsequently normalized to MNI-space via an affine transformation implemented in SPM12.²

In accordance with the Desikan-Killiany cortical parcellation template (Desikan et al., 2006), the parietal cortex in this study was segmented into the inferior parietal cortex (IP), postcentral gyrus (PoC), precuneus cortex (PreCu), superior parietal cortex (SP), and supramarginal gyrus (SMG, Figure 1). Data from contacts located in PoC ($n = 17$ contacts), PreCu ($n = 12$), SP ($n = 12$), and SMG ($n = 24$) were included in the following analysis (see more details in Table 1). IP was excluded due to the limited number of recording contacts.

2.3 Experimental paradigm and procedures

During the task, the patient reclined on a hospital bed with eyes directed toward a monitor positioned approximately 2 m away at the

end of the bed. The hand contralateral to the electrode implantation site rested toward a circular rotating platform on the table. Four distinct textured materials—synthetic fur, paper, glass, and fabric—were mounted on the circular rotating platform, each covering one-quarter of its surface. A U-shaped barrier was positioned between the participant and the platform, restricting visual access but permitting tactile contact via the fingers. When a specific texture was to be explored, the operator remotely rotated the platform to align the corresponding material to the participant's finger.

The texture cognition task was structured into three distinct phases: texture observation (TO), texture scanning (TS), and texture imagery (TI, Figure 2). At the beginning of each trial, an image of the texture material was presented on the screen for 4 s. Following a 2.5-s interval, participants actively explored the corresponding physical texture from left to right using their index finger. The speed of finger moving was guided by a moving dot which traveled across the screen at a constant speed for 4 s. After a subsequent 2-s interval, participants were asked to imagine the tactile sensation of the texture they had just explored for another 4 s. The experiment comprised 10 blocks, with each block consisting of 20 entire trials covering TO, TS, and TI. The four materials were presented in a pseudo-randomized order within each block, ensuring that each block contained 5 trials per texture type.

2.4 Data recording and preprocessing

Neural activity was recorded by a 128-channel amplifier (Neuroscan, Australia) with a sampling rate of 1,000 Hz. For participants implanted with more than 128 recording contacts, priority was given to contacts located in the parietal cortex and other cortical

¹ www.freesurfer.net/

² www.fil.ion.ucl.ac.uk/spm/

TABLE 1 Number of electrode contacts in each region of interest.

Participants	PoC	PreCu	SP	SMG
S1	4	2	1	6
S2	3	6	4	8
S3	0	3	4	3
S4	0	0	0	4
S5	10	1	3	3

gray matter regions. During data acquisition, channels exhibiting excessively great noise or impedance were manually excluded. To preprocess the EEG signals, a notch filter was applied to reduce 50 Hz power interference. Subsequently, a bandpass filter ranging from 2 to 90 Hz was implemented. To characterize the continuous neural dynamic across tasks, each epoch was extracted from -2 s to 16.5 s aligned to the onset of TO, which covered the entire task of TO, TS and TI. $-2\sim 0$ s pre-TO period was used for baseline correction. Finally, the data were downsampled to 250 Hz for further analysis.

2.5 Temporal-spectral representation (TFR)

The Short-Time Fourier Transform (STFT) was applied to the entire trial (-2 to 16.5 s aligned to the onset of TO) to compute power in the time-frequency domain. To minimize carryover effects from preceding phases and anticipatory effects from subsequent phases, baseline power was defined as the power recorded during the period from -0.5 to -0.2 s before the onset of each task phase (TO, TS, and TI). Baseline correction was performed by division, followed by log transformation.

While the function of alpha and beta bands in tactile imagery has been discussed in EEG studies (Yakovlev et al., 2023; Yao et al., 2018), recent intracranial work has demonstrated that gamma-band (>30 Hz) activity exhibits great classification performance for tactile imagery (Bashford et al., 2021). Therefore, a broader range of frequency band (from delta to high gamma) was included to enable a comprehensive understanding of the spectral signatures underlying tactile perception. Average power was computed for six distinct bands: delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), gamma1 (30–60 Hz), and gamma2 (60–90 Hz). To account for variability in task onset times due to differences in reaction speed, TFR were analyzed using the average power recorded between 0.5 and 3.5 s following task initiation.

2.6 Classification

A shallow convolutional neural network (ShallowNet) was employed to classify the three tasks based on single-channel neural activities (Schirrmester et al., 2017). For each task (TO, TS, and TI), band-filtered time-series sEEG signals recorded from 0 s to 4 s following task onset were used. The dataset was pooled across four texture conditions (50 trials per texture), resulting in 200 trials per task. The training set comprised 160 trials per task (480 trials in total), while both the validation and test sets included 20 trials per task (60 trials in total). This classification procedure was repeated for all six frequency bands.

2.7 Coherence

Coherence serves as a measure of functional connectivity by quantifying neural synchronization between brain regions within specific frequency bands. For each participant, pairwise coherence was computed between recording contacts in different parietal regions across all six frequency bands. A sliding window (2-s window with 100-ms step size) was employed to capture continuous coherence dynamics throughout the task period (-2 to 16.5 s relative to TO onset). To ensure comparability, coherence values were standardized to a standard deviation of 1 and baseline-corrected using the mean coherence from -2 to 0 s prior to the onset of each task phase (TO, TS, TI). Coherence analysis was performed using functions from the Chronux toolbox (Cold Spring Harbor Laboratory, NY, USA).

2.8 Granger causality

Granger-Geweke causality analysis was conducted to evaluate the directional information transfer among parietal regions (Dhamala et al., 2018). We applied conditional Granger causality (CGC) to assess the causal influence of one contact (i) on another (j) while accounting for the potential contributions of additional contacts (k). Within-participant CGC analysis was performed pairwise between recording contacts across different regions of interest. All contacts, except those from the same region as i, were designated as k, ensuring that their influence on j was accounted for in the analysis. The same sliding window approach (2-s window with 100-ms step size) and standardization procedure were applied to normalize CGC values.

2.9 Statistics

Non-parametric methods were employed in the current study due to small sample sizes in some tests. The Wilcoxon Signed-rank Test was used for comparisons for time-frequency representation and functional connectivity between results of the baseline and tactile processes, with the p value corrected for multiple comparison (e.g., $p*3$ when conducting multiple comparison between the baseline and TO/TS/TI). Two-sided tests were conducted as no clear hypothesis of the modulation direction was made. The Kruskal-Wallis test was used for classification accuracy among various frequency bands, with Bonferroni correction for post-hoc tests. All the statistical analyses were conducted in MATLAB 2020b (MathWorks, USA).

3 Results

3.1 Contrasting time-frequency representation for texture scanning and imagery

Firstly, we compared the local time-frequency representation for various tactile processes among parietal cortices. Across all four cortical regions of interest, power in the lower-frequency bands (below 30 Hz) exhibited significant decreases (ERD) during TS (Figures 3A,B). Weaker suppressions were observed in the delta and theta bands during TO, while the alpha band remained unaffected. In

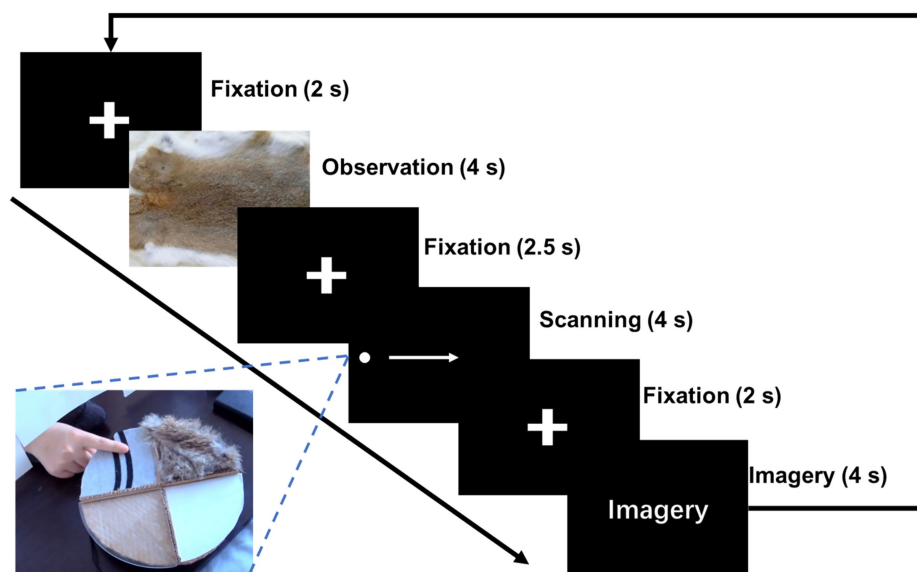


FIGURE 2
Experimental paradigm of texture cognitions. Three tasks of texture cognition were included in the experiment: Texture Observation (TO), Texture Scanning (TS), and Texture Imagery (TI).

contrast, TI showed an overall increase of TFR relative to baseline. Specifically, power for alpha and beta bands significantly increased in SP and SMG, while beta and gamma1 power showed significant increases in PoC. No significant power changes were observed in PreCu compared to baseline. These findings indicated that while all three tactile processes modulated local neural encoding in parietal cortices including both the somatosensory and the PPC, they induced distinct patterns of TFR. The opposing responses observed between TS and TI suggest that these processes are governed by independent neural mechanisms.

To further validate task-related differences, ShallowNet was employed to classify TO, TS, and TI using single-channel sEEG data. As a result, classification accuracy for each brain region exceeded chance levels (Figure 4A). In PoC, SP, and SMG, the beta band revealed the highest classification accuracy (mean $\pm$ std.: PoC: $56.96 \pm 12.51\%$, SP: $61.94 \pm 7.77\%$, SMG: $49.75 \pm 11.09\%$), highlighting the importance of beta band features in texture processing. The confusion matrix of beta band revealed the greatest precision for TS in all brain regions, indicating that TS achieved the greatest effect on parietal neural activities, while neural responses for TO and TI were weaker and were more likely to be confused against each other (Figure 4B).

3.2 Interregional coherence is frequency-related during texture processing

Coherence analysis was conducted to characterize interregional synchronization patterns, providing insights into neural communication within the parietal cortex. The coherence dynamics revealed a frequency-dependent modulation. During TS, coherence increased in lower-frequency bands (below 8 Hz) but decreased in higher-frequency bands (above 30 Hz). Conversely, during TI, coherence decreased in lower-frequency bands but increased in

higher-frequency bands. In consistent with TFR, results of coherence confirmed the distinct neural dynamics between texture scanning and imagery from the perspective of interregional communication, in which tactile processes were potentially interacted with frequency. Notably, gamma2 coherence (60–90 Hz) showed significant deviations from baseline during both TS and TI across all pairs of parietal regions, suggesting that high-frequency interregional synchronization plays a critical role in both the perception and the reconstruction of textural sensations (Figure 5).

3.3 Unique neural communication patterns for texture scanning and imagery

Furthermore, conditional Granger causality analysis was conducted to investigate the directional information flow within the parietal cortical network (Figure 1B). Firstly, bidirectional CGC between the somatosensory cortex and posterior parietal cortices were compared between texture scanning and imagery. During TS, CGCs from PoC to PPC regions were reduced compared to baseline, particularly in the alpha and beta frequency bands (Figures 6, 7), indicating that TS suppressed somatosensory-to-PPC neural communication. In contrast, during TI, CGCs from PoC to SP and SMG were enhanced in the beta and higher frequency bands, suggesting a dissociable dynamics in neural communication from the somatosensory cortex to PPC between TS and TI. In terms of projections from PPC to the somatosensory cortex, TS facilitated gamma1 CGC from SP to PoC while inhibiting gamma1 and gamma2 CGCs from PreCu to PoC. However, no significant modulation of CGC was observed from PPC regions to PoC during TI, suggesting the pathway from the somatosensory cortex to the posterior parietal cortex is unidirectional during the reconstruction of tactile sensation.

We then compared CGCs within PPC regions to identify the effect of tactile processes on intra-PPC communications. Across all

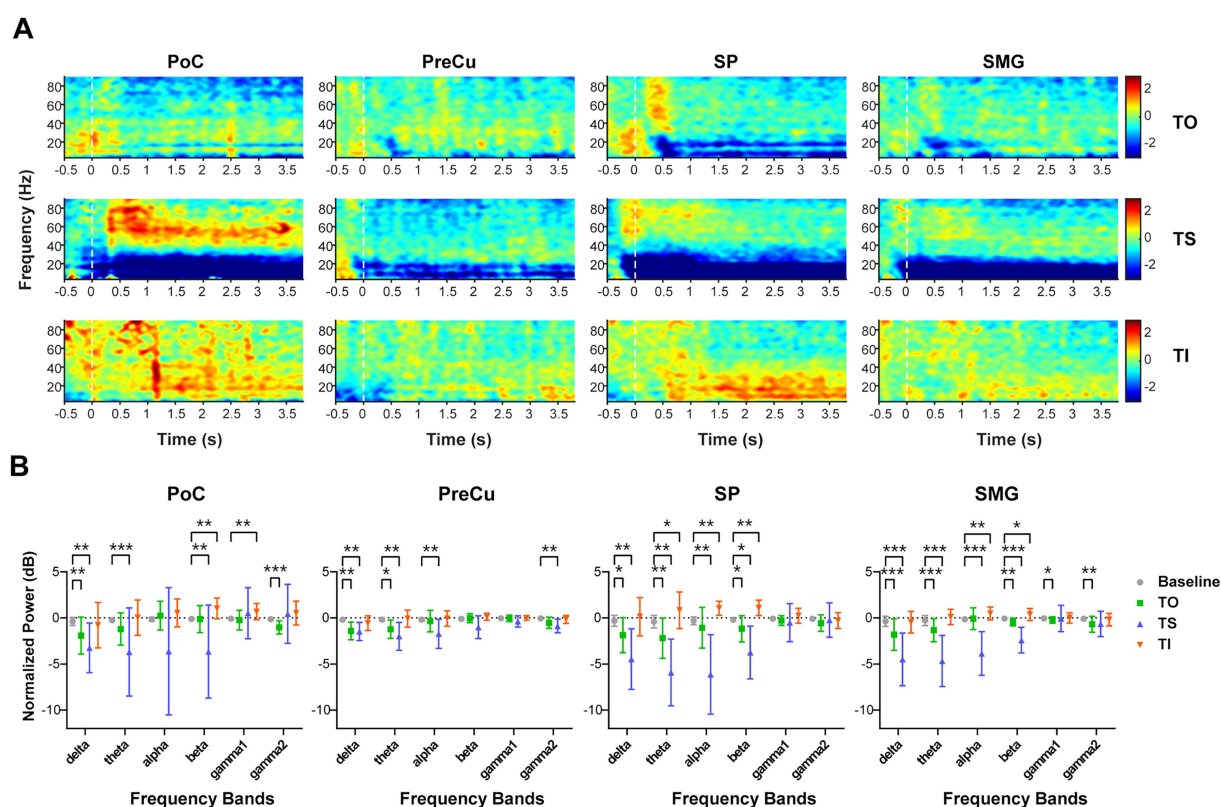


FIGURE 3

Time-frequency representation during texture processing. (A) Corrected time-frequency representation for the four brain regions at different task phases. The color map represents the calibrated power (dB). (B) Comparison of time-frequency representation between task and baseline for each frequency band. The Wilcoxon signed-rank test was used, and p -values were corrected for multiple comparisons. Sample sizes for each brain region were as follows: PoC ($n = 17$), PreCu ($n = 12$), SP ($n = 12$), SM ($n = 24$). *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. Error bars represent standard deviation.

frequency bands, TS was found to enhance CGCs from PreCu to SP but inhibit CGCs from SMG to PreCu. Conversely, TI facilitated bidirectional communication between SMG and PreCu. In fact, TI achieved an overall increase in intra-PPC CGCs, but not in CGCs from PreCu to SP. The results indicated that the reconstruction of tactile sensation activated neural communication within the PPC in a pattern completely different to tactile exploration. Together, our finding highlighted the uniqueness of functional parietal networks during texture scanning and imagery.

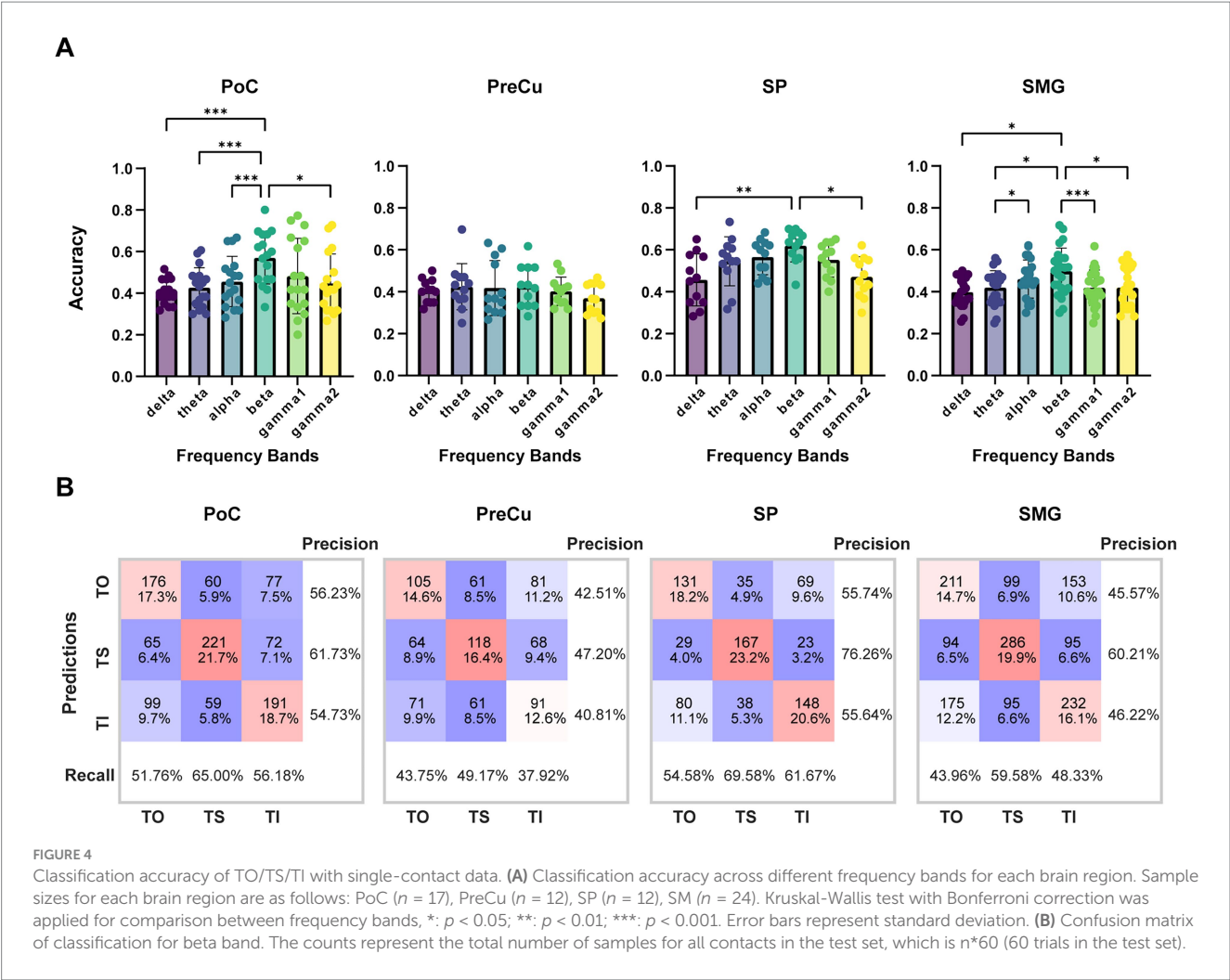
4 Discussion

The current study identified distinct patterns of neural activity and communication in the parietal cortex during texture cognitions with invasive sEEG. Texture scanning induced ERD in the low-to-mid-frequency bands of the somatosensory and posterior parietal cortices, whereas texture imagery induced ERS. Frequency-dependent interregional synchronization was observed, with opposing trends in low- and high-frequency bands. Additionally, texture scanning suppressed neural communication from the somatosensory cortex to the PPC, whereas imagery enhanced both somatosensory-to-PPC and intra-PPC communication. These findings reveal unique local and network-level neural dynamics underlying tactile perception and reconstruction. Our work shed light on the neural mechanism

underlying the formation of tactile experience, providing theoretical foundation for inducing biomimetic artificial sensations in patients with paralysis.

4.1 Local neural encoding for texture processing in parietal cortices

Neuroimaging studies suggested that tactile perception and imagery share a common neural substrate, leading to activations in the somatosensory cortex during tactile imagery (Schmidt et al., 2014; Schmidt and Blankenburg, 2019; Yoo et al., 2003). This is also supported by electrophysiological evidence, as ERD was observed in both tactile stimulation and imagery (Wen et al., 2024; Yakovlev et al., 2023). Consistent with previous findings (Henderson et al., 2022), we found that texture scanning suppressed neural oscillations below 30 Hz in the parietal cortices. However, texture imagery did not induce ERD but instead induced ERS. These results indicated distinct patterns of neural activities despite overlapped cortical locations. Limited by low spatial resolution, previous EEG studies primarily focused on the time-frequency representation of the central region, which integrated neural activity from multiple sources, including the precentral and postcentral gyri. ERS in the somatosensory cortex might be difficult to detect due to the great ERD in the motor cortex during the imagery. Though not explicitly stated, some studies



observed alpha-beta ERS in the posterior parietal and occipital regions during sensory imagery (Sengupta and Lakshminarayanan, 2024; Yakovlev et al., 2023; Yao et al., 2018), suggesting that ERS in PPC and somatosensory cortex might have been overlooked. Unlike EEG studies, we used invasive sEEG to precisely record intracortical neural activity, enabling more accurate localization of cortical representations during texture imagery.

Alpha and beta desynchronization have traditionally been considered key signatures of sensorimotor processing (Engel and Fries, 2010; Sigala et al., 2014). In the somatosensory cortex, power in both alpha (Klimesch, 2012; Su et al., 2020) and beta (Cheyne et al., 2003; Gaetz and Cheyne, 2006; Kilavik et al., 2013) bands is typically suppressed during tactile stimulation or sensorimotor coordination. This suppression is thought to reflect increased cortical excitability, thereby facilitating the processing of cutaneous and proprioceptive inputs (Gaetz and Cheyne, 2006). Alternatively, ERS is often interpreted as a marker of local neural inhibition (Klimesch, 2012; Neuper et al., 2006). In light of this framework, the ERS observed in our study may indicate a suppression of bottom-up sensory input during the imagery process, thereby allowing attention to be directed more effectively toward endogenously generated perceptual experiences. Another possibility is that the observed ERS may reflect working memory processes. The tactile imagery task in

our experiment essentially involved the mental reconstruction of a previously experienced sensation, which engages working memory—a function closely linked to beta oscillations (Engel and Fries, 2010; Spitzer and Haegens, 2017). Numerous studies have demonstrated that working memory engagement is associated with increased beta-band power (Lundqvist et al., 2016, 2018; Schmidt et al., 2019). Thus, the observed increase in beta power likely reflects working memory processing. Similarly, recent findings suggest that alpha-band ERS can occur during the retention phase of working memory tasks (Wianda and Ross, 2019; Zhodzikhavili et al., 2022). In summary, our results indicated that while both the somatosensory and posterior parietal cortices are involved in texture scanning and imagery, the neural synchronization patterns underlying these processes are distinct.

4.2 High-gamma interregional synchronization distinguishes texture scanning and imagery

We investigated the communication between the somatosensory cortex and PPC (SP, PreCu, SMG) through coherence analysis, based on the principle that effective communication occurs between

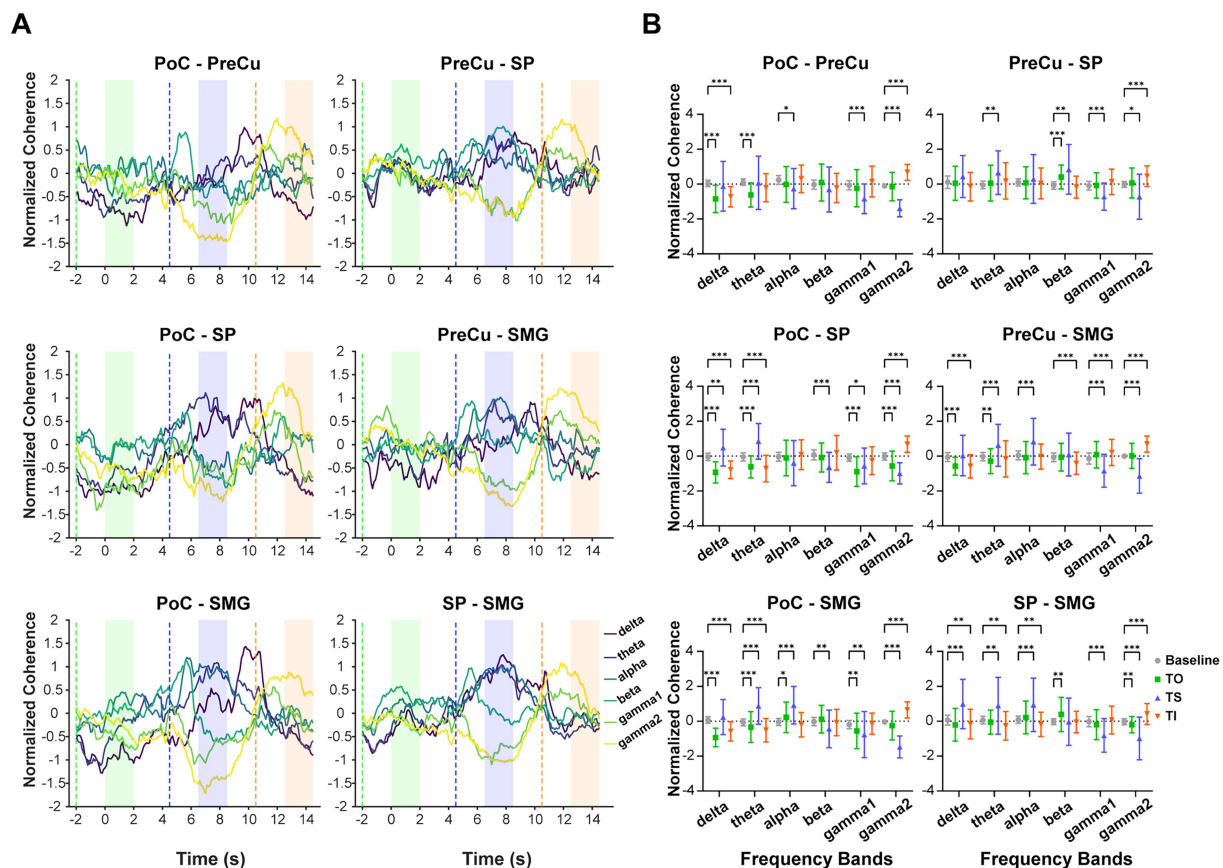


FIGURE 5

Coherence across texture processing tasks and frequency bands. (A) The mean standardized coherence between each pair of brain regions over time. Coherence was calculated using a 2-s window with a 100-ms sliding step. The x-axis represents the time corresponding to the left edge of the window, aligned with the onset of TO task at 0 s. The dashed line indicates when the moving window starts entering the task phase, while in the shaded area the moving window is fully covered by the task phase. Colors of shaded areas match with tasks: TO: green; TS: blue; TI: orange. (B) Standardized coherence compared between tasks and baseline. The sample sizes for coherence between brain regions are as follows: PoC-PreCu: $n = 36$ pairs of contacts, PoC-SP: $n = 46$, PoC-SMG: $n = 78$, PreCu-SP: $n = 41$, PreCu-SMG: $n = 72$, SP-SMG: $n = 59$. Wilcoxon Signed-rank test with adjusted p -values was applied for multiple comparisons. *: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. Error bars represent standard deviation.

phase-locked oscillations, ensuring synchronous input-output coupling (Fries, 2005). Consistent with the time-frequency representation, interregional synchronization revealed contrasting patterns between texture scanning and imagery. Notably, this coherence was frequency-dependent, indicating an interaction between tasks (scanning vs. imagery) and oscillatory frequency. Our findings highlighted the role of high-frequency gamma coherence (>60 Hz) in texture scanning and imagery. Gamma activity has been recognized as a fundamental mechanism underlying cortical information processing (Fries, 2009) and has been implicated in tactile perception (Ryun et al., 2017). Interregional gamma synchronization is known to modulate the efficacy, precision, and selectivity of neural communication (Buzsáki and Schomburg, 2015; Fries, 2005, 2015). Our results revealed a suppression of high-frequency communication across parietal regions during texture scanning, whereas the communication was enhanced during imagery. This enhancement was likely driven by selective attentions, as tactile imagery directed attentional resources toward the fingers (Ahn et al., 2014; Yao et al., 2019), a top-down process known to strengthen gamma coherence (Bauer et al., 2006; Vinck et al., 2013). The pattern of gamma2 interregional communication is also supported by results

of Granger causality, which demonstrated a significant enhancement of gamma2 information flow during imagery. Collectively, these findings suggested that high-gamma interregional communication obtains distinct task-dependent patterns, with a pronounced activation during top-down processing.

4.3 Opposing modulation of parietal communication by tactile perception and reconstruction

The posterior parietal cortex is well established as a high-level sensory region that integrates sensory inputs and modulates sensorimotor interactions (Freedman and Ibos, 2018; Whitlock, 2017). Prior research has demonstrated that specific subregions, such as the SMG and the intraparietal sulcus (IPS), are involved not only in responding to tactile stimuli but also in tactile imagery and observation (Bashford et al., 2021; Chivukula et al., 2021, 2025). One step further, our findings revealed that the PPC, particularly the SMG and SP, plays a critical role in texture processing, including both observation and imagery.

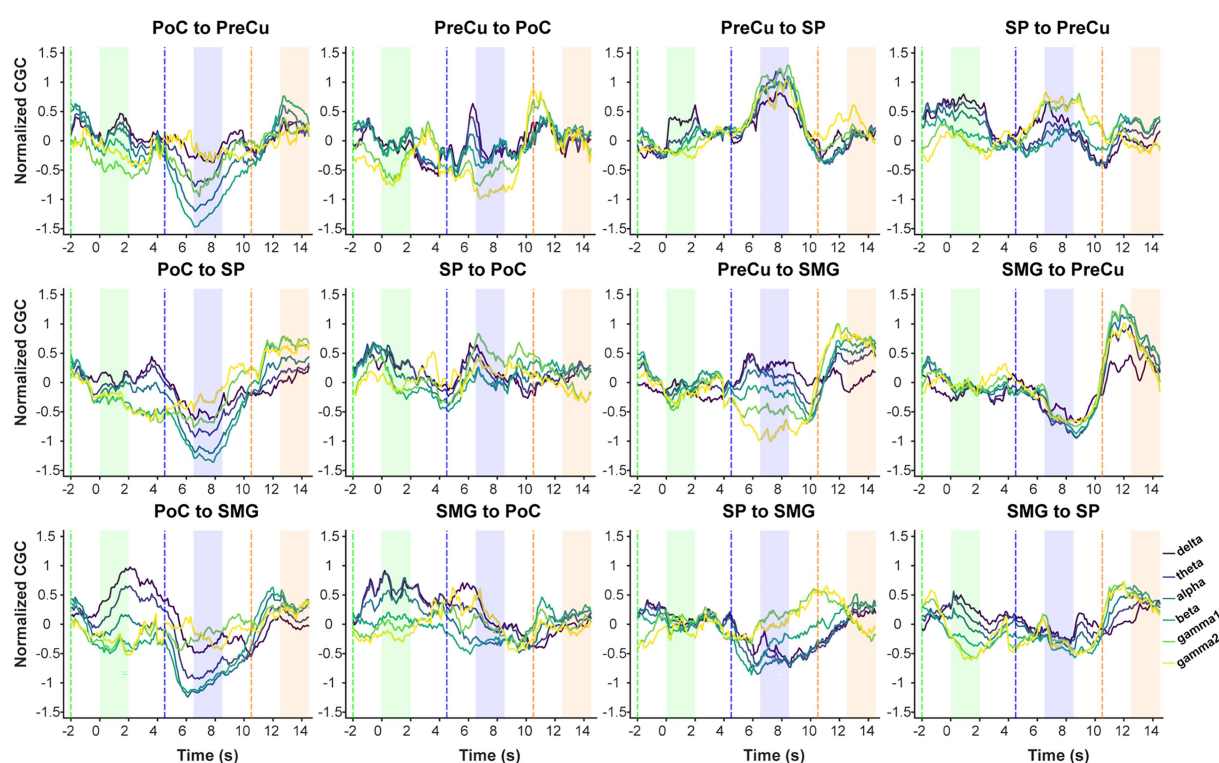


FIGURE 6

Continuous conditional Granger causality. Temporal dynamics of mean standardized CGC. CGC was computed using a 2-s sliding window with a 100-ms step. The x-axis represents the time corresponding to the left edge of the window, with 0 s aligned to the onset of the texture observation task. Dashed lines indicate the time when the sliding window entered the task phase, while in the shaded area the moving window is fully covered by the task phase. Colors of shaded areas match with tasks: TO: green; TS: blue; TI: orange.

Our study further investigated the long-range projection within the parietal cortex. Contrary to the expected bottom-up sensory flow, we observed suppressed causal relationship from the somatosensory cortex to the posterior parietal cortex. The suppression was possibly attributed to movement-related sensory gating, that texture-related neural projection was inhibited by finger movements (Chapin and Woodward, 1982; Song and Francis, 2015; Urbain and Deschênes, 2007). The finding suggested that PPC, in coordinating motor functions, actively suppressed the bottom-up projection of sensory information. During imagery, projection from the somatosensory cortex to the motor cortex was enhanced above 30 Hz, indicating that even in the absence of actual sensory input, the somatosensory cortex continued to encode and transfer tactile information to higher-order centers. Besides, although the causal relationships revealed dissociable trends between scanning and imagery from PoC to PPC, no modulation on the opposite information flow (from PPC to PoC) was observed during imagery. Thus, our results did not support the hypothesis that imagery reverses the direction of information flow of tactile perception (Dentico et al., 2014). Instead, our findings suggested that texture perception and imagery exerted a unidirectional influence on bottom-up projection, with top-down neural communication unaffected by texture cognitions.

Furthermore, we found that the internal network within PPC was actively engaged during texture imagery. Notably, bidirectional information transfer between the SMG and PreCu was significantly enhanced across frequency bands above 4 Hz. The SMG has been

implicated in both tactile observation and imagery (Bashford et al., 2021), while the PreCu is known to contribute to imagery tasks (Cabbai et al., 2024; Schmidt et al., 2014; Tomasino et al., 2022). Moreover, the PreCu is considered a key component of the core construction network, which is engaged in cognitive processes such as recalling past experiences or imagining unreal events (Dadario and Sughrue, 2023; Hassabis and Maguire, 2009; Madore et al., 2016; Spreng et al., 2009; Summerfield et al., 2010; Yamaguchi and Jitsuishi, 2024). Our results suggested that the SMG-PreCu pathway is crucial in texture-related tactile imagery. The distinct modulation of observation and imagery on SMG-PreCu pathway indicated its specific involvement in the active reconstruction of past experiences rather than in the passive recognition of texture concepts.

4.4 Limitation and future direction

Due to the limited time available for patient participation, our study did not include a passive texture stimulation condition, which could further clarify the influence of movement on sensory processing, thereby providing a clearer theoretical framework for texture-related neural projection. Future research should aim to compare texture perception under conditions with and without movement, as well as examine differences in the parietal network between passive texture perception and active tactile imagery.

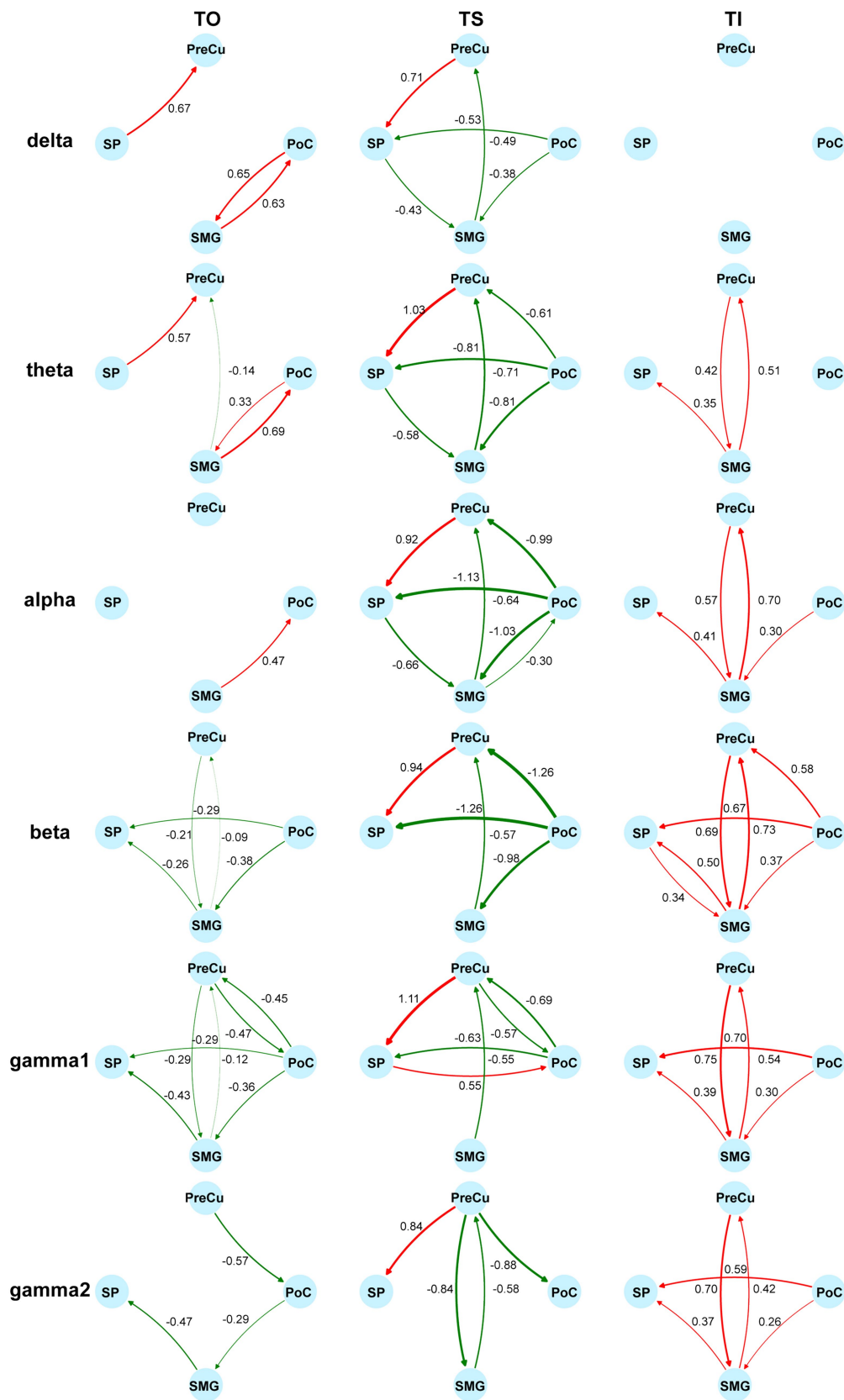


FIGURE 7
Modulation of directional information flow in the parietal network. Information flow is quantified by the difference of standardized CGC between tasks and the baseline. The columns reflect tactile processes (TO/TS/TI) and the rows reflect bands. Increases of CGCs are colored in red and decreases of CGCs are colored in green. Non-significant differences from the baseline are not shown (Wilcoxon signed-rank test, adjusted $p < 0.05$). Sample sizes are as follows: PoC-PreCu: $n = 36$, PoC-SP: $n = 46$, PoC-SMG: $n = 78$, PreCu-SP: $n = 41$, PreCu-SMG: $n = 72$, SP-SMG: $n = 59$, for both directions.

Data availability statement

The datasets presented in this article are not readily available because the datasets generated in the current study are not open to public due to data privacy regulations of patient data. Requests to access the datasets should be directed to Changyong Wang, wcy2000_zm@163.com.

Ethics statement

The studies involving humans were approved by Ethics Committee of Xuanwu Hospital, Capital Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

QZ: Conceptualization, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. YY: Conceptualization, Data curation, Formal analysis, Writing – original draft. ZW: Writing – review & editing. JiaZ: Writing – review & editing. RG: Methodology, Resources, Writing – review & editing. XY: Formal analysis, Writing – review & editing. SL: Formal analysis, Writing – review & editing. TY: Project administration, Resources, Writing – review & editing. JinZ: Conceptualization, Project administration, Writing – review & editing. CW: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

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Computational modeling of visual salience alteration and its application to eye-movement data

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Computational saliency map models have facilitated quantitative investigations into how bottom-up visual salience influences attention. Two primary approaches to modeling salience computation exist: one focuses on functional approximation, while the other explores neurobiological implementation. The former provides sufficient performance for applying saliency map models to eye-movement data analysis, whereas the latter offers hypotheses on how neuronal abnormalities affect visual salience. In this study, we propose a novel saliency map model that integrates both approaches. It handles diverse image-derived features, as seen in functional approximation models, while implementing center-surround competition—the core process of salience computation—via an artificial neural network, akin to neurobiological models. We evaluated our model using an open eye-movement dataset and confirmed that its predictive performance is comparable to the conventional saliency map model used in eye-movement analysis. Beyond eye-movement prediction, our model enables neural-level simulations of how neurobiological disturbances influence salience computation. Simulations showed that parameter changes for excitatory-inhibitory balance, baseline neural activity, and synaptic connection density affected the contrast between salient and non-salient objects—in other words—the weighting of salience. Finally, we demonstrated the model's potential for quantifying changes in salience weighting as reflected in eye movements, highlighting its ability to bridge both predictive and neurobiological perspectives. These results present a novel strategy for investigating mechanisms underlying abnormal visual salience.

KEYWORDS

visual salience, saliency map, computational model, neural network, eye movement

1 Introduction

The brain receives vast amounts of information from sensory organs, including stimuli important for survival and those that can be ignored without consequence. To enable appropriate responses, attention must be selectively directed at each moment. Studies on the visual system suggest that salience, based on low-level visual features, guides bottom-up attention and influences eye movements (Veale et al., 2017). For example, if there is a red object among many blue objects, the red one stands out and attracts attention. Typical features that elicit such “pop-out” effects in static images include luminance, color, and orientation (Turatto and Galfano, 2000; Wolfe et al., 1992). Because natural scenes contain varying levels of luminance, diverse colors, and multiple orientations, salience in these contexts is determined by the combination of these features. To elucidate the complex process of salience computing, both theoretical and experimental approaches have been employed.

The saliency map has contributed to the quantitative investigation of visual salience. It is a two-dimensional map showing how perceptually conspicuous each region is in the corresponding visual stimulus. Koch and Ullman originally proposed the saliency map as a concept (Koch and Ullman, 1985), and its computational implementation was first reported by Itti et al. (1998). In their saliency map model, visual features such as orientation, color, and luminance are extracted from a visual stimulus and separately processed in various feature maps. Within each map, center-surround competition weakens the activity corresponding to abundant features in the visual stimulus and strengthens the activity associated with unique features. Feature maps are then integrated and finally output as a saliency map.

The saliency map model has been applied to eye-movement analysis and has enabled the exploration of the neural basis of visual salience (Veale et al., 2017). Although eye movements are influenced not only by bottom-up perception but also by top-down cognition, such as the semantic understanding of scenes and goal-related information, it was shown that fixations tend to cluster in highly salient regions indicated by the saliency map (Foulsham and Underwood, 2008; Itti, 2005). Therefore, the effect of bottom-up visual salience on eye movements can be evaluated using the saliency map. Eye-movement analysis of monkeys with brain lesions indicated that visual salience involves not only the primary visual cortex but also other brain areas (Yoshida et al., 2012). Electrophysiological recordings from the brains of monkeys during free viewing have shown a correlation between the saliency map and the activity of the midbrain structure known as the superior colliculus (White et al., 2017).

Researchers have also explored how neurons implement the center-surround competition, which is supposed to be the central process of visual salience computation. One account is that the competition is achieved through lateral interaction whereby closely located neurons enhance each other's activity and distant neurons inhibit each other's activity. It is based on a simple theoretical model of local competition in the visual system (Von Der Malsburg, 1973). Such lateral interaction has been supported by *in vitro* electrophysiological recordings of the superior colliculus in mouse brain slices (Phongphanphane et al., 2014).

Recent studies have focused on abnormalities in visual salience associated with mental disorders. Patients with schizophrenia exhibit differences in eye movements compared to healthy controls, quantified as shorter scanpath length and impaired inhibition of return (Okada et al., 2021; Sprenger et al., 2013). Differences in visual salience have been observed by applying the saliency map model to analyze eye movements in patients (Yoshida et al., 2024). Another large-scale study found a relationship between affected visual salience and multiple mental disorders (Miura et al., 2025). As biological research has suggested various neurobiological abnormalities related to mental disorders, such as excitatory-inhibitory imbalance (Yizhar et al., 2011), disrupted signal-to-noise ratio (Jacob et al., 2013) and synaptic disconnectivity (Ellison-Wright and Bullmore, 2009; Garey et al., 1998), these abnormalities may affect visual salience and thereby cause symptoms. The neural basis of visual salience may also provide insights into the mechanisms underlying abnormal visual salience (Miyata, 2019). Because lateral interactions involving local excitatory connections and distant inhibitory connections are suggested to play a role in salience computing, its alteration may underlie abnormal visual salience.

A saliency map model that accounts for these abnormalities can facilitate biological investigations into the mechanisms of abnormal

visual salience. However, the conventional saliency map model (Itti et al., 1998) used in eye-movement analyses has limitations in addressing this issue. This is mainly because the neural implementation of saliency computation is not sufficiently addressed in this model; in other words, center-surround competition is not implemented through artificial neural networks. A computational model that integrates neurobiological characteristics of center-surround competition should be used to tackle this problem.

Saliency map models based on artificial neural networks have been proposed in previous research (de Breeht and Saiki, 2006; Soltani and Koch, 2010). While they can capture biophysical aspects of neurons in visual salience computing, their simulations were performed only on very simple visual stimuli, such as rectangular bars on a black background. These models did not show sufficient ability to predict eye movements, which is necessary for application to eye-movement analysis. Recent machine learning techniques have enabled models based on convolutional neural networks to accurately predict human eye movements (Kroner et al., 2020). However, owing to end-to-end learning in these models, all processes influencing eye movements, including top-down cognition, may be reflected in the same artificial neural network. Therefore, these models face challenges in testing hypotheses that focus on local circuits of the brain responsible for specific information processing (i.e., center-surround competition).

In this study, we propose a new computational saliency map model based on de Breeht and Saiki (2006), which implements center-surround competition using artificial neural networks with excitatory center-inhibitory surround lateral connections. Their model has the advantage of incorporating neurobiological characteristics, but it can only process simple visual stimuli. Therefore, we extend their model to enable salience computation for complex visual stimuli such as natural images. The feature extraction algorithm was updated to detect complex features in natural images, and we searched for proper values of lateral connection weights to ensure that the output saliency map had sufficient performance in eye-movement prediction. To evaluate its performance in eye-movement prediction, we used an open dataset for eye movements (Borji and Itti, 2015). We compared the performance of different saliency map models in predicting eye movements for complex visual stimuli and confirmed that our model achieves comparable performance to the model by Itti et al. (1998), which has been applied to eye-movement analyses.

Using our proposed model, we introduced parameter changes to simulate neurobiological disturbances implicated in mental disorders and tested how the output saliency map was affected. Parameter changes related to excitatory-inhibitory imbalance in lateral interactions, disrupted signal-to-noise ratio, and reduced synaptic connections altered saliency computing such that the difference in salience between salient and non-salient objects changed. Finally, we tested our model as a tool for quantifying individual differences in the weighting of salience by parameter estimation from artificially generated fixation points.

2 Materials and methods

2.1 Visual stimulus and fixation data

We prepared a simple visual stimulus by creating an image with bars (Figure 1A) and used complex visual stimuli obtained from an open dataset by Borji and Itti (2015). This dataset includes various

images used in eye-movement experiments, where subjects looked at each image for 5 s with no restrictions. There are 20 categories of images, including those representing natural images (e.g., Action, Indoor) as well as those with less meaningful content (e.g., Noisy, Low resolution); examples are shown in Figure 1B. For feature extraction, we used downsized images with resolutions of 384×216 , 192×108 , or 96×54 instead of the original $1920 \times 1,080$ -pixel image. In addition, the RGB values of these images were normalized to a range of 0 and 1.

This dataset also includes fixation data collected during the experiments. We used the fixation data from 18 observers per image to evaluate our models' ability to predict eye movements.

2.2 Model description

Figure 1C shows the schematic representation of our computational model. It consists of a feature extraction process and a saliency computing process, the latter of which is implemented using an artificial neural network. The extracted features provide input to the neural network, which performs center-surround competition and feature integration before outputting the saliency map. The basic structure follows the saliency map model proposed by de Breeht and Saiki (2006). While their model handles only features for two orientations and two colors, we expanded it to include features for four orientations (0, 45, 90, and 135 degrees), four colors (red, green, blue, and yellow), and luminance. In addition, we aligned the feature extraction algorithms for orientation and color similar with those used in the saliency map model by Itti et al. (1998), where orientation

features are extracted by applying Gabor filters to images at multiple resolutions, and color features are extracted based on the opponency between red and green as well as blue and yellow.

The feature extraction algorithms reflect biological observations. Gabor filters resemble the response properties of orientation-selective neurons in the primary visual cortex (V1) (De Valois et al., 1982; Jain and Farrokhnia, 1991). The red-green and blue-yellow opponent-color responses are based on studies of the early visual system, demonstrating how cone inputs (L-, M-, and S-cones) are combined to allow fine-tuned chromatic discrimination (Engel et al., 1997).

The neural network consists of nine feature maps, each corresponding to a specific type of extracted feature. Each map processes signals for its respective feature separately. Within each map, neural activity competition is regulated through lateral interactions, characterized by local excitatory connections and distant inhibitory connections. The activity within the feature map layers is transmitted to the next layer, the conspicuity map layer, where signals are integrated into three conspicuity maps—orientation, color, and luminance. These maps undergo further competitive processing before their activity is ultimately combined into the saliency map.

As in the original Brecht's model, neural activity was modeled using mean-field equations for neural populations with dynamic synapses (Tsodyks et al., 1998), rather than simulating individual neurons. This approach preserves neurobiological characteristics while reducing computational costs. As a result, we constructed the neural network with relatively low dimensionality, despite the fact that computing salience for natural images in the brain would require an enormous number of neurons. Many parameter values were retained from the original Brecht's model, as they fall within physiologically

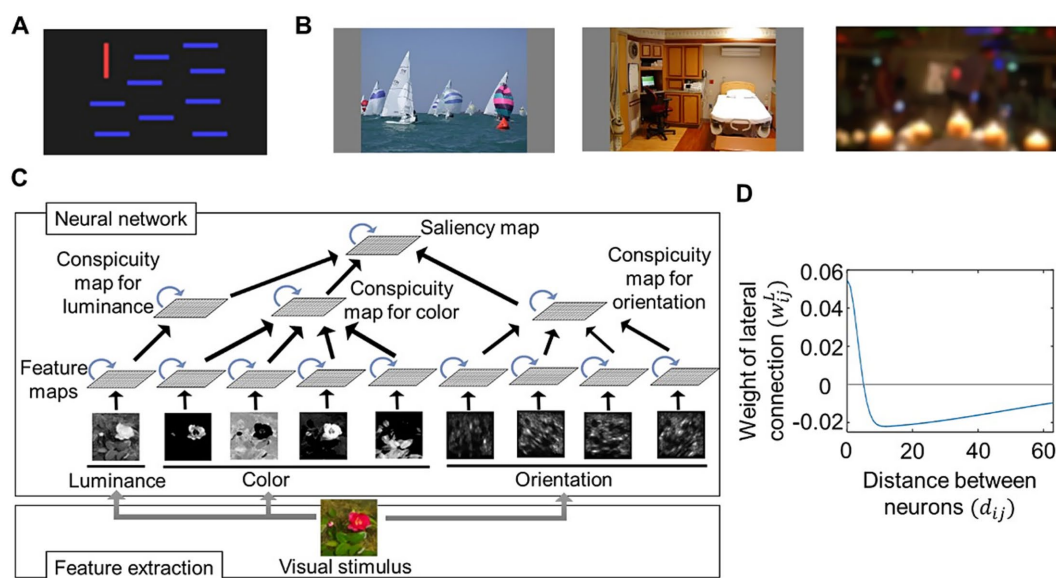


FIGURE 1

Architecture of computational modeling on visual salience. (A) An image used as a simple visual stimulus. (B) A few examples of images obtained from the CAT2000 dataset (Borji and Itti, 2015) and used as complex visual stimuli. Images included in "Action" (left), "Indoor" (middle), and "LowResolution" (right) categories. (C) Schematic diagram of our proposed computational saliency map model. Center-surround competition implemented by an artificial neural network (top) whose input was calculated through a feature extraction process (bottom). The neural network consists of multiple maps (quadrangles) implemented as two-dimensional arrays of neural populations. The neural populations within each map interact with each other via lateral connections (blue arrows) and receive signals from those in the lower layers via feedforward connections (black arrows). (D) Example distribution of lateral connection weights characterized by local excitatory and distant inhibitory connections. The weights are calculated by a difference-of-Gaussians function (Equation 17), where parameters w_I and σ_L are set as $w_I = 140$ and $\sigma_L = 3.2$.

realistic ranges. However, we adjusted the number of neural populations per map and connection weights, as these factors depend on the resolution at which the visual stimuli are processed.

The details of the model are described below, and it was implemented in MATLAB (version R2019b) with Image Processing Toolbox.

2.2.1 Feature extraction

The luminance feature was calculated as the intensity of the image with a 96×54 resolution, as follows:

$$F_{lum}(x, y) = (V_{red}(x, y) + V_{green}(x, y) + V_{blue}(x, y)) / 3, \quad (1)$$

where (x, y) represents the location of the image, and $V_{red}(x, y)$, $V_{green}(x, y)$, and $V_{blue}(x, y)$ are the RGB values normalized to a range of 0 and 1.

Color feature extraction reflects the red-green and blue-yellow opponent-color responses in the visual system (Engel et al., 1997). The four features of red, green, blue, and yellow were extracted from the image with a 96×54 resolution, as follows:

$$F_{col}(\alpha, x, y) = \begin{cases} g(V_{red}(x, y) - V_{green}(x, y)) / F_{lum}(x, y) & \alpha = 1 \\ g(V_{green}(x, y) - V_{red}(x, y)) / F_{lum}(x, y) & \alpha = 2 \\ g(V_{blue}(x, y) - V_{yellow}(x, y)) / F_{lum}(x, y) & \alpha = 3 \\ g(V_{yellow}(x, y) - V_{blue}(x, y)) / F_{lum}(x, y) & \alpha = 4, \end{cases} \quad (2)$$

where α denotes the color index, $V_{yellow}(x, y)$ is defined as:

$$V_{yellow}(x, y) = \min(V_{red}(x, y), V_{green}(x, y)), \quad (3)$$

and $g(x)$ is a linear gain function given by:

$$g(x) = \begin{cases} x & x > 0 \\ 0 & \text{otherwise.} \end{cases} \quad (4)$$

Orientation features were extracted by applying Gabor filters that approximate the response of orientation-selective neurons in the primary visual cortex (Jain and Farrokhnia, 1991). We used the Gabor filter function given by:

$$G_{\theta}(x, y) = \exp\left(-\frac{x_{\theta}^2 + (\gamma y_{\theta})^2}{2\sigma^2}\right) \exp(i\omega_0 x_{\theta}) \quad (5)$$

$$\begin{aligned} x_{\theta} &= x \cos \theta + y \sin \theta \\ y_{\theta} &= -x \sin \theta + y \cos \theta, \end{aligned}$$

where θ represents the orientation of the Gabor filters set as $\theta \in \{0^\circ, 45^\circ, 90^\circ, 135^\circ\}$, and γ , σ , and ω_0 are filter parameters denoting the spatial aspect ratio, the standard deviation of the Gaussian kernel, and the frequency of the sinusoidal factor, respectively. We set the parameter values $\gamma = 0.5$, $\sigma = 2$, and $\omega_0 = 2$, following the implementation of the Itti-Koch model in the Graph-Based Visual

Saliency (GBVS) toolbox for Matlab software (Harel et al., 2006). An image with a 96×54 resolution was convolved with Gabor filters, as follows:

$$O_{\theta}(x, y) = \sum_u \sum_v G_{\theta}(x - u, y - v) V_{int}(u, v) \quad (6)$$

where $V_{int}(x, y)$ is the image intensity given by:

$$V_{int}(x, y) = (V_{red}(x, y) + V_{green}(x, y) + V_{blue}(x, y)) / 3 \quad (7)$$

Owing to the complex Gabor function defined in Equation 5, $O_{\theta}(x, y)$ has a complex value, and the orientation feature is calculated based on its absolute value. In addition, we applied Gabor filters to images at three different resolutions and averaged the resulting filter responses, as applying Gabor filters only to 96×54 images may capture only coarse-grained features. Therefore, the orientation feature is given by:

$$F_{ori}(\theta, x, y) = \frac{(|O_{\theta}(x, y)| + |O'_{\theta}(x, y)| + |O''_{\theta}(x, y)|)}{3} \quad (8)$$

where $O'_{\theta}(x, y)$ and $O''_{\theta}(x, y)$ represent the values obtained by convolving the images with 192×108 and 384×216 resolutions, respectively, with the Gabor filters, and downsizing them to 96×54 resolutions. Fine-grained features can be extracted from 192×108 and 384×216 images and incorporated into the 96×54 orientation feature image. When Gabor filters are applied to 384×216 or 192×108 images, the extracted features span multiple pixels, enabling them to be preserved after downsampling to a resolution of 96×54 .

2.2.2 Neural network

The artificial neural network comprises a feature map layer, conspicuity map layer, and saliency map layer. The feature map layer has nine feature maps corresponding to nine features extracted from the image (luminance, four colors [red, green, blue, and yellow], and four orientations [0, 45, 90, and 135 degrees]). The conspicuity map layer has three conspicuity maps corresponding to luminance, color, and orientation features. The saliency map layer has a saliency map as the output. Each map was implemented as a 96×54 array of neural populations. Based on Equations 1–8 the input $I_{m,i}$ for neural population i in feature map m is given by:

$$I_{m,i} = \begin{cases} C_{lum} F_{lum}(x_i, y_i) & m = 1 \\ C_{col} F_{col}(m-1, x_i, y_i) & m = 2, 3, 4, 5 \\ C_{ori} F_{ori}(45(m-6), x_i, y_i) & m = 6, 7, 8, 9 \end{cases} \quad (9)$$

where (x_i, y_i) denotes the coordinates of the neural population i , and $C_{lum} (= 30)$, $C_{col} (= 15)$, and $C_{ori} (= 20)$ are constants that cause neural activity within a reasonable range.

Each neural population receives signals from populations in the same map via lateral connections and signals from populations in the lower layer via feedforward connections. The activity $A_{m,i}(t)$ for

neural population i in map m at time t was updated depending on these signals:

$$\tau \frac{dA_{m,i}}{dT} = -A_{m,i}(t) + b + 0.5g\left(S_L(m,i,t) + S_F^{Post}(m,i,t)\right), \quad (10)$$

where $S_L(m,i,t)$ represents signals via lateral connections; $S_F^{Post}(m,i,t)$, feedforward connections; τ , time constant set to 0.03 s (30 ms); and $g(x)$, linear gain function defined in Equation 4. Herein, we introduced b as the baseline activity, allowing the neural population to be active even in the absence of signals from other populations. We set $b=0$ for most simulations and $b>0$ for other simulations, assuming an abnormality in the neuronal signal-to-noise ratio. Because we consider t as time in milliseconds and $\frac{dA_{m,i}}{dT}$ as the change in $A_{m,i}(t)$ per second, $A_{m,i}(t+1)$ is given by:

$$A_{m,i}(t+1) = A_{m,i}(t) + 0.001 \frac{dA_{m,i}}{dT}. \quad (11)$$

The feedforward signal $S_F^{Post}(m,i,t)$ depends on the connection between the maps. In our model, feature maps ($m=1, \dots, 9$) received the input $I_{m,i}$ as defined in Equation 9; the conspicuity maps for luminance, color, and orientation ($m=10, 11, 12$, respectively) received signals from feature maps for luminance ($m=1$), color ($m=2, 3, 4, 5$), and orientation ($m=6, 7, 8, 9$); and the saliency map ($m=13$) received signals from the three conspicuity maps:

$$S_F^{Post}(m,i,t) = \begin{cases} I_{m,i} & m=1, \dots, 9 \\ \sum_{p=1}^1 S_F^{Pre}(p,i,t) & m=10 \\ \sum_{p=2}^5 S_F^{Pre}(p,i,t) & m=11 \\ \sum_{p=6}^9 S_F^{Pre}(p,i,t) & m=12 \\ \sum_{p=10}^{12} S_F^{Pre}(p,i,t) & m=13 \end{cases} \quad (12)$$

where $S_F^{Pre}(p,i,t)$ represents the signal from map p at the presynaptic layer to neural population i at the postsynaptic layer.

Synaptic transmission between each neural population is modeled based on the equations for dynamic synapses (Tsodyks et al., 1998), which describe the synaptic resources used by activated neurons that recover gradually over time. The lateral signals $S_L(m,i,t)$ and feedforward signals $S_F^{Pre}(p,i,t)$ are expressed as follows:

$$\begin{aligned} S_L(m,i,t) &= U_{SE}^L \sum_j w_{ij}^L z_{m,j}^L(t) A_{m,j}(t) \\ S_F^{Pre}(p,i,t) &= U_{SE}^F \sum_k w_{ik}^F z_{p,k}^F(t) A_{p,k}(t), \end{aligned} \quad (13)$$

where $U_{SE}^L (=0.5)$ and $U_{SE}^F (=0.5)$ are the utilization of synaptic efficacy parameters that denote the fractions of synaptic resources activated by an action potential; w_{ij}^L and w_{ik}^F are the weights of the lateral connections and feedforward connections, respectively; and $z_{m,j}^L(t)$ and $z_{p,k}^F(t)$ are the depressing effects of dynamic synapses for lateral

connections and feedforward connections, respectively, which represent the fractions of available synaptic resources and are updated as follows:

$$\begin{aligned} \frac{dz_{m,j}^L}{dT} &= -U_{SE}^L A_{m,j}(t) z_{m,j}^L(t) + \frac{1 - z_{m,j}^L(t)}{\tau_{rec}^L} \\ \frac{dz_{p,k}^F}{dT} &= -U_{SE}^F A_{p,k}(t) z_{p,k}^F(t) + \frac{1 - z_{p,k}^F(t)}{\tau_{rec}^F}, \end{aligned} \quad (14)$$

where $\tau_{rec}^L (=0.1 \text{ sec})$ and $\tau_{rec}^F (=0.05 \text{ sec})$ are time constants that govern the rate of recovery of synaptic resources. As in Equation 11, $z_{m,j}^L(t+1)$ and $z_{p,k}^F(t+1)$ are given by:

$$\begin{aligned} z_{m,j}^L(t+1) &= z_{m,j}^L(t) + 0.001 \frac{dz_{m,j}^L}{dT} \\ z_{p,k}^F(t+1) &= z_{p,k}^F(t) + 0.001 \frac{dz_{p,k}^F}{dT} \end{aligned} \quad (15)$$

These depressing effects cause a temporary decrease in the strength of synaptic transmission if the neural populations are highly active, which contributes to the normalization of neural activity. We used the same values for parameters τ , U_{SE}^L , U_{SE}^F , τ_{rec}^L , and τ_{rec}^F as those in the Brecht–Saiki model (de Brecht and Saiki, 2006), as they are within a physiologically realistic range (Markram et al., 1998; Tsodyks et al., 1998).

The connection weights for the feedforward and lateral connections w_{ik}^F and w_{ij}^L depend on the locations of the presynaptic and postsynaptic neural populations within the maps. The feedforward connection weights w_{ik}^F were set as follows:

$$\begin{aligned} w_{ik}^F &= \hat{w}(x_i - x_k) \hat{w}(y_i - y_k) \\ \hat{w}(x) &= \begin{cases} 0.14 & x = -2, 2 \\ 0.71 & x = -1, 1, \\ 1.13 & x = 0 \end{cases} \end{aligned} \quad (16)$$

where (x_i, y_i) and (x_k, y_k) denote the coordinates of neural population i in the postsynaptic map and neural population k in the presynaptic map, respectively. In this setting, excitatory feedforward connections exist if the coordinates (x_i, y_i) and (x_k, y_k) are in close proximity.

The lateral connection weights w_{ij}^L were defined by a difference-of-Gaussian function to implement local excitatory connections and distant inhibitory connections (Figure 1D):

$$w_{ij}^L = \frac{w_E}{2\pi\sigma_L^2} \exp\left[-\frac{d_{ij}^2}{2\sigma_L^2}\right] - \frac{w_I}{2\pi(\beta\sigma_L)^2} \exp\left[-\frac{d_{ij}^2}{2(\beta\sigma_L)^2}\right], \quad (17)$$

in which w_E and w_I determine the amplitudes of the Gaussian components; σ_L and β determine the standard deviations of the Gaussian components; and d_{ij} is the distance between the two neural populations i and j given by:

$$d_{ij} = \sqrt{(x_i - x_j)^2 + (y_i - y_j)^2}. \quad (18)$$

The lateral connections enabled center-surround competition for saliency computing, but the optimal values for w_E , w_I , σ_L , and β depend on the resolution at which the visual stimuli are processed. In addition, we assumed that there were individual differences in lateral interactions owing to variations in neurobiological characteristics. Therefore, we tested our model using various lateral connections by varying the values of w_I and σ_L . We fixed $w_E = 2.0$ for simplicity and $\beta = 15$ to maintain the excitatory-center, inhibitory-surround structure.

2.3 Models for comparison

We used two additional models—the Brecht-Saiki model (de Brecht and Saiki, 2006) and the Itti-Koch model (Itti et al., 1998)—to compare eye-movement prediction performance with our proposed model. The Brecht-Saiki model was implemented with slight modifications to accommodate differences in visual stimuli while preserving its fundamental structure. This model processes two color features (red and green) and two orientation features (0 and 90 degrees). The color features are derived directly from RGB values, while the orientation features are extracted using Gabor filters applied to images with a 96×54 resolution. These features serve as inputs to the artificial neural network. Therefore, input $I_{m,i}$ for neural population i in feature map m is represented as:

$$\tilde{I}_{m,i} = \begin{cases} \tilde{C}_{col} V_{red}(x_i, y_i) & m=1 \\ \tilde{C}_{col} V_{green}(x_i, y_i) & m=2 \\ \tilde{C}_{ori} |O_0(x_i, y_i)| & m=3 \\ \tilde{C}_{ori} |O_{90}(x_i, y_i)| & m=4 \end{cases}, \quad (19)$$

where the constants $\tilde{C}_{col}$ ($=30$) and $\tilde{C}_{ori}$ ($=30$) are set to cause neural activity within a reasonable range. The neural network consists of maps, each of which is implemented as a 96×54 array of neural populations. The main differences in the neural network implementation from our proposed model (Equations 10–18) are the number of the maps and connections between them that underlie the feedforward signals. It has four feature maps ($m=1, 2, 3, 4$), two conspicuity maps for color and orientation ($m=5, 6$, respectively), and a saliency map ($m=7$). The feedforward signals received by neural population i in map m at time t are given by:

$$\tilde{S}_F^{Post}(m, i, t) = \begin{cases} \tilde{I}_{m,i} & m=1, \dots, 4 \\ \sum_{p=1}^2 \tilde{S}_F^{Pre}(p, i, t) & m=5 \\ \sum_{p=3}^4 \tilde{S}_F^{Pre}(p, i, t) & m=6 \\ \sum_{p=5}^6 \tilde{S}_F^{Pre}(p, i, t) & m=7 \end{cases}, \quad (20)$$

instead of Equation 12. Apart from the input (Equation 19) and feedforward signals (Equation 20), the other difference from the proposed model is that the lateral connection weights were set to be the same as those in the original Brecht-Saiki model. They are

determined by Equation 17 with $w_E = 5.0$, $w_I = 250$, $\sigma_L = 3.2$, and $\beta = 15$ for feature maps and conspicuity maps, and there are no lateral connections in the saliency map.

We used the Itti-Koch model implemented in the GBVS toolbox for Matlab software (Harel et al., 2006). It computes saliency based on a luminance feature, color features for red-green opponency and blue-yellow opponency, and orientation features for 0, 45, 90, and 135 degrees extracted using Gabor filters. The features were extracted from images at multiple scales (Gaussian pyramids) obtained from a visual stimulus. The center-surround competition was implemented without artificial neural networks. Instead, it followed these steps: first, normalization: each feature image was normalized to a fixed range $[0 \dots M_g]$; second, local maxima averaging: the average $\bar{M}_l$ of local maxima was computed, excluding global maximum M_g ; third, global

scaling: the entire map was multiplied by $(M_g - \bar{M}_l)^2$. After the center-surround competition for each feature, the feature images were integrated into the saliency map.

2.4 Evaluation of the model performance in eye-movement prediction

We evaluated the performance of our proposed model with various lateral connections, alongside the Brecht-Saiki and Itti-Koch models, by applying them to eye-movement data. Performance was evaluated by quantifying the correspondence between the saliency map and fixation points (ground truth) obtained from eye-movement measurements. We used the Normalized Scanpath Saliency (NSS) metric for evaluation (Bylinskii et al., 2019; Kümmerer et al., 2018). To compute NSS, the saliency map was normalized to have zero mean and unit variance, and the normalized saliency values at fixation locations were averaged. An NSS value greater than 0 indicated correspondence between the saliency map and fixation points, with higher values suggesting better eye-movement prediction. We used visual stimuli and fixation data from the CAT2000 dataset (Borji and Itti, 2015). Considering the computational cost of simulating our proposed model with various lateral connection parameters, we selected five random visual stimuli from each of the 20 categories (100 stimuli in total) and corresponding fixation data instead of using the entire dataset. The saliency map at steady state (timepoint $t = 400$) was used for NSS metrics.

Here, we did not reproduce eye movement trajectories from the saliency map; instead, we simply used the saliency map as a reference metric for assessing the spatial distribution of fixation points. Predicting gaze trajectories requires incorporating additional characteristics into the model—such as saccade length, fixation duration, and inhibition of return—which increases model complexity. By using the NSS metric, we did not consider the individual sequence or path of eye movements, which offers a more tractable, though less precise, means of evaluating model performance.

2.5 Testing parameter estimation from simulated data

To assess our model's ability to quantify individual differences in eye movements, we performed parameter estimation using artificially generated fixation points. This approach follows the parameter

recovery method, which evaluates whether a computational model can be effectively applied to behavioral data analysis (Wilson and Collins, 2019). The testing process consisted of the following steps. First, fixation points were artificially generated based on the saliency map computed by our model using a predefined parameter value. Second, the model was used to compute saliency maps for the same visual stimulus with various parameter values. Third, the NSS metric was used to quantify the correspondence between the generated fixation points and the computed saliency maps. Ideally, the best correspondence (highest NSS score) should occur when the estimation parameter matches the value used to generate fixations. We tested the estimation of w_I , which determines the strength of lateral connections (as described in Equation 17), while keeping σ_L fixed at 6.4. Fixation points were generated under the assumption that the normalized saliency map represents their probability distribution. Therefore, the saliency map was normalized such that its sum equaled 1, and fixation points were sampled accordingly. For each visual stimulus and parameter setting, 20 fixation points were generated, reflecting the scale of real experimental data used in saliency analysis. We used the same 100 CAT2000 visual stimuli from the model performance evaluation. The average NSS score across these 100 stimuli was computed, using the steady-state saliency map (timepoint $t = 400$) for both fixation generation and NSS evaluation.

3 Results

Our model computes the time course of neural population activity. Figure 2A shows an example of the time series of activity in the saliency map caused by the simple visual stimulus shown in Figure 1A, which includes a vertical red bar as a salient object and many horizontal blue bars as non-salient objects. The activity of neural populations increased after stimulus presentation and then reached a steady state. The activity corresponding to the red bar became larger than that corresponding to the blue bars, indicating that the center-surround competition weakened the activity for non-salient objects. There is still substantial activity for the blue bars (non-salient objects) at the steady state compared to the background (Figure 1B).

We evaluated the ability of our model to predict eye movements using visual stimuli and fixation data included in the CAT2000 dataset (Borji and Itti, 2015). The correspondence between the saliency map and the fixation points for each visual stimulus was measured using

the NSS metric, and the model's performance in eye-movement prediction was quantified as the average NSS score for 100 visual stimuli. We tested the model with various values of parameters w_I and σ_L , which determine the lateral connection weights as described in Equation 17 in the Methods section. Figure 3A shows that the model's performance in predicting eye movements varied depending on these parameter values. The distribution of lateral connection weights corresponding to some of these parameter values is plotted in Figure 3B. Lateral connections with excessive excitatory or inhibitory connections showed relatively low performance. We then compared the performance of our model with two other models. One is the Itti-Koch model (Itti et al., 1998), which has been used for eye-movement analyses (Foulsham and Underwood, 2008; Miura et al., 2025; Yoshida et al., 2024) but does not address the neural implementation of center-surround competition. Our model, when using parameter values that provide balanced lateral connections, achieved comparable performance with the Itti-Koch model (Figure 3C). The second model is the Brecht-Saiki model (de Brecht and Saiki, 2006), which implements center-surround competition using an artificial neural network but is limited to simple features. The average NSS score for this model was close to zero, indicating that its ability to predict eye movements for complex visual stimuli was nearly at chance level.

We next examined how saliency computation is altered by changes in the neural network parameters of our proposed model. We tested lateral connections with different excitatory-inhibitory balances and compared the resulting saliency maps. For clarity, we set w_I as $w_I \in \{40, 140, 500\}$ and σ_L fixed at 3.2 to construct lateral connections, which differ from the parameter settings used for model performance evaluation in Figure 3. Figures 4A,B show some examples of visual stimuli and the corresponding output saliency maps, while Figure 4C shows the distribution of lateral connections used in these cases. When inhibitory connections were reduced, our model computed similar saliency values for both salient objects and non-salient objects. In contrast, when inhibitory connections are increased, the saliency of non-salient objects became significantly weaker. These results indicate that the difference in saliency between salient and non-salient objects is influenced by the excitatory-inhibitory balance. We also tested parameter changes related to the signal-to-noise ratio and reduced synaptic connections. We introduced baseline activity for neural populations by setting the parameter b in Equation 10 to $b = 1$ ($b = 0$ for other simulations), allowing each neural population to exhibit weak activity even in the absence of signals from other neural

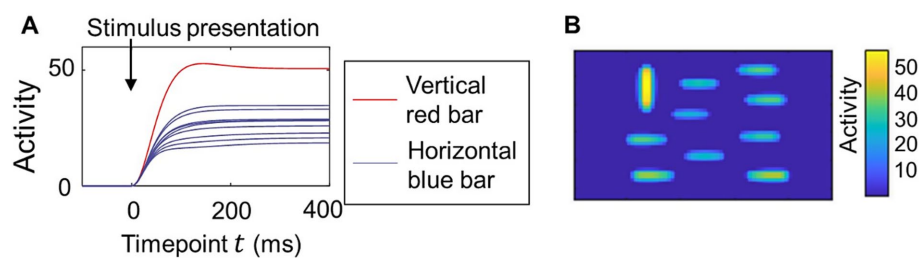


FIGURE 2

Transition of the neural activity computed in the proposed model for a simple visual stimulus. (A) Time course of the neural activity in the saliency map. Image of a vertical red bar and nine horizontal blue bars shown in Figure 1A used for the visual stimulus. The parameters for the lateral connections w_I and σ_L were set as $w_I = 140$ and $\sigma_L = 3.2$, as in Figure 1D. The activity of neural populations in the region corresponding to each bar was averaged. (B) The activity of all neural populations in the saliency map at timepoint $t = 400$ in the same simulation as that of (A).

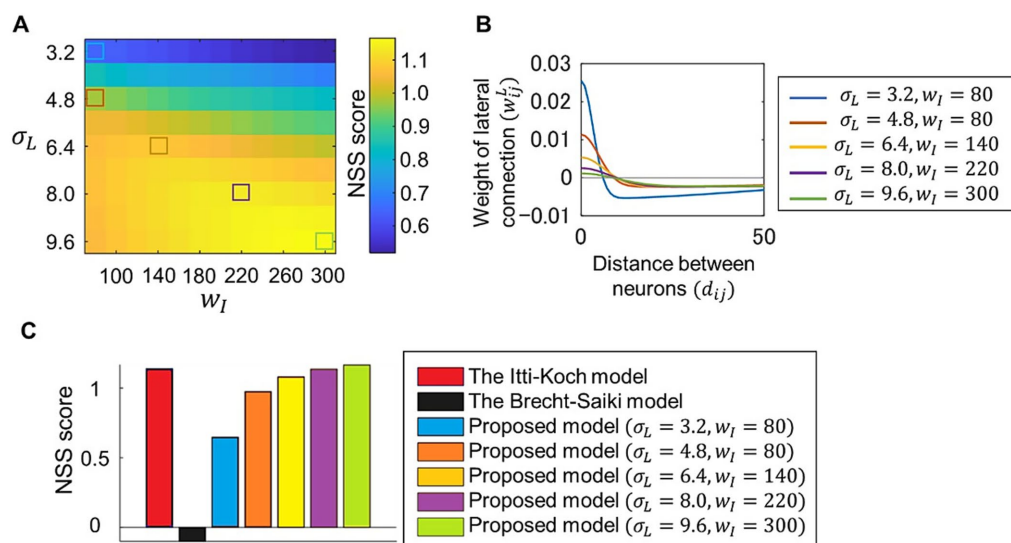


FIGURE 3

Evaluation of model performance in eye-movement prediction. (A) Correspondence between fixation data measured in experiments and the saliency map computed by the proposed model, in which various parameter values w_I and σ_L for lateral connections were set. Visual stimuli and fixation data included in CAT2000 dataset was used. Correspondence between fixations and the saliency map for each visual stimulus was calculated using NSS metrics, and the average NSS scores for 100 visual stimuli are plotted. (B) Distribution of lateral connection weights determined by five sets of parameter values corresponding to those denoted by colored squares in (A). (C) Comparison of performances of different models. Performances are quantified utilizing NSS metrics as in (A). Performances for the Itti-Koch model, the Brecht-Saiki model, and our proposed model with the five parameter sets denoted by colored squares in (A) are plotted.

populations. This adjustment, which can be regarded as modifying the signal-to-noise ratio of neural responses, resulted in a larger difference in saliency between salient and non-salient objects (Figure 4D, left). For reduced synaptic connections, we set the connection weights of 60% of randomly chosen lateral connections to 0, which increased saliency values for non-salient objects (Figure 4D, right).

The results described above suggest that individual differences in saliency computation could be quantified by applying our model to eye-movement data analysis. To evaluate whether our model could function as a tool for analyzing eye-movement data, we tested parameter estimation by comparing the computed saliency map with artificial fixation data. The analysis was based on estimating the parameter value that provided the best correspondence between the computed saliency map and eye-movement data. Here, we used fixation data artificially generated from the saliency map computed by our model with specific parameters, which allowed us to directly compare the results of the parameter estimation with the true parameter value (i.e., the value used for generating data). The artificial fixation data was generated based on our model using five different settings where the parameters w_I , which determine lateral connection weights, were set as $w_I \in \{120, 160, 200, 240, 280\}$ (See Section 2.5 for more detailed methods). Representative examples of generated fixation points are shown in Figure 5A. When w_I was set to the higher value, the model computed the saliency map in which saliency for non-salient objects was weakened as shown in Figure 4B. Consequently, the generated fixations tended to cluster in regions of high saliency. We then calculated NSS scores to evaluate the correspondence between the artificially generated fixation points and the saliency map computed by our model using various values of w_I for estimation. The average NSS scores for 100 visual stimuli are plotted in Figure 5B, showing that NSS scores were highest when the estimated w_I value for parameter estimation was close to the one used for generating the

fixation data. This distribution is desirable because the estimated parameter value, which achieves the highest correspondence (i.e., the highest NSS score), should ideally match the true value used to generate the fixation data. These findings demonstrate our model's potential for accurate parameter estimation from eye-movement data.

4 Discussion

In this study, we proposed a new computational model of abnormal bottom-up visual salience to facilitate the investigation of how neurobiological abnormalities alter salience computation. We designed the model to meet two key requirements. First, the core process of salience computing (i.e., center-surround competition) had to be implemented at the neural level. Second, the model had to achieve eye-movement prediction performance comparable to that of established saliency map models used in previous eye-movement studies. We developed our model by extending the Brecht-Saiki model, which satisfies the first requirement but not the second, to ensure that both criteria were met. Our model incorporates an artificial neural network with excitatory center-inhibitory surround lateral connections (Figure 1), simulating the time course of neural population activity underlying center-surround competition (Figure 2). We demonstrated that its performance in predicting eye movements is comparable to that of the Itti-Koch model, a widely used model for eye-movement analysis, by setting balanced lateral connection parameters (Figure 3). We introduced disturbances into the neural network by modifying parameters, which resulted in changes in the computed salience difference between salient and non-salient objects. In other words, they altered the weighting of salience (Figure 4). Finally, we tested parameter estimation using artificially generated fixation data and demonstrated the potential application of our model in eye-movement

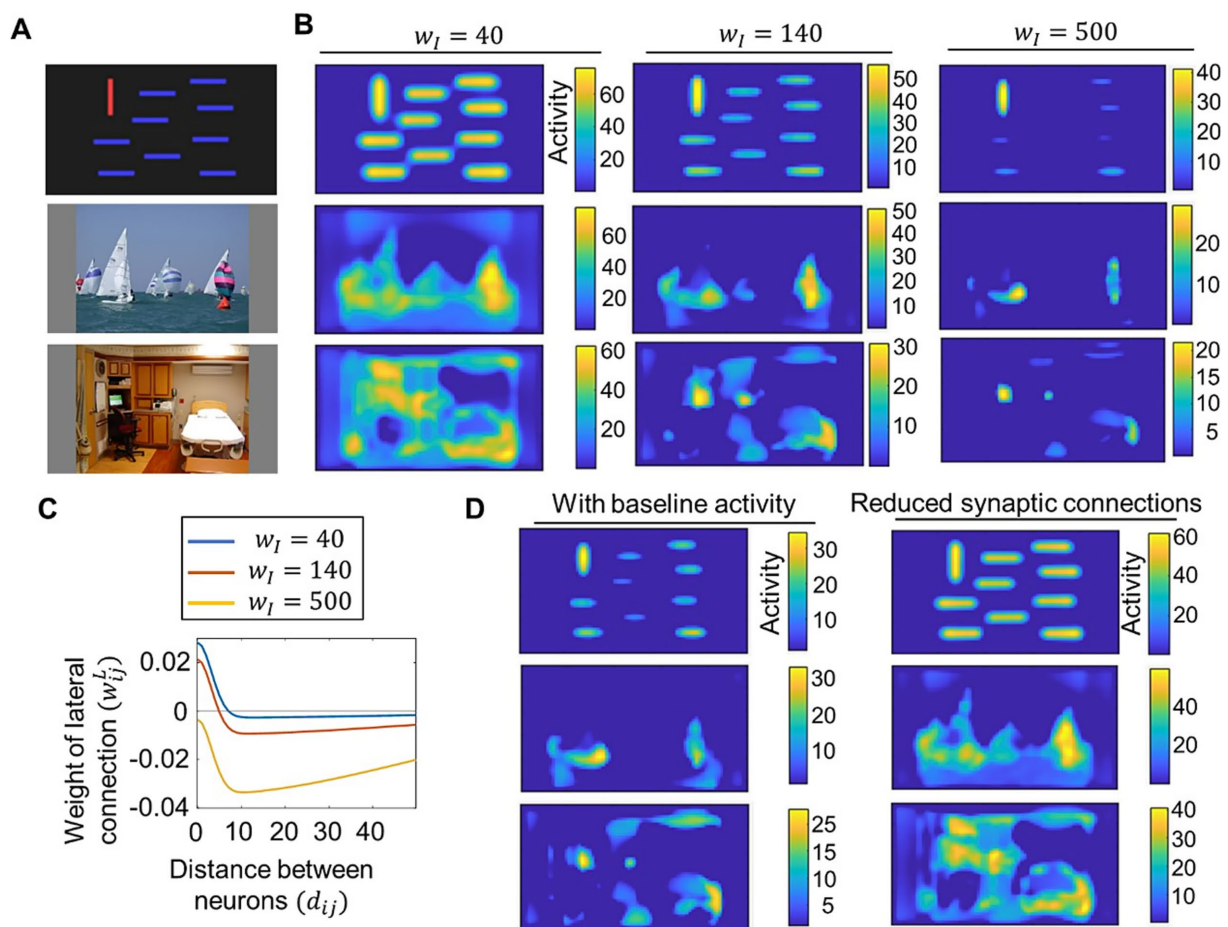


FIGURE 4

Demonstration of how saliency computing is altered by parameter changes in the proposed model. (A) Visual stimuli of bars (top), sailing (middle), and a room (bottom) used for the test. The latter two stimuli were obtained from CAT2000 dataset (Borji and Itti, 2015). (B) Saliency maps computed by the proposed model with varied values of the parameter w_I that determined lateral connections. Neural activity of saliency maps at the steady state (timepoint $t = 400$) for visual stimuli of bars (top row), sailing (middle row), and a room (bottom row). (C) Distribution of lateral connections used for computing saliency maps in (B). (D) Saliency maps computed by the proposed model with baseline neural activity (left column) and with reduced synaptic connections (right column). Neural activity of saliency maps at the steady state (timepoint $t = 400$) for visual stimuli of bars (top row), sailing (middle row), and a room (bottom row).

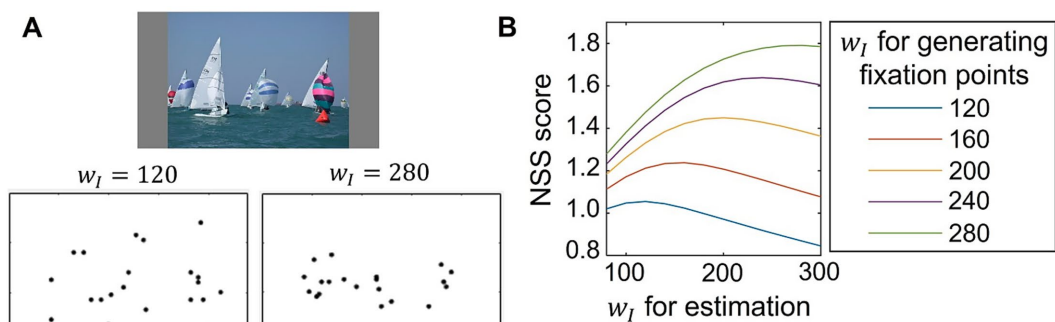


FIGURE 5

Test of parameter estimation from generated fixations. (A) Example of artificially generated fixation points for a visual stimulus (top) obtained from CAT2000 dataset (Borji and Itti, 2015). Fixation points were generated from the saliency map computed by the proposed model, where the parameter w_I , which modulates lateral connections, was set to 120 (bottom left) or 280 (bottom right). (B) Estimation of the parameter w_I using fixation points generated artificially from the saliency map of the proposed model with varied values of $w_I \in \{120, 160, 200, 240, 280\}$. The NSS metric was used to quantify the correspondence between the generated fixation points and the saliency map computed by the proposed model with various values of w_I for estimation. The NSS scores, averaged for 100 visual stimuli, are plotted.

analysis (Figure 5). These results suggest that individual differences in salience computing, particularly in terms of salience weighting, can be quantified by applying our model to eye-movement data.

Our findings indicate that salience must be appropriately weighted through balanced center-surround competition. This contrasts with a simple winner-take-all strategy, which detects only the most salient object and works even if salience for non-salient objects is completely eliminated. Neural networks with lateral connections are at risk of excessive competition owing to continuous and iterative interactions. One key mechanism to overcome this risk is the normalization of neural activity within a reasonable range. As in the Brecht-Saiki model, we introduced depressing effects (Equation 13) to simulate synaptic depression (Abbott et al., 1997), which helps regulate the activity of each neural population. The Brecht-Saiki model indicated that synaptic depression prevents overcompetition (de Brecht and Saiki, 2006), and our model similarly showed that steady-state activity for non-salient objects was not entirely eliminated (Figure 2). Our simulations with parameter modifications (Figure 4) suggest additional mechanisms for achieving balanced competition. Introducing excitatory-inhibitory imbalance, baseline neural activity, and reduced synaptic connections each affected lateral interactions and altered the weighting of salience. Notably, baseline neural activity did not modify lateral connections themselves but influenced salience weighting, likely owing to increased lateral signaling. Although the neural basis of abnormal visual salience remains unknown, our computational modeling in this study provides a hypothesis on how neurobiological characteristics influence visual salience. We showed that salience computing is normally well-balanced, but neurobiological abnormalities can cause unbalanced lateral interactions, thereby altering the weighting of salience.

The disturbances introduced into our model are relevant to neural mechanisms implicated in mental disorders. First, Yizhar et al. (2011) reported that excitatory-inhibitory imbalance in the mouse neocortex was associated with social dysfunction (Yizhar et al., 2011). Since excitatory glutamatergic pyramidal neurons and inhibitory GABAergic interneurons are indicated to play central roles in maintaining this balance, its disruption is linked to the glutamatergic hypothesis of schizophrenia (Uliana et al., 2024). Second, Jacob et al. showed that dopamine, a neurotransmitter implicated in mental disorders including schizophrenia, modulated the neural signal-to-noise ratio by altering the baseline activity of prefrontal neurons in monkeys (Jacob et al., 2013). Accordingly, changes in baseline activity can be associated with the dopaminergic hypothesis of schizophrenia (McCutcheon et al., 2020; Ott and Nieder, 2019). Finally, reduced synaptic connections are consistent to a study in which reduced dendritic spine density was observed in neocortical neurons of patients with schizophrenia in histological examinations (Garey et al., 1998).

The altered weighting of salience differs from the concept of abnormal salience described in conventional theory. The aberrant salience hypothesis, a theory of schizophrenia pathophysiology, suggests that the misattribution of motivational salience to stimuli irrelevant to external conditions may underlie schizophrenia symptoms (Kapur, 2003). Motivational salience is attributed based on reward prediction and is associated with reward-related learning, in which phasic changes in dopamine activity corresponding to reward prediction errors adjust corticostriatal learning to ensure accurate reward prediction (Bromberg-Martin et al., 2010). If phasic dopamine activity occurs independently of stimuli, motivational salience can become disturbed. Indeed, spontaneous phasic dopamine activity was observed in animals treated with amphetamine (Daberkow et al., 2013),

which may lead to randomly assigned reward prediction and motivational salience unrelated to actual stimuli. In contrast to such random generation of salience, the altered weighting of salience proposed by our model remains stimuli-dependent. In this case, salience that should be moderate becomes excessively high or low (Figure 4). This pattern of alteration is also supported by empirical findings in eye-movement studies. Patients with schizophrenia tend to concentrate their gaze within a narrower area of the visual stimulus compared to healthy controls (Okada et al., 2021). Furthermore, the mean value of salience at fixation points, quantified using the Itti-Koch model, was higher in participants with schizophrenia than in healthy controls (Miura et al., 2025; Yoshida et al., 2024). These findings are consistent with our simulations, in which salience for non-salient object was attenuated by enhanced lateral interactions (Figure 4), and fixations artificially generated from saliency maps with such altered weighting tended to cluster in regions of high salience (Figure 5). Therefore, disturbances in salience processing may take different forms—some individuals may experience random salience generation, others may exhibit altered salience weighting, and some may be affected by both. To detect abnormalities in salience processing from experimental data, models that explicitly address how salience is disturbed are needed (Miyata et al., 2024).

Our computational modeling is based on simplified assumptions as we focused on bottom-up salience computing associated with excitatory center-inhibitory surround lateral interactions. In our model, signals corresponding to extracted features are sent to multiple maps within the artificial neural network and processed separately. However, the corresponding structures in the brain remain unclear, and these maps may not be spatially distinct in actual neural circuits. This issue relates to the binding problem (Treisman, 1996), which concerns how different types of feature information are processed separately and integrated. One proposed solution to the binding problem is temporal binding (Engel and Singer, 2001), which suggests that information integration and separation depends on whether neural activity synchronizes or not. Therefore, one possible extension of our model would be to introduce neural phase synchronization. Another approach is to separate information processing through more complex lateral connections. Although we did not consider neuron types in this study, the brain consists of various types of neurons, and synaptic connectivity depends on neuron type. A simple computational saliency map model proposed by Li includes pyramidal cells and interneurons in the primary visual cortex, where excitatory connections depend on whether neurons prefer similar orientations (Li, 2002). Information processing may be separable through connectivity patterns based on the specific features that presynaptic and postsynaptic neurons respond. Models incorporating various types of connectivity may account for additional bottom-up attentional mechanisms. A recent study on avian midbrain networks involved in salience computation indicated that bottom-up stimulus selection is modulated by local inhibitory surrounds that depend on stimulus feature similarity, in combination with global inhibitory surrounds that are independent of feature similarity (Qian et al., 2025). While incorporating such complex biological characteristics is beyond the scope of our current study, computational modeling based on detailed neurobiological findings may enable a more biologically realistic implementation of visual salience computation.

In this study, we considered the effect of altered bottom-up salience on eye movements; however, eye movements do not depend

solely on bottom-up salience. They can also be influenced by top-down cognition (i.e., semantic understanding of scenes and goal-related information). In addition, the balance between bottom-up and top-down processes may be important for visual attention, as an eye-movement study suggested that schizophrenia patients tend to prioritize bottom-up visual salience over top-down cognition (Adámek et al., 2024). Evaluating abnormalities in bottom-up visual salience is still possible by applying saliency map models to eye-movement data (Miura et al., 2025; Yoshida et al., 2024) because bottom-up salience computation itself may not be disturbed by top-down cognition, and eye movements reflect the effect of bottom-up salience, which can be extracted using saliency map models.

For more precise analyses of abnormal salience, however, we face the challenge of distinguishing altered bottom-up salience, altered top-down cognition, and an imbalance between bottom-up and top-down processes. To address this issue, it is important to consider that top-down cognition depends heavily on whether visual stimuli are interpretable. For example, top-down cognition would have strong effects on eye movements for meaningful stimuli and weak effects for meaningless stimuli. Measuring eye movements with various types of visual stimuli is therefore useful, as demonstrated by the CAT2000 dataset used in this study, which includes 20 categories of images (Borji and Itti, 2015). It is also notable that the effects of top-down processes do not appear immediately after stimulus presentation but occur later in time (Theeuwes, 2010). Data acquisition and analysis based on stimulus type and time after presentation may help distinguish top-down and bottom-up factors. Using computational models that incorporate top-down cognition in combination with models designed solely for bottom-up salience is also beneficial. Deep learning-based saliency map models are typically trained in an end-to-end manner to predict eye movements directly from visual stimuli, and are thus considered to reflect both bottom-up salience and top-down cognition. This characteristic may explain their high performance in eye-movement prediction. Indeed, such models outperform those designed only to capture bottom-up salience. For example, Kroner et al. evaluated their proposed deep learning-based model using the same dataset and the metrics (CAT2000 and NSS) as those employed in the present study, reporting an NSS score of 2.30 (Kroner et al., 2020)—substantially higher than the scores achieved by bottom-up salience models, including ours, which reached at most around 1.15, as shown in Figure 3. However, simply applying such deep learning-based models to data analysis makes it difficult to disentangle bottom-up and top-down effects on eye movements. As demonstrated by Adámek et al., analyzing eye movements with both bottom-up and deep learning-based models, and comparing their results, enables a more distinct evaluation of these two types of influences (Adámek et al., 2024). Taken together, our proposed model has the potential to quantify altered weighting of salience as reflected in eye movements, and this potential can be further enhanced through refined experimental designs and analyses.

Data availability statement

The data supporting the findings of this study were obtained through simulations based on the computational model, as well as derived from model-driven analyses applied to the publicly available CAT2000 dataset. The MATLAB codes used for the model and simulations are available on GitHub at <https://github.com/fujitaysim/>

[saliency_map](#). The CAT2000 dataset can be accessed at <https://saliency.tuebingen.ai/datasets.html>.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

YF: Writing – original draft, Conceptualization, Methodology, Investigation, Writing – review & editing, Visualization. TM: Writing – review & editing, Conceptualization. JM: Writing – review & editing, Conceptualization.

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Conflict of interest

JM received research funding from Advanced Telecommunications Research Institute International (ATR) and Boehringer Ingelheim. These organizations had no role in the design, analysis, or interpretation of the study.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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