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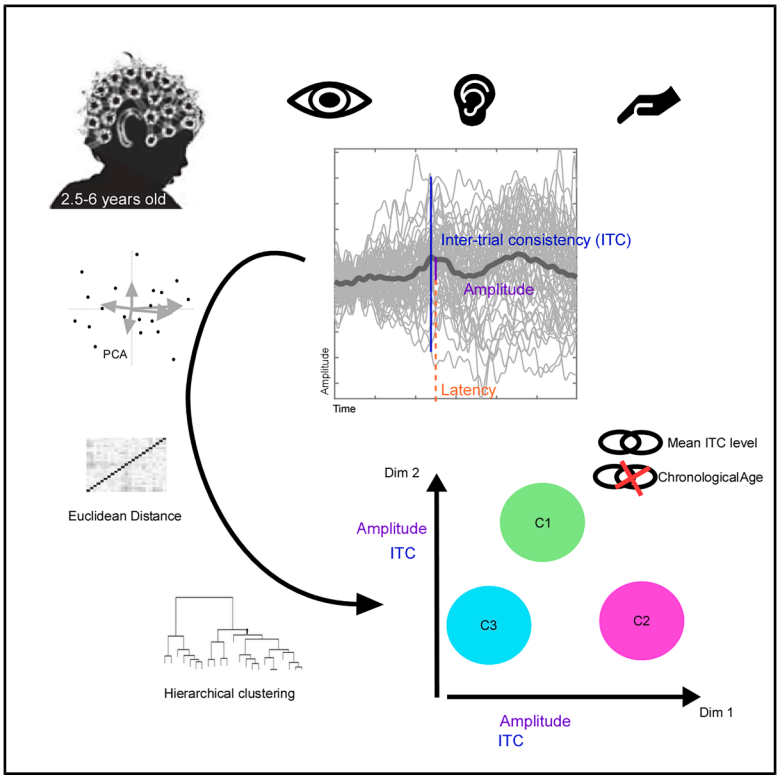
Unraveling variability in young children's brain responses to varied sensory stimulations

Graphical abstract



Highlights

- Young children can be separated into three clusters according to their brain responses
- The neurophysiological profiles were not differentiated based on chronological age
- Brain response to complex auditory and visual stimuli better explained cluster separation
- Cluster differed in mean inter-trial variability that serves as a proxy for neural noise

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In brief

Natural sciences; Biological sciences; Neuroscience; Clinical neuroscience

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Unraveling variability in young children's brain responses to varied sensory stimulations

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SUMMARY

Early childhood is a sensitive period of development, marked by high between and within individual variability in the acquisition of cognitive and social abilities. Our aim was to characterize electrophysiological individual sensory profiles of young children with electroencephalography. We recorded visual, auditory, and somesthetic event-related potentials (ERPs) to low-level, complex, and social sensory stimulations in 23 children (13 girls) without neurodevelopmental disorders (mean age: 47.8 months (±10.5) [30 64]). For each participant and condition, we analyzed ERPs' peak amplitudes and latencies and inter-trial consistency (ITC) as a measure of intra-individual variability. A hierarchical cluster analysis, following a principal-component analysis including all ERP measures, revealed 3 clusters; cluster separation was explained by mean ITC level. Neither age nor sensory-cognitive profiles explained cluster membership. Neurophysiological sensory profiles of young children differ mainly according to visual and auditory processing of complex information and do not rely solely on chronological age.

INTRODUCTION

Early childhood is characterized by high inter-individual variability, particularly in the developmental dynamics of milestones acquisition such as walking and language. Around the age of one, some children develop language first, while others develop walking first. This developmental variability is cerebrally underpinned by a high degree of plasticity. In particular, in early development, there is a big increase in synaptic density affecting, in chronological order, sensory areas, receptive language areas, and higher cognitive areas, followed by a region-specific pruning.[1] Cerebral maturation, estimated by gray matter density, follows broadly the same region-specific dynamics, with motor and sensory areas maturing earliest, notably somatosensory and visual cortices, followed by areas involved in spatial orientation, speech, and language development, and finally higher-order areas involved in executive functions, attention, and motor coordination maturing later in life.[2] This variability in the developmental dynamics of different domains also underlies variability at an inter-individual level, since they may vary from one child to another. These observations suggest that maturation of low-level sensory processes takes place first and is followed by that of higher-level sensory, language, and cognitive processes. These different dynamics lead to greater variability in children than in adults, both within and between individuals, referred to as intra- and inter-individual variability, respectively. Developmental variability in the acquisition of behavioral milestones is also linked to intra-individual variability, since age differences in the acquisition of these milestones within a child derive from varying dynamics of brain maturation in different domains. The succession of periods of increased synaptic density and synaptic pruning that characterizes early brain development may have a particular neurophysiological signature, measurable with electroencephalography (EEG). Indeed, EEG-based event-related potentials (ERPs) are objective measures of brain activity, with specific patterns depending on the type of stimuli being processed and the sensory modality being stimulated. What is more, ERPs can be used to assess inter- and intra-individual variability.[3–5] Single trial analyses of EEG allow the characterization of the variability in the cerebral response to the same stimulus and revealed the existence of intra-individual variability,[3–5] which is higher in children than in adults.[6,7] The aim of this study was therefore to investigate the multi-sensory electrophysiological profiles of young children. Low-level sensory processes were assessed alongside more complex stimuli, and social processing in three sensory modalities, in line with the dynamics of brain maturation. These profiles were explored from the vantage point of children's sensory, cognitive, and language abilities.

ERP components represent different processing steps that are in part linked to low-level features of the stimuli, but also to the type of stimuli, and whether the stimulus is social or not. In addition, ERPs vary with age and can be used to assess development of different functions; mainly ERPs' amplitude and latency decreases with age although the age range where adult-like pattern is observed depends on the stimulus being processed and the component being studied.[8,9] Therefore, ERPs are a useful tool to

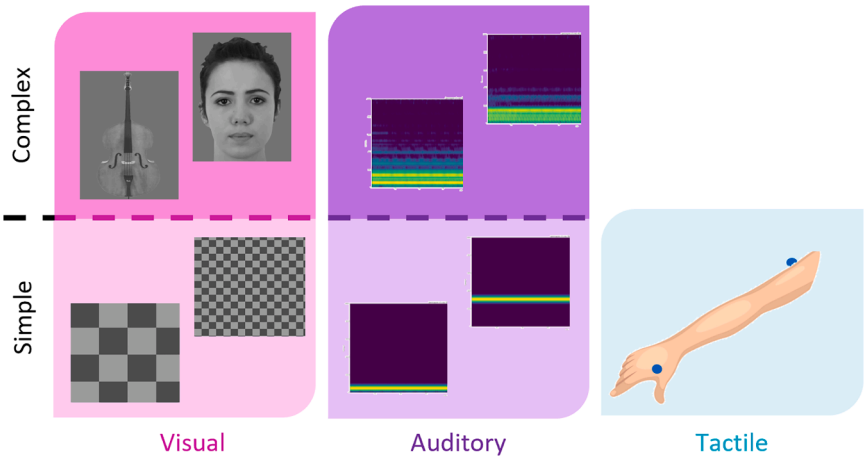

Figure 1. Overview of the task design and stimuli

Pale colors (bottom) correspond to block of low-level stimuli (checkboards of different spatial frequencies, pure tones of different frequencies and tactile stimulations), and dark colors (top) correspond to high-level stimuli, including social and non-social nature (pictures of musical instruments and faces, sounds of musical instruments and voices).

index the development of different processing steps of sensory information. In the visual modality, checkerboards of varying frequencies target different areas of the retina, yielding different ERP patterns: higher spatial frequencies (smaller squares) yield larger ERPs. ERPs also index processing of higher-level information; in particular, the N170, a negative component recorded between 140 and 190 ms in older children and adults, has been shown to be specifically sensitive to human faces, both neutral or emotional,[10] with a shorter latency and larger amplitude in response to human faces than to non-human faces and objects.[11] N170 can be observed as early as age four, but mature well into adolescence.[9] The visual P1, in response to faces originating from the low-level visual area, appears to mature faster, with adult-like latency and amplitude reached around age 10.[9]

In the auditory modality, ERP components, and particularly the P1 and N1, are sensitive to sound frequency and intensity.[12,13] N1 amplitude decreases with increasing frequency and with decreasing intensity.[13,14] The prominent ERPs in children aged seven and over consist of three successive components over the temporal regions: a first negative peak named Na or N1a around 80 ms, followed by a positive Ta peak around 100 ms, and finally a second negative deflection around 170 ms in children, referred as Tb or N1c.[12,15] Auditory-evoked responses to pure tones in young children are mainly characterized by a P1 and an N2, respectively, occurring 100 and 200 ms after the stimulus (the last refers to the N250 component), when other studies identified also N1 and P2 in children aged five to six, around 100–150 and 140–210 ms.[16,17] The fronto-temporal positivity to voice is a slow component, specific to vocal sounds (speech and non-speech) recorded in adults[18] and in 4- to 5-year-old children.[19] This preferential response to speech sounds over nonvocal sounds also affects P1, with speech sounds yielding a larger and earlier P1 than other non-speech sounds.[20–22]

Somatosensory ERPs (S-ERPs) have been less studied, in particular, during development. In adults, four successive positive-negative deflections have been described: an early-latency positive component peaking at 50 ms post-stimulus onset, corresponding to activation of the primary somatosensory cortex, followed by a negative deflection at 70–80 ms after the tactile stimulation. Then, two other components have been identified, a positive peak at 100 ms and a negative one at 140 ms, described as generated by the secondary somatosensory cortex and modulated by attention for N140.[23–26] S-ERPs are sensitive to the type of stimulation, their location, and their duration.

A better understanding of the development of pluri-sensory processing of different stimuli is crucial as sensory processing is at the root of the multiple cognitive abilities. To our knowledge, no study has evaluated the processing of sensory information in three sensory modalities in the same individual, in young children between two and six. Hence, we aimed to define multisensorial electrophysiological profiles of young children to better understand the different developmental profiles of children. We then explored how these profiles relate to maturation as evaluated by chronological age but also by inter-trial consistency, a measure of internal neural noise.[4,27,28] Finally, we explored the relationship between electrophysiological profiles and measures of sensory and cognitive development.

Due to important inter-individual differences in the acquisition of milestones during development, our first hypothesis was that children's brain data would classify children into at least two clusters. We expected these clusters to reflect other aspects of children's development, either maturational aspects or more cognitive aspects, such as sensory reactivity, visuo-spatial abilities, or phoneme discrimination. We expected older children to present higher inter-trial consistency (ITC) than younger children; i.e., they would present less variable brain responses. We expected to find at least one cluster corresponding to older children, characterized by high ITC and brain response patterns resembling those of children above six or even adults, and one cluster of younger children, characterized by low consistency.

RESULTS

ERPs evoked by sensory stimulations in different sensory modalities (visual, auditive, and tactile) and with different levels of complexity (stimuli of low perceptual level, complex, and social stimuli; Figure 1) were recorded in 23 children (13 girls; Table 1) without neurodevelopmental disorders, aged 47.8 months (±10.5) [30 64]. For each participant and condition, we analyzed ERPs' peak amplitudes and latencies (Table 2) and ITC as a measure of intra-individual variability.

In the visual modality, checkerboards elicited the expected biphasic positive-negative ERP complex, showing a larger amplitude to high-frequency checkerboards. Faces elicited the pattern

Table 1. Mean participant characteristics

Total	Gender (*n*)	Age (months) μ (±σ) [min max]	NVIQ μ (±σ) [min max]	SP visual μ (±σ) [min max]	SP auditory μ (±σ) [min max]	SP tactile μ (±σ) [min max]	Phoneme discrimination μ (±σ) [min max]
n = 23	F (13) M (10)	47.8 (±10.5) [30 64]	114.3 (±10.1) [91 132]	12.9 (±5.3) [6 24]	16.7 (±6.2) [9 30]	15 (±3.6) [11 24]	0.25 (±0.85) [-2.3 1.1]

NVIQ, nonverbal intellectual quotient: visuo-spatial index from Wechsler Preschool and Primary Scale of Intelligence; SP, sensory profile scores for each modality Dunn's Sensory Profile 2.

classically found in young children, consisting of sub-components between 170 and 300 ms post-stimulus; N170 tended to be more negative for faces than musical instruments (Figure 2; Table 3). In the auditory modality, we also observed the expected response pattern: the Ta-Tb complex (positive-negative peaks at 100 and 170 ms). In addition, evoked responses to voices were more positive than those evoked by musical instrumental sounds, consistent with previous results. Tactile stimulation evoked the expected pattern of four successive components.

A significant positive correlation (r = 0.43, r2 = 0.19, $p = 0.035$) was found between age and mean ITC level, suggesting that they both index maturation; however, the correlation remains moderate ($r < 0.5$) suggesting that age alone does not explain cerebral maturation as indexed by mean ITC level. The older the children, the greater the consistency of their brain responses between trials.

Two components account for 31% in data variability

Electrophysiological data ($n = 120$) from the 23 children were included in a principal-component analysis (PCA). Two principal components (PCs) accounted for 31.1% in data variability (18.5% by PC1; 12.6% by PC2) (Figure 3). Contributing factors were identified as those factors with loadings greater than one standard deviation away from the mean: 14 factors contributed to PC1, for an overall cumulative contribution of 62.5%, and 12 to PC2, corresponding to an overall contribution of 60.1% (Figure 3). PCs reflected only the contribution of ERPs' amplitudes and ITC.

The first PC was essentially characterized by ERPs' amplitude and ITC measures obtained in the visual complex block. Features with significant loadings also included ITC of the P100 for low spatial frequency visual stimuli and amplitude of early components of ERPs in simple auditory and tactile conditions (Figures 4A and 4C).

PC2 was mainly explained by contribution of ITC and ERPs amplitude to auditory and visual complex stimulations, in the latency range when social and non-social stimulation yields different brain responses (i.e., N170 for visual stimuli and Tb for auditory stimuli). PC2 was explained to a lesser extent by responses to simple auditory and visual stimuli (Figures 4B and 4D).

PCs were correlated to age and mean ITC level for each child to evaluate the relationship between electrophysiological dimensions and maturations. This analysis revealed a significant negative correlation between PC2 and mean ITC level (r2 = 0.5; p-corrected < 0.001): higher loadings on PC2 corresponded to smaller average ITC value, i.e., noisier brain responses. Correlations between PC1 and age (r2 = 0.04, p-uncorrected = 0.39), PC1 and mean ITC level (r2 = 0.19, p-corrected = 0.15), and PC2 and age (r2 = 0.22, p-corrected = 0.064) did not reach significance after correction for multiple comparisons (4 comparisons).

Table 2. Spatiotemporal parameters for peak measurements

Component	Time window (ms)	Electrodes
Simple visual block		
P100	92–139	PO7,PO3,O1, PO8, PO4, O2
N1	183–217	P7, P5, PO7,P8, P6, PO8
Complex visual block		
P1	123–161	PO7, PO3, O1,PO8, PO4, O2
N170	201–247	PO7, PO3, O1, PO8, PO4, O2
Simple auditory block		
P1	68–122	FC5, FC3, C3, C5, FC6, FC4, C4, C6
N2	152–192	FT7, FC5, T7, C5, FT8, FC6, T8, C6
Complex auditory block		
Ta	68–122	FC5, FC3, T7, C3, C5, FC6, FC4, T8, C4, C6
Tb	152–192	FC5, FC3, C3, C5,FC6, FC4, C4, C6
Simple tactile block		
P50	27–92	C3, CP3
N70	45–104	C3, Cz
P100	74–116	C1, C3, Fz, FCz
N140	152–194	C5, T7, Fz

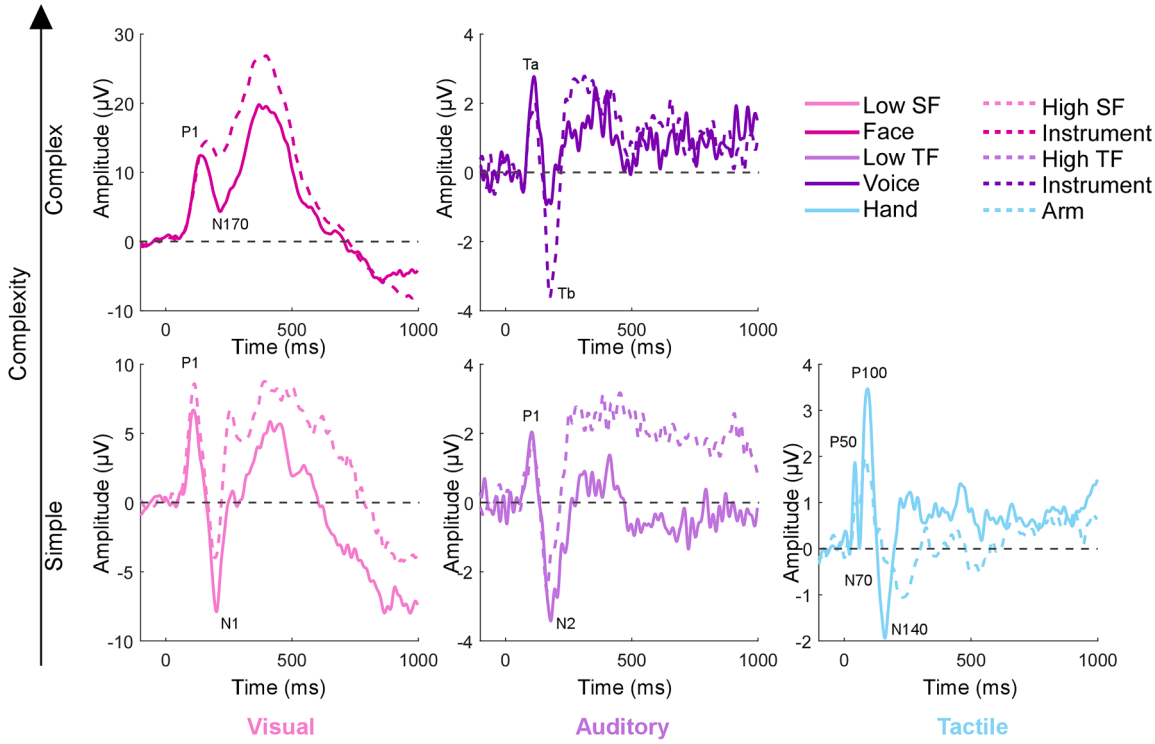

Figure 2. Grand average ERPs for each experimental condition

Visual ERPs are represented on PO8, auditory ERPs on T8, and somatosensorial ERPs on C3. Pale colors correspond to blocks of low-level stimuli, and dark colors correspond to social (solid lines) and non-social stimuli (dashed lines). Line types differentiate stimuli in each condition: for simple complexity, solid lines represent low-frequency (and hand condition for tactile modality), and dashed lines represent high-frequency stimuli (and arm condition for tactile modality). SF, spatial frequency; TF, tone frequency.

The hierarchical clustering analysis reveals 3 clusters

Agglomerative hierarchical clustering analysis on the Euclidean distance matrix in the 2D PCA space highlighted three clusters as the optimum number of clusters (silhouette score = 0.44; Figure 5). Cluster 1 (green cluster) comprised 10 participants; cluster 2 (red cluster) 9 participants and the last one (blue cluster) had four participants.

Clusters differed principally on the ERPs amplitude and ITC observed in visual complex and auditory complex blocks (Figures 4 and 5). Dimension 1 (Figures 4A and 4C) of the PCA distinguished principally cluster 3 from cluster 1. ERPs' amplitudes were overall more negative in cluster 3 than in clusters 1 and 2: i.e., smaller amplitude of the P100 in visual conditions, and larger N1 and N70 in auditory and tactile conditions, respectively. ITC was larger in cluster 2 for positive component but larger in cluster 3 for negative components (i.e., N170). This suggest that cluster 2 presented more mature early responses to visual stimulation (corresponding to the positive components), but cluster 3 presented more mature higher-level processes (i.e., later negative components). Dimension 2 (Figures 4B and 4D), which principally included amplitude and ITC of negative components for visual and auditory stimulation, mainly separated cluster 2 from clusters 1 and 3. Negative ERP components were overall of a smaller amplitude (i.e., more positive), and trial-to-trial response was less consistent (i.e., smaller ITC) in cluster 1.

Visual exploration of the ERPs (Figure 6) showed that overall ERPs in cluster 2 appear more mature, i.e., more adult like, than those of clusters 1 and 3.

Cluster membership is not driven by chronological age

A PCA on non-physiological individual parameters revealed that 3 dimensions explained about 75% of the inter-subject variance. The first dimension reflected principally sensory responsiveness in the tactile modality and to a lesser extent in the visual modality. The second dimension reflected sensory responsiveness in the auditory modality. The third dimension was linked to visuo-spatial abilities. We fitted a multinomial logistic regression model to assess the respective influence of these PCA dimensions on the likelihood of cluster membership (Figure 7, Table 4). We tested the full model with the 3 dimensions of the PCA, with cluster 2 as the reference. The logistic regression goodness of fit, assessed using a likelihood ratio test, revealed a non-significant chi-squared statistic of $\chi 2(6) = 11.6$, $p = 0.07$. This indicates that the model with the 3 dimensions as predictors did not provide a significantly better fit to the data than a model without these predictors. Consequently, we did not find non-physiological parameters that separated the three clusters. Qualitative exploration of data suggest that cluster 3 may differ from cluster 2 based on their sensory responsiveness in the visual modality: children in cluster 3 seem to have lower scores, maybe reflecting a slight hyposensitivity.

Table 3. Mean amplitudes and latencies for each ERPs component

Modality	Complexity	Component	Stimulus type	Mean amplitude (μV)	Mean latency (ms)
Visual	simple	P1/P100	low-frequency checkerboards	9.06	117.24
			high-frequency checkerboards	8.71	121.41
	complex		musical instrument	18.41	157.67
			face	16.45	147.35
	simple	N1/N170	low-frequency checkerboards	−6.75	199.28
			high-frequency checkerboards	−3.89	198.81
	complex		musical instrument	12.92	228.70
			face	3.83	226.20
Auditory	simple	P1/Ta	low-frequency tone	2.07	95.61
			high-frequency tone	1.94	94.12
	complex		musical-instrument	2.18	97.52
			voice	1.92	93.57
	simple	N2/Tb	low-frequency tone	−3.59	172.04
			high-frequency tone	−2.86	170.38
	complex		musical-instrument	−2.23	165.84
			voice	−2.85	166.52
Tactile	simple	P50	arm	2.24	58.69
			hand	2.94	57.67
		N70	arm	−0.04	62.01
			hand	0.01	65.23
		P100	arm	1.73	100.47
			hand	1.63	96.65
		N140	arm	−1.26	180.13
			hand	−2.06	179.02

DISCUSSION

Our aim was to explore the pluri-sensorial electrophysiological profiles of young children. Our first objective was to determine whether ERPs could allow identifying different profiles among children with typical neurodevelopment. Our second objective was to explore how these profiles related to other aspects of development, e.g., chronological age, brain maturation as index by ITC, verbal and nonverbal abilities, and sensory responsiveness.

First, we checked whether ITC, a measure of internal noise, could be used as an index of maturation. Previous studies have shown that adults have less variability in their cerebral responses than children.[6,7] ITC measures the consistency of cerebral response across repeated stimulations, either exactly similar or belonging to the same category; hence ITC can be seen as a measure of internal noise in cerebral processing of sensory information.[4,27] A significant correlation between age and ITC confirmed that ITC might be a good index of cerebral maturation and demonstrated that cerebral maturation yields to noise reduction during typical development. Yet, the moderate correlation coefficient suggests that ITC may capture different maturational aspects than chronological age.

A PCA revealed that 30% of the variability between children was accounted for by two dimensions. The first dimension captured early brain responses to complex stimulation, in particular ITC and ERPs' amplitude. The second dimension reflected the processing of complex information in the auditory and visual modalities; interestingly, the second component was sensitive to brain processing of complex information in the latency range where differences between social and non-social information are observed in adults, i.e., N170 for visual information[9,29] and Tb for auditory information.[4,18,19] ERP component latency is often reported to decrease with cerebral maturation in developmental studies,[9,30] and, consistently, components reported here had longer latencies than those reported in adults or older children.[9,30–32] However, here, we did not find any influence of ERP component latency on the children's profiles. Most developmental studies either looked at infants up to 2 years of age or after 5 years,[9] leading to a lack of knowledge on the development of sensory processing in the 2 to 6 years old. The lack of influence of ERPs components latency on cluster separation could be explained by the fact that steep changes in latency are generally observed in older children.[30,33]

Using the PCA components in a hierarchical clustering analysis revealed the existence of three clusters in our sample of 23 young children. Hence, ERPs provided evidence of different developmental pluri-sensorial profiles in a sample of young children. Cluster 2, comprising 9 children, presented larger and less noisy brain responses in all sensory modalities, with ERPs' morphologies more adult like than the other clusters. Cluster 1 showed adult-like visual ERP components in the low-level block, but their responses did not differentiate faces from pictures of

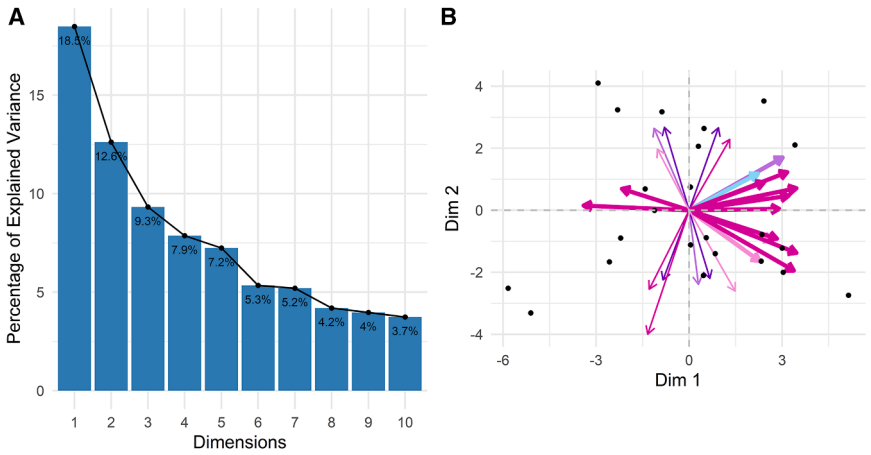

Figure 3. Two components account for 31% in data variability

(A) Scree plot illustrating percentage of explained variance for the first 10 components.

(B) Variable contribution to the first two dimensions of the PCA. Only variables that contribute more than one standard deviation from the mean are displayed. Thick lines: contribution to PC1; thin lines: contribution to PC2. Line colors correspond to conditions: light pink, simple visual; dark pink, complex visual; light purple, simple auditory; dark purple, complex auditory; light blue, simple tactile.

instruments, and the auditory and tactile ERPs were noisy. Children in cluster 3 seemed to have relatively mature ERPs in all modalities except in response to low-level visual stimuli for which ERPs' amplitude was much smaller. Interestingly, the qualitative analysis showed that cluster 3 may have a slight visual hyposensitivity. This is consistent with previous studies in the tactile modality that showed a link between tactile reactivity and early components of S-ERP amplitude in autistic development.[34]

Contrary to our expectations, chronological age did not explain cluster separation, either when tested against PCA dimensions or in the multinomial logistic regression. Yet, ITC correlated with dimension 2 of the PCA, suggesting that

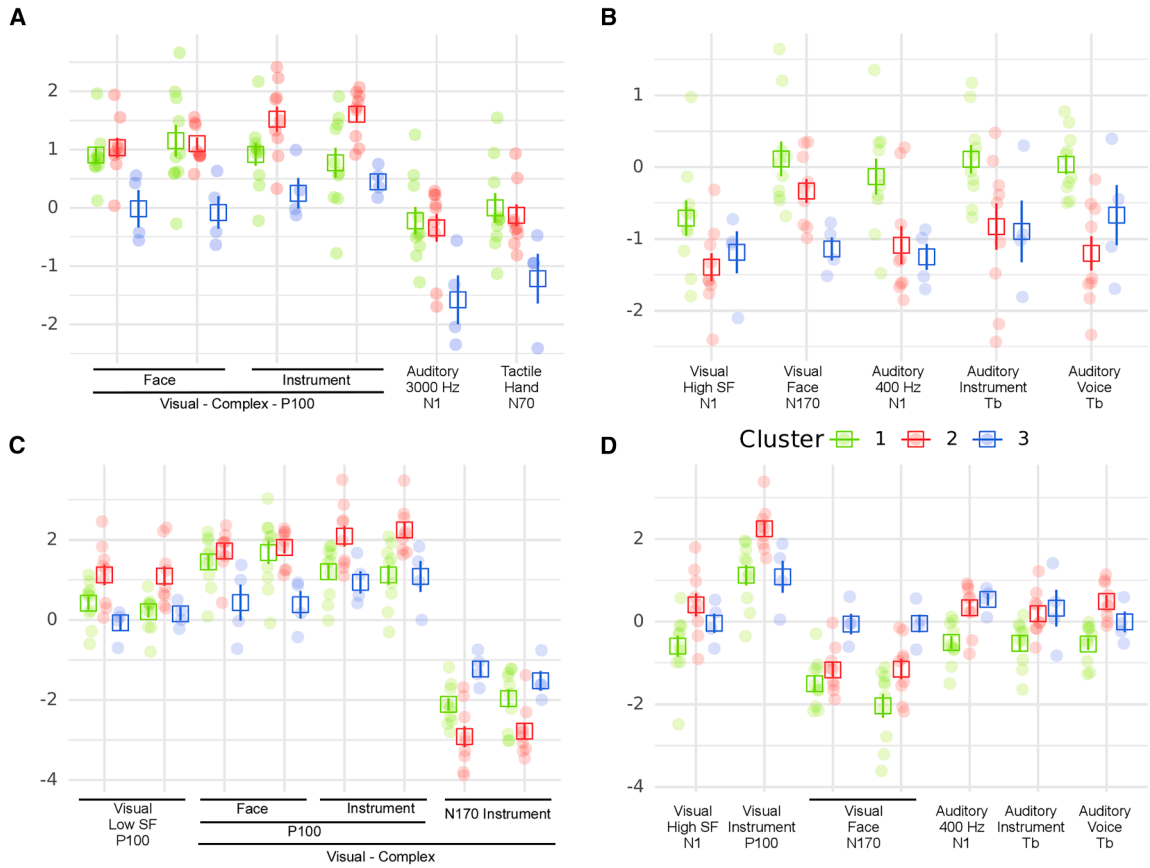

Figure 4. Variables contributing to the two principal components

Individual data points (*Z*-scored) are represented for each of the clusters identified in the hierarchical clustering analysis. Data are represented as mean (square) +/− standard error of mean (SEM). (A) ERP amplitude contributing to PC1, (B) ERP amplitude contributing to PC2, (C) ITC contributing to PC1, and (D) PC2.

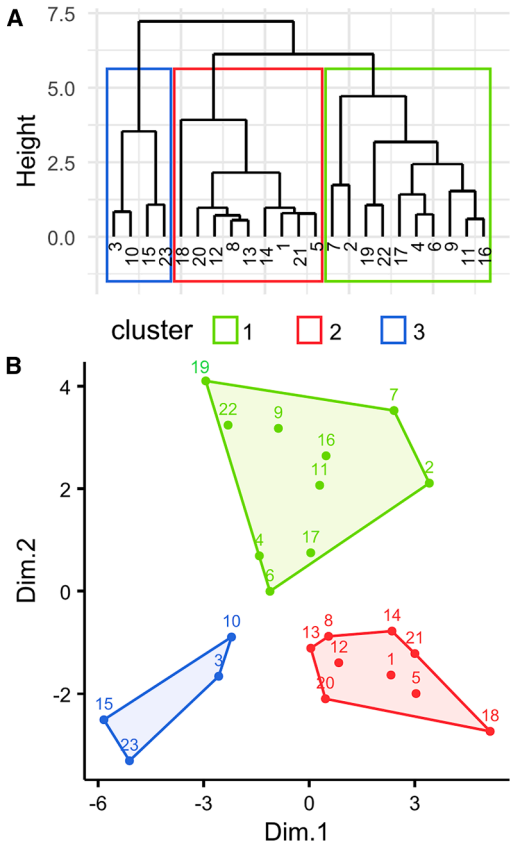

Figure 5. The hierarchical clustering analysis reveals 3 clusters

(A) Dendrogram tree representing agglomerative hierarchical clustering analysis on three clusters. Each branch represents the connection of one group of participants with another, in a hierarchical way: from the first connections on the right to the last on the left. Square boxes allow the visualization of the three clusters: cluster 1 in green, cluster 2 in red, and cluster 3 in blue.

(B) Bidimensional representation of the three clusters.

cerebral maturation, e.g., a less noisy brain signal, partly independent of chronological age, may be more discriminant than chronological age in the sensory response profile of children. Most of our knowledge on development of sensory processing comes from cross-sectional studies, where groups of children with different mean ages are compared to one another. This approach masks important differences in children's individual response and does not consider developmental stages of the children.[2,35] The approach highlighted here does not make any assumptions regarding developmental stages and reveals that age alone does not explain differences in children's electrophysiological profiles, suggesting a different approach to tackle the study of neurodevelopment considering the high heterogeneity of children profiles in sensitive developmental time periods. The lack of an age effect could be explained by the small sample of children tested, with regards to the high developmental variability inherent in this age range. Children's cortical development is under the influence of external factors and sensory experience,[36] and, for instance, children's cortical structure development in primary sensory areas has been linked to nonverbal cognitive performance in 5-year-olds children.[37] Yet, no measure of sensory responsiveness, phonological abilities, or visuo-spatial abilities differed across clusters. This lack of effect could either reflect a lack of power due to our small sample size or that the chosen parameters were not sensitive enough. Testing a larger number of children in the whole age range, in particular older ones, may have allowed us to identify larger clusters or sensory-cognitive parameters that could distinguish between clusters.

We deliberately chose to analyze all sensory modalities together, rather than having a sensory modality-based approach. The findings schematized in Figures 6 and 7, together with the results of the sensory profiles survey showing hypo- or hyper-sensitive children in the three sensory modalities assessed, suggest that different clusters might be identified if the analyses were carried out independently for the three sensory modalities. In this study, we chose to consider both inter-individual variability and intra-individual variability. Intra-individual variability could also be assessed independently in the different sensory modalities, in relation to differential dynamics of brain maturation. Since visual and somatosensorial cortices seem to maturate earlier,[2] we would expect to find greater inter- and intra-individual variability in auditory responses than in visual or tactile responses; consistently results showed a larger cross-cluster variability in auditory-evoked potential than in tactile and visual ERPs. In line with our findings that, as children age, they show better brain coherence, it could also be that the auditory modality, which matures at a slower pace, is characterized by greater inter-trial variability. As these brain development dynamics also vary from one child to the next, the brain coherence measured in each sensory modality could also be related to higher-level visual-spatial, cognitive, and language skills.

This work represents a significant contribution to knowledge of brain development and maturation in the context of early development. Indeed, most of the research carried out in typical development often considers children before 2 or after 5 years of age and often considers only chronological age as a factor; yet, here we have shown that chronological age is not the main parameter influencing ERPs. In line with what has been demonstrated by recent work in neurodevelopmental disorders and autism,[4,38] the data presented here suggest that dividing experimental groups of children on the basis of chronological age, IQ, or language skills alone may be inappropriate. It would be more appropriate to propose multimodal assessments, crossing measures from different domains and modalities, to establish comprehensive profiles that better account for the different heterogeneities characterizing early development.

Conclusion

To our knowledge, this study is the first to focus on the development of sensory processing in three sensory modalities in the same children, exploring simple, complex, and social stimuli, in young children aged two and a half to six years of age, enabling a multimodal mapping of the sensory development of young children. The cluster analysis used here allows a single subject approach to further our understanding of the developmental of typically developing children.

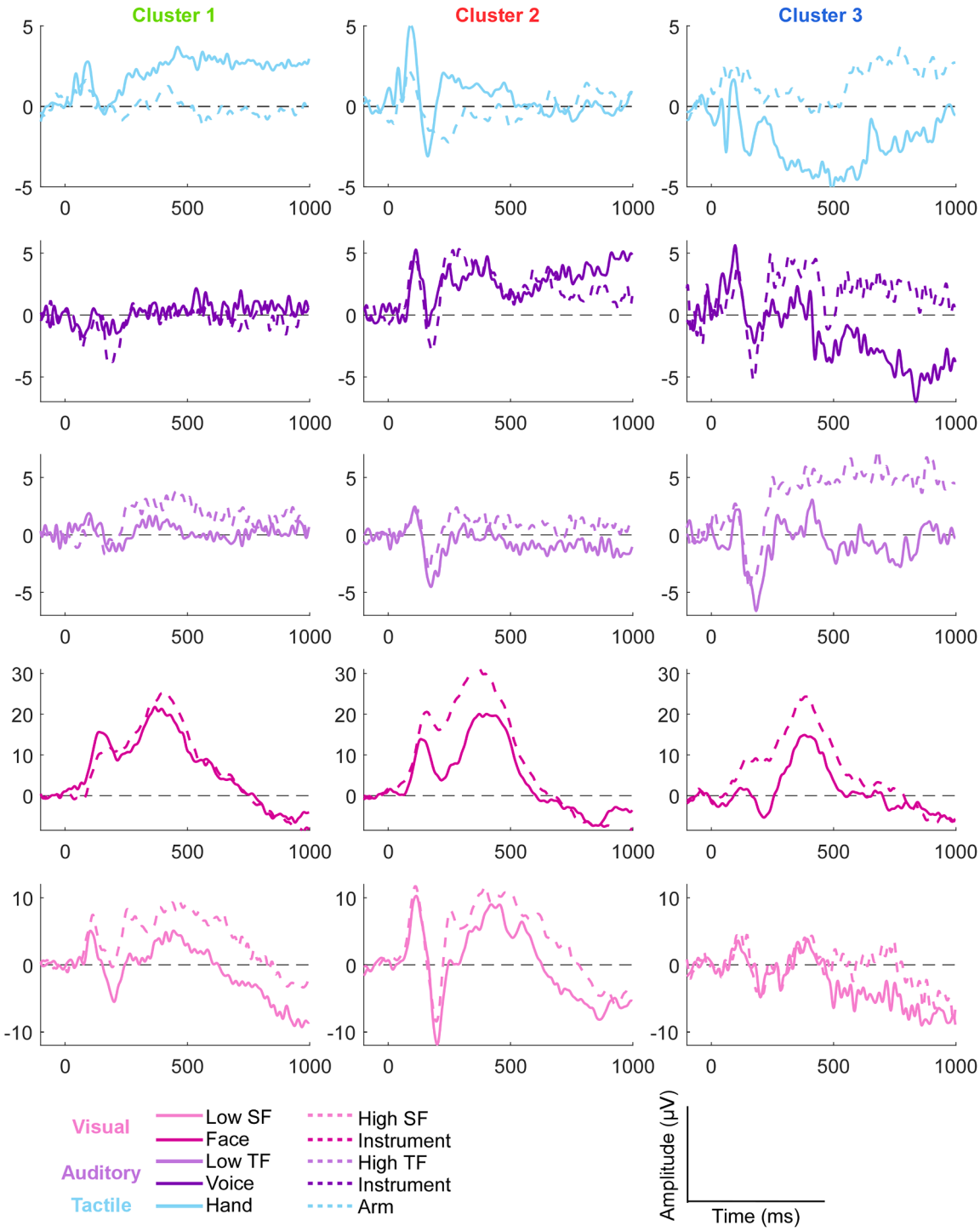

Figure 6. Tactile, auditory, and visual ERPs for the three clusters

From top to bottom: tactile ERPs to simple stimuli (blue; solid line: hand; dash line: arm); auditory ERPs to complex stimuli (purple; solid line: voices; dash line: instruments); auditory ERPs to simple stimuli (light purple; solid line: 400 Hz; dash line: 3000 Hz); visual ERPs to complex stimuli (dark pink; solid line: faces; dash line: pictures of instruments); visual ERPs to simple stimuli (light pink; solid line: large checkerboards; dash line: small checkerboards).

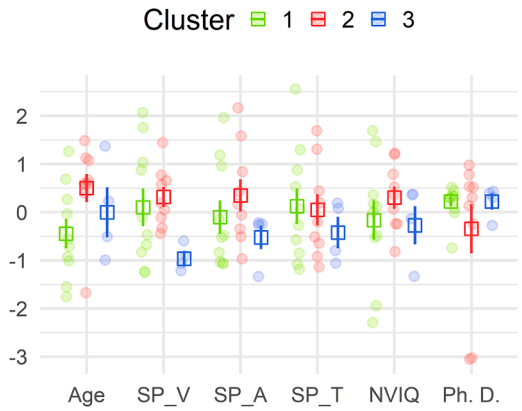

Figure 7. Cluster membership is not driven by chronological age
Data (*Z*-scored) are represented as mean ±standard error of mean (SEM). SP, sensory-profile for visual, audio, and tactile daily responsiveness; NVIQ, non-verbal intellectual quotient-visuo-spatial index from WPPSI-IV Wechsler battery; Ph. D., phoneme discrimination abilities indexed with EVALO.

We showed that young children can be distinguished by their brain responses to complex visual and auditory stimuli into three main groups. Contrary to our expectations these groups did not separate according to age, but rather by cerebral maturation and neural noise, measured with ITC. Finally, we showed that maturational parameters also characterized electrophysiological responses, with younger children showing greater variability in their cerebral responses than older children.

Limitations of the study

The main limitation of the study is the small sample size, which reduced the statistical power of the multinomial logistic regression in particular. We use an agglomerative hierarchical clustering after a PCA dimension reduction to mitigate the effect of our sample size. A bigger sample size may have allowed a better assessment of the different sensory-cognitive profiles across the clusters, and the inclusion of older children may have revealed an age effect on the electrophysiological profiles. Nonetheless, the approach used in our study relying on a cluster analysis does not make assumptions regarding expected developmental stages, contrarily to cross-sectional studies comparing age groups. It provides a strategy to look at children's development while considering the high variability of children's profile in this age range, allowing to better consider individual profiles and the developmental age of the children.

RESOURCE AVAILABILITY

Lead contact

Requests for further information and resources should be directed to and will be fulfilled by the lead contact, Marianne Latinus (marianne.latinus@univ-tours.fr).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- De-identified processed datasets (individual and group data) have been deposited at Zenodo at https://doi.org/10.5281/zenodo.16876786 and are publicly available as of the date of publication. Zenodo Database: https://zenodo.org/badge/DOI/10.5281/zenodo.16876786.svg.
- All original code has been deposited at Zenodo at https://doi.org/10.5281/zenodo.16876786 and is publicly available as of the date of publication. Zenodo Database: https://zenodo.org/badge/DOI/10.5281/zenodo.16876786.svg.
- Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

L.M.: methodology, investigation, data curation, formal analysis, investigation, funding acquisition, software, visualization, writing – original draft, and writing – review and editing; M.S.-R.: investigation, formal analysis, and writing – review and editing; C.W.: conceptualization, methodology, project administration, and writing – review and editing; M.L.: conceptualization, data curation, methodology, funding acquisition, project administration, resources, software, supervision, visualization, writing – original draft, and writing – review and editing.

DECLARATION OF INTERESTS

The authors declare no competing interests.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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Table 4. Mean of non-physiological parameters for each cluster

	N	Age (months) (±SEM)[range]	NVIQ(±SEM) [range]	Phon. D(±SEM) [range]	SP visual(±SEM) [range]	SP audio(±SEM) [range]	SP tact(±SEM) [range]
Cluster 1	10	43.1 (±3.2) [30 61]	112.6 (±4.11) [91 132]	0.436 (±0.09) [-0.3 0.66]	13.4 (±2.08) [6 24]	16.1 (±2.16) [10 29]	15.5 (±1.34) [11 24]
Cluster 2	9	53(±3.05)[31 64]	117.3(±2.32)[106 126]	−0.05(±0.44)[-2.29 1.05]	14.6(±1.1)[11 21]	18.9(±2.07)[11 30]	15.2[11 21]
Cluster 3	4	47.7(±5.5)[37 62]	111(±4.01)[100 117]	0.44(±0.15)[0.01 0.66]	7.7(±0.9)[6 10]	13.5(±1.5)[9 15]	13.5(±1.2)[11 16]

SP, sensory-profile for visual, audio, and tact daily responsiveness; NVIQ, non-verbal intellectual quotient-visuo-spatial index from WPPSI-IV Wechsler battery; Phon. D., phoneme discrimination abilities indexed with EVALO. For ease of reading, raw scores are presented instead of *Z*-scored values.

SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
De-identified processed experimental data	Own	https://zenodo.org/records/16876786
Analysis Code	Own	https://zenodo.org/records/16876786
Software and algorithms		
MATLAB	The Mathworks	RRID:SCR_001622; https://fr.mathworks.com/
EEGLab	SCCN/UCSD	RRID:SCR_007292; https://eeglab.org/
APICE	UNICOG BabyLab, NeuroSpin	https://github.com/neurokidslab/eeg_preprocessing
R (version 4.4.1)	R Core Team[39]	RRID:SCR_001905; https://www.r-project.org
R Studio 2024.09.1	Posit team (2024)[40]	http://www.posit.co/
Stringr	Wickham H (2023)[41]	RRID:SCR_022813; https://CRAN.R-project.org/package=stringr
Tidyr	Wickham et al., (2024)[42]	RRID:SCR_017102; https://CRAN.R-project.org/package=tidyr
Dplyr	Wickham et al., (2023)[43]	RRID:SCR_016707; https://CRAN.R-project.org/package=dplyr
Tidyverse	Wickham et al., (2019)[44] https://doi.org/10.21105/joss.01686	RRID:SCR_019186; https://www.tidyverse.org/
ggplot2	Springer-Verlag New York	RRID: SCR_014601; https://ggplot2.tidyverse.org
Ggpubr	Kassambara, 2023[45]	RRID:SCR_021139; https://CRAN.R-project.org/package=ggpubr
FactoMineR	Lê et al., 2008[46] https://doi.org/10.18637/jss.v025.i01	RRID:SCR_014602; http://factominer.free.fr/index_fr.html
Devtools	Wickham et al., 2022[47]	RRID:SCR_016961; https://CRAN.R-project.org/package=devtools
Factoextra	Kassambara & Mundt, 2020[48]	RRID:SCR_016692; https://CRAN.R-project.org/package=factoextra
Rstatix	Kassambara 2023[49]	RRID:SCR_021240; https://CRAN.R-project.org/package=rstatix
Ggdendro	de Vries & Ripley (2024)[50]	https://CRAN.R-project.org/package=ggdendro
Readr	Wickham et al., 2024[51]	https://CRAN.R-project.org/package=readr
dendextend	Galili (2015)[52] https://doi.org/10.1093/bioinformatics/btv428	RRID:SCR_026116; https://cran.r-project.org/web/packages/dendextend/index.html
Nnet	Venables, W. N. & Ripley, B. D. (2002)[53] ISBN 0-387-95457-0	https://www.stats.ox.ac.uk/pub/MASS4/
Lmtest	Zeileis & Hothorn (2002)[54]	https://CRAN.R-project.org/doc/Rnews/

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Twenty-three all-comer children (13 girls; mean age: 47.9 months old (±10.5) [30 64]) took part in the study. These children had no history of neurological or psychiatric disorders or early learning disabilities and had not been diagnosed for a neurodevelopmental condition. All children had normal or corrected-to-normal vision and normal hearing, based on parental reports. They were recruited in kindergartens and by word of mouth. Cognitive abilities were assessed using subtests (Block Design and Object Assembly) from the age-appropriate Wechsler Preschool and Primary Scale of Intelligence (4th ed.).[55] Phonemic discrimination abilities, as the auditory prerequisite for language comprehension, were assessed with a subtest of EVALO (Evaluation du Langage Oral)[56] and a parental survey was used to measure the sensory responsiveness of children in daily life, in vision, audition and tactile modalities (Dunn'Sensory Profile 2[57]). Visual sensory responsiveness is evaluated on a scale from 0 to 30 with the normal range between 9 and 17, auditory sensory responsiveness is evaluated on a scale from 0 to 40 with a normal range between 10 and 24, and tactile sensory

responsiveness is based on a scale from 0 to 55 with the normal range between 8 and 21. Phoneme discrimination evaluated with EVALO 2–6 is expressed as a standard error of mean corrected for age, with the normal range comprised between −0.99 and 0.1. Participant characteristics are summarized in Table 1. This study was approved by the Comité de Protection des Personnes EST I the 2017-04-20 (2017/23-ID RCB: 2017-A00756-47; PROSCEA) ethics committee. Parents and children were informed of their rights and of all aspects of the experimental design; parental consent was obtained in the form of a signed written consent form and children's consent was sought verbally or based on their behavior.

METHOD DETAILS

Stimuli

Stimuli were chosen to stimulate independently three sensory modalities: vision, audition and tact. Visual and auditory stimuli included low-level and complex stimuli, both social and non-social. The tactile stimuli were only simple mechanical stimulations. Figure 1 presents an overview of the task design and stimuli.

Low-level visual stimuli were light and dark gray checkerboards with different spatial frequency (low and high) that fitted a screen of 41.5° (wide) × 24.1° (high) visual angle; there were two exemplars per condition (inverted patterns). Low frequency checkerboards comprised 44 x 25 squares; each square measured 1 ° × 1 ° visual angle. High frequency checkerboards comprised 175 x 98 squares, each subtending a 0.2 ° × 0.2 ° visual angle. These low-level stimuli of various spatial frequencies were designed to stimulate different regions of the retina. Higher-level visual stimuli were grayscale photographs of neutral faces (social) and musical instruments (non-social). Photographs of six different individuals (three women) and of six different musical instruments (three winds and three percussions) were used. Gray levels and the object-to-background ratio (portion occupied by object on the entire image) were adjusted to be equivalent across conditions within a complexity level and to have an overall luminance at the level of the participant's head of approximately 48.4 lux.

Low-level auditory stimuli were pure tones with fundamental frequencies of 400 Hz and 3000 Hz. These low-level stimuli of various auditory frequencies were designed to stimulate different regions of the cochlea. High-level auditory stimuli were extracted from sustained vowels uttered by human beings and long instrumental sound clips, respectively for social and non-social content; six individual stimuli were used per condition (three female voices and three male voices, and three clarinet recordings and three saxophone recordings). Complex nonvocal stimuli were selected so that their fundamental frequencies matched those of the vocal stimuli, using speech analysis software Praat 6.1.16.[58] All sounds were normalized according to the root-mean-square of their amplitude. Sound duration was adjusted to 300 ms or 1500 ms, and an envelope of 5 ms day time was applied to the start and end of each sound to minimize clicks at sound onset and offset. Overall intensity was adjusted to 50 dB SPL at the subject's head.

Tactile stimuli were delivered by two miniature vibrotactile electromagnetic solenoid-type stimulators (Tactors stimulators, Dancer Design, Ingleton, England). These 18-mm diameter cylindrical tactors delivered a 50-ms single stimulation on a 4-mm diameter circular surface, with an estimated force of 0.35 N. They were placed on the back of the participant's right hand and back of the upper arm, respectively between the thumb and forefinger, and equidistant from the elbow and shoulder to stimulate different cutaneous territories of the radial nerve.

Experimental procedure

Participants were seated in a comfortable armchair, either alone or on their parents' lap, approximately 70 cm away from the screen and speakers, in a dimly lit and sound-attenuated room. Stimuli consisting of different modalities and complexity levels were presented in five different blocks (Figure 1), with durations varying between 4 and 5 min. The task was entirely passive, with no task asked of participants during the protocol, except to be as attentive as possible to the stimuli. Block order was randomized across participants. In each block stimuli were presented in a random order using Presentation 21.1 (NeuroBehavioral Systems Inc., Berkeley, USA). Each of these five blocks included two conditions and two stimulus onset asynchrony (SOA) durations (short trials; long trials). We included both short and long trials to enable recording of other physiological responses, such as pupillary dilatation, alongside EEG data; only EEG data are presented here. There were 120 stimuli in each block for EEG analysis (short trials) and 24 for autonomous parameters (long trials). In all blocks, stimulus onset asynchrony (SOA) varied between 1100 and 1500 ms for short trials and between 4300 and 4800 ms for long trials.

Low-level visual stimuli were repeated 30 times each, for a total of 60 low frequency checkerboards and 60 high frequency checkerboards. Individual photographs of faces and musical instruments were repeated 10 times each, for a total of 60 faces and 60 instruments. Visual stimuli were presented on a 1920 x 1080 screen (Dell U2419HC; refreshing rate: 60 Hz) for 300 ms in short trials and 1500 ms in long trials. A black cross on a gray background was presented on the screen at the level of the nose during inter-stimulus interval.

For the auditory and tactile blocks, a black fixation cross on a gray background was always present on the screen. Auditory stimuli were delivered through two loudspeakers placed on either side of the screen in front of the participant, at approximately 10° on both sides of the interaural axis. Pure tones were repeated 30 times each, for a total of 60 low and 60 high frequency tones. Vocal and musical instrumental sounds were repeated 10 times each, for a total of 60 voices and 60 instruments. As for the visual blocks, longer stimuli were presented during long trials. Tactile stimulations were repeated 60 times at each location.

Data recording and analysis

Electrophysiological data were collected using 64-active electrodes located according to the International 10–20 System (ActiveTwo Systems Biosemi, The Netherlands). There was no reference during acquisition; an average reference was calculated offline. Impedance was kept under 25 kOhm as per manufacturer recommendation. Data were recorded with a sampling frequency of 512 Hz.

Continuous EEG was preprocessed using EEGLab[59] working in the MATLAB environment (The Mathworks). The pre-processing pipeline used in this study applied some of the recommendations from the specific APICE pipeline for infants' continuous EEG.[60]

EEG data were first digitally re-referenced to FCz and filtered with a 100 Hz low-pass filter and a 0.1 Hz high-pass filter.[61] Bad electrodes and bad times-window were identified and corrected with APICE based on a 30% cut-off (electrodes with at least 30% of time segments with poor-signal and time periods with at least 30% of electrodes with poor-signal).[60] An Independent Component Analysis (ICA) on continuous EEG data allowed for the identification and correction of blinks and lateral eye movements. Continuous EEG was then epoched into 1100 ms sweeps including a 100 ms pre-stimulus baseline. Epochs with bad times and bad channels were identified and corrected using interpolation as implemented in APICE. Epochs with remaining artifacts were rejected; remaining epochs were digitally filtered with a 40 Hz low-pass filter using a Finite Impulse Response (FIR) filter. Finally, data were referenced to an average reference, and epoch were baseline corrected.

Time periods and electrodes of interest used for measuring each peak are presented in Table 2, and were identified based on the literature and by visual inspection of grand average per block. For visual and auditory modalities, the first two components were measured. For tactile modality, the first four components were included in the analysis. For visual and auditory modality, ERPs components were identified and measured on both hemispheres. For the tactile modality, only central electrodes or electrodes contralateral to the stimulation were considered, as responses are strongly lateralised.[25] Peak latencies and amplitudes, and maximal Inter-Trial Consistency within the components time-windows were measured for all components (Figure 2). ITC values were transformed so that 100% corresponds to a robust response for both negative and positive components.

Electrophysiological data included peak amplitudes and latencies of each component averaged across electrodes per hemisphere, for each participant (n = 23), and each experimental condition (sensory modality (3) x complexity level (2/1) x type of stimuli (2)). Following Latinus et al.,[4] we also measured Inter-Trial Consistency (ITC) as an indicator of intra-participant variability. ITC is based on the principle that the same sensory stimulation should generate the same cerebral response 28. In each participant, the proportion of trials showing a positive response was calculated at each time point; ITC was calculated as the percentage of trials eliciting the expected response in the time window of interest (a positive peak for positive ERPs components and a negative one for negative ERPs components). For each participant, 120 data points were included in the analysis. In addition, we measured mean ITC level, i.e., the average ITC across all experimental conditions and ERPs components as a putative index of cerebral maturation. We verify this using a Pearson correlational analysis, as normality and collinearity assumptions were verified, between age and ITC expecting a weak-to-moderate (e.g., Pearson's coefficient <0.5) but significant relationship.

QUANTIFICATION AND STATISTICAL ANALYSIS

Quantification, statistical analyses and Figures 3, 4, 5, and 7 were done with R (v.4.4.1)[39] and R Studio (2024.09.1)[40] using the following packages: stringr,[41] tidyr,[42] dplyr,[43] tidyverse,[44] ggplot2,[62] ggpubr,[45] FactoMineR,[46] devtools,[47] factoextra,[48] rstatix,[49] ggdendro,[50] readr,[51] dendextend,[52] nnet,[53] lmtest.[54]

Prior to further analyses, to keep the intra-individual relationship between the different components across conditions and sensory modalities, electrophysiological data were z-scored as follows (Figure S1): ERPs latencies were z-scored across participants and all experimental conditions (i.e., the mean and standard deviations of all participants, experimental conditions and components were used), a similar procedure was used for ITC. For ERPs amplitude, due to the much larger amplitudes observed in the visual modality than in the auditory and tactile modalities which could artificially increase the weight of the visual modality,[63] ERPs amplitudes were z-scored across participants and complexity level and components independently for each sensory modality (Figure S1).

Z-scored data were then entered into a principal component analysis (PCA) to reduce dimensions of our high-dimension and low-sample-size dataset. Euclidean distance in the two-dimensions PCA space were then used in an agglomerative hierarchical clustering analysis, using the McQuitty distance linkage method. A hierarchical clustering combined with the McQuitty linkage methods was used as this study was exploratory without an expected number of clusters and to avoid biases toward larger clusters; furthermore, hierarchical analysis is better suited for small samples.[64] Silhouette method was used to determine the optimal number of clusters. To explore the relationship between the electrophysiological dimensions that distinguished clusters, and maturation, we performed Pearson correlational analysis (normality and collinearity assumptions were verified) between Principal Components (dimensions) and two measures: chronological age and mean ITC level. Finally, we explored how clusters separability was explained by other non-physiological parameters, such as age, daily sensory responsiveness, NVIQ, and phoneme discrimination. First, we reduced dimensions of our data using a PCA, then we fitted Multinomial Logistic Regression models to explore how clusters were linked to the first 3 dimensions of the non-physiological PCA.