



# **BRAININFO 2026**

The Eleventh International Conference on Neuroscience and Cognitive Brain  
Information

ISBN: 978-1-68558-354-5

March 8th –12th, 2026

Valencia, Spain

**BRAININFO 2026 Editors**

Dip Patel, OSF Healthcare, USA

# BRAININFO 2026

## Forward

The Eleventh International Conference on Neuroscience and Cognitive Brain Information (BRAININFO 2026), held between March 8-th, 2026 and March 12-th, 2026 in Valencia, Spain, continued a series of events that evaluate current achievements and identify potential ways of making use of the acquired knowledge in neuroscience, brain connectivity, brain intelligence paradigms, cognitive information, and specific applications.

The complexity of the human brain and its cognitive actions prompted extensive research for decades. Most of the findings were adapted in virtual/artificial systems with the idea of modeling them and used in a brain-like manner for human-centered medical cures, especially for neurotechnology. Information representation, retrieval, and internal data connections still constitute a domain where solutions are either missing or in a very early stage.

We take here the opportunity to warmly thank all the members of the BRAININFO 2026 technical program committee, as well as all the reviewers. The creation of such a high-quality conference program would not have been possible without their involvement. We also kindly thank all the authors who dedicated much of their time and effort to contribute to BRAININFO 2026. We truly believe that, thanks to all these efforts, the final conference program consisted of top-quality contributions. We also thank the members of the BRAININFO 2026 organizing committee for their help in handling the logistics of this event.

We hope that BRAININFO 2026 was a successful international forum for the exchange of ideas and results between academia and industry for the promotion of progress in the field of neuroscience and cognitive brain information.

### **BRAININFO 2026 Chairs**

#### **BRAININFO 2026 Steering Committee**

Erwin Lemche, Institute of Psychiatry, Psychology & Neuroscience | King's College School of Medicine and Dentistry, UK

Yu-Dong (Eugene) Zhang, University of Leicester, UK

Chih Lai, University of St. Thomas Minnesota, USA

William Speier, UCLA David Geffen School of Medicine, USA

Sule Yildirim-Yayilgan, Norwegian University of Science and Technology, Norway

Ricardo Ron-Angevin, University of Málaga, Spain

Rory Lewis, University of Colorado at Colorado Springs, USA

#### **BRAININFO 2026 Publicity Chairs**

Francisco Javier Díaz Blasco, Universitat Politècnica de València, Spain

Ali Ahmad, Universitat Politècnica de València, Spain

José Miguel Jiménez, Universitat Politècnica de València, Spain

Sandra Viciano Tudela, Universitat Politècnica de València, Spain

## **BRAININFO 2026 Committee**

### **BRAININFO 2026 Steering Committee**

Erwin Lemche, Institute of Psychiatry, Psychology & Neuroscience | King's College School of Medicine and Dentistry, UK

Yu-Dong (Eugene) Zhang, University of Leicester, UK

Chih Lai, University of St. Thomas Minnesota, USA

William Speier, UCLA David Geffen School of Medicine, USA

Sule Yildirim-Yayilgan, Norwegian University of Science and Technology, Norway

Ricardo Ron-Angevin, University of Málaga, Spain

Rory Lewis, University of Colorado at Colorado Springs, USA

### **BRAININFO 2026 Publicity Chairs**

Francisco Javier Díaz Blasco, Universitat Politècnica de València, Spain

Ali Ahmad, Universitat Politècnica de València, Spain

José Miguel Jiménez, Universitat Politècnica de València, Spain

Sandra Viciano Tudela, Universitat Politècnica de València, Spain

### **BRAININFO 2026 Technical Program Committee**

Aftab Ahmad, John Jay, The City University of New York (CUNY), USA

Saad Alqithami, Albaha University, Saudi Arabia

Panagiotis Bamidis, Aristotle University of Thessaloniki, Greece

Gema Benedicto Rodríguez, Polytechnic University of Cartagena, Spain

Nadejda Bocheva, Institute of Neurobiology | Bulgarian Academy of Sciences, Bulgaria

Gian Carlo Cardarilli, University of Rome Tor Vergata, Italy

German Castellanos-Dominguez, Universidad Nacional de Colombia, Sede Manizales, Colombia

Manoj Chandrasekaran, Meta Platforms Inc., USA

Ahana Roy Choudhury, Valdosta State University, USA

Gopikrishna Deshpande, Auburn University, USA

Shiaofen Fang, Indiana University Purdue University Indianapolis, USA

Mai Gamal, German University in Cairo, Egypt

Faizal Hajamohideen, University of Technology and Applied Sciences, Oman

Monte Hancock, 4Digital Inc., USA

Cosimo Ieracitano, University Mediterranea of Reggio Calabria, Italy

Kavikumar Jacob, Universiti Tun Hussein Onn Malaysia, Malaysia

M. Shamim Kaiser, Jahangirnagar University, Bangladesh

Stamatis Karlos, University of Patras, Greece

Peter Kieseberg, St. Poelten University of Applied Sciences, Austria

Hongzhi Kuai, Maebashi Institute of Technology, Japan

Chih Lai, University of St. Thomas Minnesota, USA

Erwin Lemche, Institute of Psychiatry, Psychology & Neuroscience | King's College School of Medicine / Dentistry Department of Psychosis Studies | Section of Cognitive Neuropsychiatry, UK

Clement Leung, Chinese University of Hong Kong, China  
Rory Lewis, University of Colorado at Colorado Springs, USA  
Junhua Li, University of Essex, UK  
Pablo Martínez Cañada, University of Granada, Spain  
Vasilis Megalooikonomou, University of Patras, Greece  
Marta Molinas, NTNU, Norway  
Rafael Morales Herrera, Universidad de Castilla-La Mancha, Spain  
Shahryar Noei, Fondazione Bruno Kessler, Italy  
Ricardo Nuno Vigário, Nova School of Science and Technology, Lisbon, Portugal  
Lauren Reinerman-Jones, UCF Institute for Simulation and Training, USA  
Izabela Rejer, West Pomeranian University of Szczecin, Poland  
Ricardo Ron Angevin, University of Málaga, Spain  
Alessia Sarica, Magna Graecia University of Catanzaro, Italy  
Md. Shahriare Satu, Noakhali Science and Technology University, Bangladesh  
Noushath Shaffi, College of Applied Sciences, Oman  
Linlin Shen, Shenzhen University, China / University of Nottingham, UK / University of Macau, China  
Bo Song, University of Southern Queensland, Australia  
Suraj Sood, University of West Georgia / Polytechnique Inc. / LB Tutoring Academy LLC, USA  
Cristina Soto Sánchez, Miguel Hernández University, Spain  
William Speier, UCLA David Geffen School of Medicine, USA  
Ryszard Tadeusiewicz, AGH University of Science and Technology, Poland  
Giorgio Terracina, University of Calabria, Italy  
Héctor Fabio Torres Cardona, Universidad de Caldas, Colombia  
Christos Troussas, University of West Attica, Greece  
Boris M. Velichkovsky, Kurchatov Institute and the Russian State University for the Humanities, Moscow, Russia  
Sule Yildirim Yayilgan, NTNU, Norway  
Yu-Dong Zhang, University of Leicester, UK

## Copyright Information

For your reference, this is the text governing the copyright release for material published by IARIA.

The copyright release is a transfer of publication rights, which allows IARIA and its partners to drive the dissemination of the published material. This allows IARIA to give articles increased visibility via distribution, inclusion in libraries, and arrangements for submission to indexes.

I, the undersigned, declare that the article is original, and that I represent the authors of this article in the copyright release matters. If this work has been done as work-for-hire, I have obtained all necessary clearances to execute a copyright release. I hereby irrevocably transfer exclusive copyright for this material to IARIA. I give IARIA permission to reproduce the work in any media format such as, but not limited to, print, digital, or electronic. I give IARIA permission to distribute the materials without restriction to any institutions or individuals. I give IARIA permission to submit the work for inclusion in article repositories as IARIA sees fit.

I, the undersigned, declare that to the best of my knowledge, the article does not contain libelous or otherwise unlawful contents or invading the right of privacy or infringing on a proprietary right.

Following the copyright release, any circulated version of the article must bear the copyright notice and any header and footer information that IARIA applies to the published article.

IARIA grants royalty-free permission to the authors to disseminate the work, under the above provisions, for any academic, commercial, or industrial use. IARIA grants royalty-free permission to any individuals or institutions to make the article available electronically, online, or in print.

IARIA acknowledges that rights to any algorithm, process, procedure, apparatus, or articles of manufacture remain with the authors and their employers.

I, the undersigned, understand that IARIA will not be liable, in contract, tort (including, without limitation, negligence), pre-contract or other representations (other than fraudulent misrepresentations) or otherwise in connection with the publication of my work.

Exception to the above is made for work-for-hire performed while employed by the government. In that case, copyright to the material remains with the said government. The rightful owners (authors and government entity) grant unlimited and unrestricted permission to IARIA, IARIA's contractors, and IARIA's partners to further distribute the work.

## Table of Contents

Comparison of Patterns of Neuronal Activity in VWFA Depending on Stimuli Lexicality during Silent Reading Task in Healthy Child and Adult Participants: a Magnetoencephalography Study <i>Renata Mamina</i>	1
Brain to Bedside: Using Neuroscience to Cultivate Empathy in Medicine <i>Tia Chakraborty and Michael DeWilde</i>	10

# Comparison of Patterns of Neuronal Activity in VWFA Depending on Stimuli Lexicality during Silent Reading Task in Healthy Child and Adult Participants: a Magnetoencephalography Study

Renata Mamina

Faculty of Human Sciences

Department of Linguistics

The University of Potsdam

Potsdam, Germany

email: rena.mamina@outlook.com

**Abstract**—This study examines how the lexicality of visual stimuli modulates neuronal activation in the Ventral Occipitotemporal Cortex (VOTC), with a focus on the Visual Word Form Area (VWFA), during silent reading. Magnetoencephalography (MEG) was used to record cortical responses to high-frequency Russian words, low-frequency words, and pseudowords in healthy adults and children. Individualized source localization and linear mixed-effects modeling revealed significant stimulus-dependent modulation along the superior–inferior (z) axis ( $p = 0.0098$ ), with both high-frequency words and pseudowords eliciting stronger responses than low-frequency words, while no reliable anterior–posterior dissociation between VWFA-1 and VWFA-2 was observed. The results suggest a nonlinear tuning of lexical properties coupled with a high degree of variability across individuals, suggesting that the way the VWFA functions is likely to be more continuous than categorical. This is evidenced by our investigation into Russian lexical processing, a language with Cyrillic orthography that has been underrepresented in neuroimaging studies. The research fills a significant cross-linguistic gap in the models used to explain visual word recognition.

**Keywords**—lexicality; silent reading; MEG; VWFA.

## I. INTRODUCTION

Reading is a fundamental skill that relies on specialized brain regions, particularly the VWFA, which plays a crucial role in recognizing written words [1]. The VWFA, located in the left fusiform gyrus, processes visual word forms rapidly and efficiently, enabling fluent reading [2][3]. Understanding how this region distinguishes between real words (lexical stimuli) and meaningless letter strings (non-lexical stimuli, like pseudowords) is essential for refining models of reading and developing interventions for reading disorders such as dyslexia [4][5]. While previous research has used Functional Magnetic Resonance Imaging (fMRI) to study VWFA activation, MEG offers superior temporal resolution, making it ideal for tracking the rapid neural dynamics of reading [6][7].

The VWFA is thought to process words and pseudowords differently due to their lexical properties. According to dual-route models, familiar words are

recognized holistically, while pseudowords require slower, serial decoding [8][9]. fMRI studies have shown that pseudowords often elicit stronger VWFA activation than real words, likely because they demand more effortful processing [9]. However, fMRI cannot capture the precise timing of these neural events. MEG studies have revealed early VWFA responses to written stimuli (~150–200 ms), but the exact timing of lexicality effects, whether they occur during initial visual processing or later linguistic stages, remains unclear [6].

Despite these advances, critical gaps remain. Individualized functional localizer scans and detailed anatomical mapping may help uncover the sequence of computations underlying word recognition [10]. Enhanced characterization of the VOTC substructure will enable the development of a model of the word-selective cortex that describes differences in functional responses and accounts for its anatomical boundaries. Furthermore, integrating functional and anatomical data could clarify the nature of subdivisions within this critical reading region.

This study represents a significant methodological and empirical advancement in the cognitive neuroscience of Russian language processing. While previous neuroimaging research has extensively explored the VWFA in languages with Latin-based orthographies, the neural mechanisms underlying reading in Slavic languages with Cyrillic script remain markedly understudied. This work directly addresses this gap by providing the inaugural MEG-based mapping of VWFA specialization for Russian lexical processing.

This study employs a developmental-comparative approach that has not been applied to these stimulus types. The direct comparison between children and adults using MEG represents a novel contribution, as existing research has typically examined these populations in isolation. The combined application of MEG neuroimaging and precise anatomical mapping of VWFA subdivisions specifically for Russian-language processing. This methodological integration enables the resolution of the spatiotemporal dynamics of orthographic and lexical processing with millisecond precision while maintaining anatomical specificity. By correlating functional activation time courses with individually defined VWFA-1 and VWFA-2 territories,

we overcome the limitations of previous group-averaged approaches that may obscure significant individual differences in brain organization.

MEG is used to investigate the spatiotemporal dynamics of VWFA activation during silent reading of lexical and non-lexical stimuli. Several factors endorsed the experimental procedure, including the choice of silent reading. It eliminates articulatory and phonological processing demands associated with overt speech production, thereby isolating the visual-orthographic decoding functions specifically attributed to the VWFA. When participants read aloud, activation patterns become contaminated by motor planning, articulatory execution, and auditory feedback processing, which engage distributed networks beyond the ventral visual stream [11]. This confound is particularly problematic for studying the VWFA's early (<200ms) visual response characteristics, which may be obscured by subsequent speech-related activity.

Another point is that silent reading reduces task-induced variability and movement artifacts that are critical for MEG signal quality. Overt articulation generates substantial head movement and muscle artifacts that can compromise the spatial precision of source localization and temporal accuracy of neural response latencies [12]. MEG's exceptional temporal resolution (~1ms) is especially vulnerable to such artifacts, making silent reading essential for capturing the rapid, hierarchical processing stages within the VWFA.

Neurophysiologically, silent reading preferentially engages the dorsal and ventral streams in a manner that reflects natural reading conditions. Studies comparing silent versus overt reading consistently show that while both conditions activate core reading networks, silent reading produces more focal VWFA activation with cleaner response profiles that better correlate with lexical properties [13]. This is particularly relevant for investigating the hypothesized functional gradient within the VWFA, where posterior regions (VWFA-1) show early visual form responses and anterior regions (VWFA-2) exhibit later lexical sensitivity. Overt articulation demands may mask this temporal hierarchy.

Specifically, this study aims to demonstrate that high-frequency, low-frequency, and pseudowords activate distinct regions depending on stimulus type.

To achieve this aim, three specific goals are proposed:

- Preprocess and otherwise prepare the MEG data for further work.
- Map out necessary peak-activity areas for each patient.
- Conduct a statistical analysis of the gathered data.

The main hypotheses are:

1) Anterior VOTC (VWFA-2) will show stronger activation for lexical properties, while posterior VOTC (VWFA-1) will respond to low-level orthographic features.

2) Lexicality of stimuli will directly affect the activation of the VWFA, with high-frequency words eliciting the weakest response and pseudowords eliciting the strongest response.

The remainder of this paper is organized as follows. Section II reviews the current state of research on the VWFA, lexicality effects, and developmental differences in reading-related neural activation. Section III describes the methodology, including participant characteristics, stimulus design, experimental procedure, MEG and MRI data acquisition, source localization, and statistical analysis. Section IV presents the results for adults and children separately, followed by a direct comparative analysis of activation patterns across age groups. Section V discusses the findings in relation to existing neurocognitive models of reading, highlighting theoretical implications, developmental considerations, and individual variability. Finally, Section VI concludes the paper and outlines directions for future research.

## II. CURRENT STATE OF RESEARCH

Developmental studies on reading acquisition in children highlight the neuroplastic changes induced by literacy, particularly within the ventral visual stream and left-hemisphere language networks. Dehaene et al. demonstrate that literacy acquisition, whether in children or previously illiterate adults, reorganizes the brain by specializing the VWFA for print processing, underscoring its pivotal role as an interface between visual and linguistic systems [3]. Supporting this, Brem et al. found that the left occipitotemporal cortex, including the VWFA, becomes increasingly sensitive to print as children master grapheme-phoneme correspondences, suggesting that this specialization is experience-dependent and emerges through exposure to systematic letter-speech-sound mappings [14]. Together, these studies indicate that reading development is marked by the progressive tuning of the VWFA and associated left-hemisphere circuits, driven by both bottom-up perceptual learning (grapheme-phoneme integration) and top-down linguistic influences (phonological awareness), offering critical insights into the neurocognitive mechanisms underlying typical and atypical literacy acquisition.

Martin et al. conducted a meta-analysis of brain activation data from children and adults while reading, examining differences in patterns and regions of activation, as well as similarities [15]. The researchers' results were as follows: the same areas of activation were observed in both children and adults in the ventral occipito-temporal cortex, including the region where the VWFA is located, among others. There are also differences in the activation of other zones, such as the left superior temporal gyrus. However, the authors highlight that these results do not reflect differences in the level of activation in the areas of children's and adults' brains, but rather differences in the consistency across studies used in the analysis.

Another interesting finding is that VWFA activation during reversed-letter viewing differs between adults and children. Reversing letters is a common error made by children when they first start learning to read and write. For instance, the English letter "R" can be reversed as "Я" and so on. This phenomenon can be seen even in texts written by older children aged ten to twelve, who should have had sufficient reading and writing skills. The results of the letter

presentation experiment reported by Blackburne et al. showed that event-related potentials P1 and N170 showed a greater difference between normal and reversed letters in adults than in children. P1, or P100, is a positive-going component linked with visual areas, and N170 is a component that reflects the neuronal processing of faces and words [16]. Aside from event-related potentials, different activation patterns were observed in children and adults. Adults exhibited widespread occipital, parietal, and temporal lobe activations, while children showed activation only in a limited frontal area. This indicates that the processing of the word and its symbols develops over time and is itself a process, since at the early stage of processing, children do not distinguish between the symbols.

The articles mentioned above are united by the idea that the VWFA works differently in children and adults, in the same way as with teaching macaques, exposure to the language in its written form, and reading experience influence whether people notice errors and, in general, how quickly and actively words are processed.

In healthy adults, the VWFA is consistently localized in the left midfusiform gyrus, with peak activation coordinates typically around  $x = -43$ ,  $y = -54$ ,  $z = -12$  in standard brain atlases [1][17]. This region shows robust activation during tasks involving the visual presentation of words and pseudowords, but not during auditory word processing or the presentation of non-linguistic visual stimuli [18]. The VWFA's location and functional properties are highly reproducible across individuals, suggesting a degree of functional specialization for orthographic processing [3]. Studies have shown that the VWFA is more active during the processing of familiar words than during the processing of unfamiliar or meaningless letter strings, reflecting its role in lexical access and visual word-form recognition [8]. The VWFA exhibits a length-by-lexicality interaction, with stronger activation for longer pseudowords than for words, supporting the idea that it is involved in serial sublexical processing of unfamiliar stimuli [9].

In reading, healthy adults typically show left-lateralized activation in the VWFA, with stronger responses in the left hemisphere than in the right [19][20]. This lateralization is thought to reflect the left hemisphere's dominance for language processing [2]. The VWFA's activation is also modulated by reading skill, with more proficient readers showing stronger and more efficient activation patterns [4]. For example, skilled readers exhibit reduced activation in the VWFA for high-frequency words, suggesting that they process these words more efficiently [9]. In contrast, less skilled readers or individuals with reading difficulties, such as dyslexia, often exhibit atypical VWFA activation, including reduced activation or delayed responses [20]. These findings highlight the importance of the VWFA in normal reading processes and suggest that its functional properties are shaped by both experience and individual differences in reading ability [7]. Overall, the VWFA's consistent localization and functional properties in healthy adults provide a foundation for understanding its role in reading and its potential dysfunction in reading disorders [3].

One of the most robust findings is that the VWFA shows greater activation for pseudowords than for real words [8][9]. This effect, often referred to as the lexicality effect, is thought to arise because pseudowords require more extensive sublexical processing due to their unfamiliarity. Pseudowords, which are pronounceable letter strings that resemble real words but have no meaning (e.g., "flirp"), engage the VWFA in serial grapheme-to-phoneme conversion. This process demands greater computational resources than the recognition of familiar words [8]. In contrast, real words, which have established orthographic representations, are processed more efficiently, leading to reduced activation in the VWFA [9]. The reduced activation for familiar words aligns with the orthographic familiarity effect, where familiar orthographic forms elicit less neural activity due to their efficient recognition [8].

The length-by-lexicality interaction further highlights the VWFA's sensitivity to lexical status. For words, the VWFA shows little to no effect of length, consistent with the idea that familiar words are processed holistically as whole-word units [8]. However, for pseudowords, longer letter strings elicit significantly higher activation, reflecting the increased demand for serial sublexical processing [9]. This interaction supports the dual-route model of reading, which posits that familiar words are processed via a lexical route (whole-word recognition). In contrast, unfamiliar letter strings are processed via a sublexical route (grapheme-to-phoneme conversion) [8].

The VWFA's response to non-linguistic stimuli, such as false fonts or consonant strings, further underscores its specialization for orthographic processing. Studies have shown that the VWFA exhibits minimal activation for non-linguistic stimuli compared to words and pseudowords, indicating that it is not merely a general visual processing area but is specifically tuned to letter strings [1][18]. For example, false fonts, which are visually similar to letters but lack linguistic content, elicit significantly lower activation in the VWFA compared to real words and pseudowords [21]. This suggests that the VWFA is sensitive to the linguistic relevance of visual stimuli, with its activation patterns reflecting the degree to which stimuli engage orthographic and lexical processes.

During lexical decision tasks in which participants must determine whether a letter string is a real word or a pseudoword, the VWFA shows heightened activation for pseudowords relative to real words [9]. This task-dependent modulation suggests that the VWFA's response to lexicality is not purely bottom-up but is also shaped by top-down linguistic influences from higher-order language regions, such as Broca's area and the Superior Temporal Gyrus (STG) [21]. In contrast, during passive viewing tasks, where participants are not explicitly required to process the linguistic content of stimuli, the lexicality effect in the VWFA is less pronounced, though still present [6]. This indicates that the VWFA's sensitivity to lexicality is modulated by the task's attentional and cognitive demands.

The neural mechanisms underlying the lexicality effect in the VWFA are thought to involve both bottom-up visual processing and top-down linguistic feedback. At the bottom-

up level, the VWFA is sensitive to the orthographic regularity of letter strings, with pseudowords eliciting stronger activation due to their unfamiliarity and the need for more extensive processing [8]. At the top-down level, the VWFA receives input from language regions, such as Broca's area and the STG, which help to refine its response based on the linguistic context and task demands [21]. This interplay between bottom-up and top-down processes allows the VWFA to dynamically adjust its activation patterns in response to the lexical status of stimuli and the cognitive demands of the task.

The lexicality effect in the VWFA has essential implications for understanding reading development and dyslexia. In skilled readers, the VWFA shows efficient processing of familiar words, with reduced activation for high-frequency words and increased activation for pseudowords [9]. However, in individuals with dyslexia, the VWFA often exhibits atypical activation patterns, including reduced sensitivity to lexicality and weaker differentiation between words and pseudowords [20]. These findings suggest that the VWFA's ability to process lexical information is compromised in dyslexia, contributing to the reading difficulties observed in this population.

### III. METHODOLOGY

#### A. Stimuli

The experiment employed three stimulus categories: high-frequency Russian words, low-frequency Russian words, and pseudowords, with 65 stimuli in each. High- and low-frequency words were selected from the Frequency Dictionary of Modern Russian [22], with semantic categories (e.g., animals, food) included to ensure diversity. High-frequency words were further screened for early age of acquisition (mean < 1.69 years, SD = 0.63) based on normative data [23].

Familiarity ratings for high-frequency words ranged from 4.9 to 5.0, while low-frequency words scored between 1.2 and 3.0. Pseudowords were generated using a computational algorithm [24], derived from real words with varying corpus frequencies (2.6–35,801 instances per million). Of the 65 pseudowords, 32 were based on low-frequency words and 33 on high-frequency words. A subset (31 items) contained consonant clusters resembling those in real Russian words (e.g., *kniga* → *knitsa*). All stimuli were matched for length (5–7 letters), yielding 195 total items (65 per category).

From now on, high-frequency words will be referred to as HF, low-frequency words as LF, and pseudowords as PW in the tables and graphs from the statistical analysis.

#### B. Children Behavioral assessment

Raven's Colored Progressive Matrices were used to evaluate the non-verbal intelligence of the children participating in the experiment, and the Russian Child Language Assessment Battery (RuCLAB) was used to assess their language abilities [50]. RuCLAB is suitable for children aged 3 to 11 and includes tasks on comprehension and production of phonology, vocabulary, morphosyntax, and discourse. With tasks in both comprehension and generation,

RuCLAB is an efficient way to evaluate one's language skills at different levels [26]. A standard average score was calculated across all subtests, presenting a Mean Language Score (MLS) for each child [25]. Reading skills were evaluated via the Standardized Assessment of Reading Skills in Russian (SARS). The procedure includes tasks on both reading fluency and comprehension [27][28]. Children read the text aloud, articulating the words as quickly as possible for one minute, and later answer ten questions about the text. Thus, the test allows for measuring both reading techniques since the articulation is taken into account and comprehension.

Children who performed under the typical maturation level on at least one of the mentioned tests were excluded from the final sample.

#### C. Experimental Procedure

Stimuli were presented in a silent reading task using PsychoPy [29]. Each word or pseudoword appeared centrally for 3 seconds, followed by a 1-second fixation interval. The stimuli were divided into three blocks (65 trials each), with order randomized per participant to prevent sequential repetition of the same type (>3 consecutive trials).

To monitor attention, participants were prompted to verbally repeat the last-read word when a question mark appeared (16 times per block, 48 total). These probes were evenly distributed across stimulus types. Each block lasted ~5 minutes (306 seconds), and the sequence order was counterbalanced across participants (e.g., 1-2-3, 1-3-2).

The experimental procedure and the stimuli did not differ between age groups.

#### D. MRI Data Acquisition

Structural T1-weighted images were acquired on a 1.5 T Siemens Avanto scanner (TR = 1900 ms, TE = 3.37 ms, flip angle = 15°, matrix = 256 × 256 × 176, voxel size = 1.0 mm<sup>3</sup>). Cortical reconstruction and segmentation were performed via FreeSurfer [30]. For MEG co-registration, anatomical landmarks (nasion, pre-auricular points, etc.) and ~150 head-surface points were digitized using Brainstorm [31].

#### E. MEG Recording and Preprocessing

Neuromagnetic activity was recorded with a 306-channel Elekta Neuromag system (sampling rate = 1000 Hz). Head position was tracked via four HPI coils. Data were preprocessed using temporal signal-space separation [32] and motion-corrected with MaxFilter (Elekta). Artifacts (e.g., blinks and heartbeats) were removed using independent component analysis [51]. Continuous data were bandpass-filtered (0.1–330 Hz) and notch-filtered (50 Hz). Epochs spanned –1000 to 3500 ms, baseline-corrected (–100 to –2 ms).

#### F. Source Analysis

Cortical activity was estimated using gradiometer data due to their superior noise profile [33]. A head model was constructed via the overlapping-spheres method [34], and inverse solutions were computed using depth-weighted

minimum-norm estimation [35], constrained to cortical normals. Regularization ( $\lambda = 0.33$ ) mitigated ill-posedness [36]. Individual noise covariance was derived from empty-room recordings.

For group-level analysis, source estimates were projected onto the ICBM152 template. Event-related fields (ERFs) were z-scored relative to baseline (-100 to -2 ms). To account for individual variability, 15 left-hemisphere vertices in the visual word form area with peak activation were selected per participant [37][38].

G. Statistical Analysis

Analyses were conducted in R [39] using linear mixed-effects models [40]. Data visualization was performed with ggplot2 [41], Plotly [42], dplyr [43], ggpubr [44], ggridges [45], knitr [46].

IV. RESULTS

Mean results for healthy adults are presented under three stimulus conditions (HF, LF, PW). Mean activation values were similar across conditions: M = 17.79 (SD = 7.28) for HF, M = 17.04 (SD = 6.61) for LF, and M = 17.43 (SD = 5.90) for PW. Variability, as indicated by standard deviations, was moderately high in all conditions (range: 5.90-7.28). Minimum and maximum activation values differed across conditions, with LF showing the lowest observed activation (2.77) and HF the highest (35.44). Each condition included 30 observations (N = 30), suggesting balanced data. The results indicate consistent mean activation levels despite varying stimulus intensities, with notable individual variability in responses.

The statistical analysis examined whether varying stimulus levels influenced brain activation across three spatial dimensions (x, y, z) and activation intensity (Value), while accounting for individual variability (ID).

TABLE I. MEAN RESULTS FOR HEALTHY ADULTS

Condition	Mean	SD	Min	Max	N
HF	17.79	7.28	6.80	35.44	30
LF	17.04	6.61	2.77	30.48	30
PW	17.43	5.90	6.36	30.61	30

A series of ANOVAs, presented in Table 2, revealed differential effects of stimulus level on brain activation. For the x-coordinate (left-right activation), the impact of lexicality was marginally significant,  $F(2, 1318) = 2.454, p = 0.086$ , suggesting a weak trend toward stimulus-dependent modulation, though it did not reach conventional significance ( $p < 0.05$ ). In contrast, no significant effect was found for the y-coordinate (anterior-posterior activation),  $F(2, 1318) = 0.195, p = 0.823$ , indicating that stimulus level did not influence front-back activation patterns. However, a significant effect emerged for the z-coordinate (superior-inferior activation),  $F(2, 1318) = 4.64, p = 0.0098$ , demonstrating that stimulus level modulated up-down brain activation.

TABLE II. ANOVA RESULTS ACROSS VARIABLES FOR HEALTHY ADULTS

Model	Sum Sq	Mean Sq	Num DF	Den DF	F value	Pr(>F)
x Stim ~	1.9322	0.96611	2	1318	2.454	0.08634
y Stim ~	0.3195	0.15975	2	1318	0.1947	0.8231
z Stim ~	1.4811	0.74055	2	1318	4.6397	0.009818
Value ~ Stim	2.2717	1.1359	2	1318	2.9528	0.05254

Post-hoc comparisons were warranted to clarify which stimulus conditions differed. Finally, activation intensity (Value) showed a marginal effect of lexicality,  $F(2, 1318) = 2.95, p = 0.053$ , suggesting a potential trend toward stimulus-dependent changes in neural response strength. However, this effect was not statistically conclusive.

A. Post-Hoc Comparisons (Tukey-Adjusted)

Post hoc pairwise comparisons (Tukey-adjusted) for the z-coordinate in Tables 3 and 4 revealed significant differences among stimulus conditions. Specifically, HF elicited stronger activation than LF ( $\beta = 0.074, SE = 0.027, t(1318) = 2.78, p = 0.015$ ), and PW also produced greater activation than LF ( $\beta = -0.066, SE = 0.027, t(1318) = -2.48, p = 0.036$ ). However, no significant difference was observed between HF and PW ( $\beta = 0.008, SE = 0.027, t(1318) = 0.30, p = 0.952$ ).

Estimated marginal means further supported these findings, with LF exhibiting the lowest activation ( $M = -0.047, 95\% \text{ CI } [-0.396, 0.303]$ ), while HF ( $M = 0.027, 95\% \text{ CI } [-0.322, 0.377]$ ) and PW ( $M = 0.019, 95\% \text{ CI } [-0.330, 0.369]$ ) showed comparable, slightly elevated responses.

TABLE III. Z-COORDINATE DATA ACROSS STIMULI FOR HEALTHY ADULTS

Stimulus Condition	Mean Activation ( $\beta$ )	Standard Error	df	95% Confidence Interval
10	0.027	0.171	29.5	[-0.322, 0.377]
20	-0.047	0.171	29.5	[-0.396, 0.303]
30	0.019	0.171	29.5	[-0.330, 0.369]

TABLE IV. POST-HOC PAIRWISE COMPARISONS (TUKEY-ADJUSTED) FOR THE Z-COORDINATE I FOR HEALTHY ADULTS

Contrast	Estimate ( $\beta$ )	SE	df	t-value	p-value	Significance
HF - LF	0.074	0.027	1318	2.78	0.015	*
HF - PW	0.008	0.027	1318	0.30	0.952	ns
LF - PW	-0.066	0.027	1318	-2.48	0.036	*

These results suggest a nonlinear modulation of neural activity along the z-axis, with intermediate stimulus intensity (LF) eliciting weaker activation than both lower (HF) and higher (PW) intensities. No such differential effects were

found for medio-lateral (x-axis) or anterior-posterior (y-axis) activation patterns.

**B. Children**

Mean activation levels in healthy children showed minor variation across conditions, ranging from M = 17.06 (LF) to M = 18.43 (PW), with HF intermediate at M = 17.79. Standard deviations were moderate and comparable across conditions (SD range: 4.75-5.66), suggesting similar degrees of inter-individual variability in neural responses. The minimum and maximum values reveal the full range of observed activations, with LF showing both the lowest minimum activation (7.71) and the most constrained maximum activation (25.9). At the same time, HF exhibited the highest activation value (31.3). Each condition included 30 observations (N = 30), indicating balanced data collection. These results suggest that while mean activation levels remained relatively stable across conditions, PW elicited slightly higher average activation than the other two conditions, potentially reflecting greater cognitive demands.

TABLE V. MEAN RESULTS FOR HEALTHY CHILDREN

Condition	Mean	SD	Min	Max	N
HF	17.79	5.42	9.17	31.3	30
LF	17.06	4.75	7.71	25.9	30
PW	18.43	5.66	8.76	29.2	30

The comparable variability across conditions (as evidenced by similar SDs) implies consistent response patterns among participants. The presence of outliers (particularly in HF's maximum value) warrants further investigation into individual differences in neural processing during reading tasks.

The ANOVA results presented in Table 6 demonstrated differential effects of stimulus conditions (Stim) across four neural or behavioral variables (x, y, z, and Value) in healthy children. For variables x ( $F(2,1318) = 0.5546, p = 0.5744$ ), y ( $F(2,1318) = 1.3077, p = 0.2708$ ), and z ( $F(2,1318) = 0.7128, p = 0.4905$ ), the analyses yielded non-significant main effects of Stim, indicating that these measures did not show statistically reliable variation across experimental conditions. In contrast, the analysis for Value demonstrated a significant effect of Stim ( $F(2,1318) = 5.52, p = 0.0041$ ), with a between-conditions mean square (3.6725) substantially larger than the corresponding values for non-significant variables. The consistent denominator degrees of freedom (DenDF = 1318) across analyses indicate a balanced design with substantial statistical power to detect effects. The significant finding for Value ( $p < 0.005$ ) would survive conservative corrections for multiple comparisons, suggesting a robust effect worthy of further investigation regarding its neurocognitive underpinnings in developing readers.

TABLE VI. ANOVA RESULTS ACROSS VARIABLES FOR HEALTHY CHILDREN

Model	Sum Sq	Mean Sq	Num DF	Den DF	F value	Pr(>F)
x ~ Stim	0.53264	0.26632	2	1318	0.5546	0.5744
y ~ Stim	1.7176	0.85878	2	1318	1.3077	0.2708
z ~ Stim	0.48256	0.24128	2	1318	0.7128	0.4905
Value ~ Stim	7.345	3.6725	2	1318	5.52	0.004099

TABLE VII. ESTIMATED MARGINAL MEANS AND POST-HOC COMPARISONS FOR STIMULUS CONDITIONS FOR HEALTHY CHILDREN

Value	M	SE	df	95% CI
10	0.002	0.113	34	[-0.229, 0.232]
20	-0.091	0.113	34	[-0.322, 0.139]
30	0.090	0.113	34	[-0.141, 0.320]

The significant omnibus ANOVA (as indicated by post-hoc tests) was followed up with Tukey-adjusted pairwise comparisons to control for Type I error (Tables 7 and 8). The only statistically significant difference was between LF and PW ( $*p* = .003$ ), with PW showing higher values ( $M = 0.090$ ) compared to LF ( $M = -0.091$ ). No other comparisons were significant. The mean difference between LF and PW was  $-0.181$  (95% CI  $\approx [-0.29, -0.07]$ ), suggesting a small-to-moderate effect.

**C. Comparison**

It was expected that participants would demonstrate marked heterogeneity in response magnitudes to identical stimuli. While some individuals exhibit robust activation across all stimulus categories, others show selective amplification only for high-frequency words, with high-frequency words yielding the most activation, and pseudowords the least. However, there were no meaningful correlations in this category, with responses varying greatly between participants in both age groups.

TABLE VIII. POST-HOC PAIRWISE COMPARISONS (TUKEY-ADJUSTED) FOR HEALTHY CHILDREN

Contrast	Estimate	SE	*t*	*p*	Contrast
HF - LF	0.093	0.054	1.706	.203	HF - LF
HF - PW	-0.088	0.054	-1.616	.239	HF - PW
LF - PW	-0.181	0.054	-3.322	.003	LF - PW

As for the correlation between zones of peak activation and their localization in the brain, there was an expectation for VFWA-2, anterior VOTC, which in the coordinates used in this paper would be placed higher on the y-axis and farther on the x-axis, to show stronger activation for lexical properties, namely, HF, and the posterior VOTC (VFWA-1), stronger activation for pseudowords, PW.

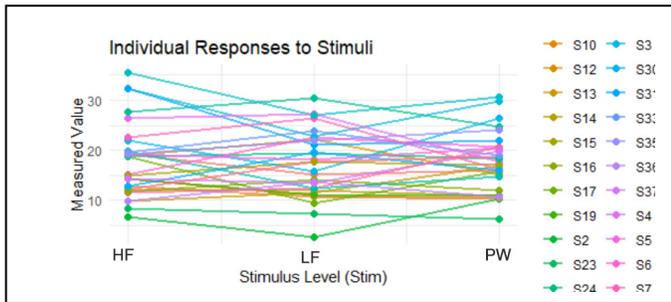


Figure 1. Individual Responses to Stimuli for Each Adult.

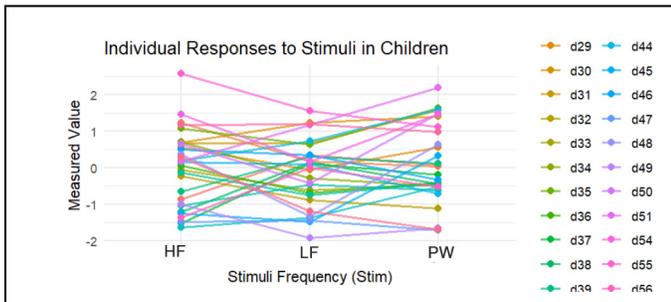


Figure 2. Individual Responses for Each Child.

As depicted in Figures 1 and 2 below, there are some differences in the localization of peak activity depending on stimuli, but, with no relevant majority, the lexicality of the stimuli cannot be associated with a specific VWFA type.

V. DISCUSSION

The present study examined how varying stimulus lexicality modulates brain activation across spatial dimensions and intensity, while accounting for individual variability. The results revealed a complex pattern of neural responses. Below is the interpretation of these findings in light of prior research, discussing their theoretical implications, and highlighting key limitations.

A. Adults

The most robust finding was a significant effect of stimulus level on z-axis activation ( $p = 0.0098$ ), with post hoc tests indicating that both HF and PW elicited stronger responses than LF. This nonlinear pattern aligns with evidence that intermediate stimulus intensities may fail to optimally engage neural populations, as observed in studies of the visual word form area (VWFA) during lexical processing [4][9]. The lack of significant differences between HF and PW suggests that neural tuning along the z-axis may reflect a U-shaped response profile, consistent with findings that the VWFA exhibits selective sharpening for both high- and low-frequency inputs [6][47]. Additionally, the observed differences may reflect stimulus-specific neural recruitment, in which high-frequency words engage slightly distinct brain regions compared to low-frequency words,

possibly due to external factors such as attentional demands and sensory processing.

In contrast, the absence of significant effects on the x- and y-coordinates suggests that stimulus intensity does not systematically shift activation laterally or along the anterior-posterior axis. This supports the view that spatial encoding in these dimensions is more strongly influenced by structural connectivity [48] than by stimulus properties. The marginally significant trend for x-axis modulation ( $p = 0.086$ ) is consistent with reports of hemispheric asymmetries in language processing [8]. However, the results did not reach conventional levels of significance, possibly due to limited spatial resolution or sample size.

B. Children

Children showed stronger activation for the pseudowords ( $M = 18.43$ ), likely because decoding unfamiliar letter strings demands greater phonological assembly and attentional resources. The moderate and comparable standard deviations (SD range: 4.75–5.66) across conditions suggest consistent inter-individual variability, though the presence of outliers - particularly the maximum activation in HF (31.3) - highlights the importance of considering individual differences in neural responsiveness during reading tasks.

The ANOVA analysis revealed that only one of the four examined variables—Value—showed a statistically significant effect of stimulus condition ( $F(2,1318) = 5.52$ ,  $*p* = .004$ ), surviving conservative multiple-comparison corrections. Follow-up Tukey-adjusted pairwise comparisons confirmed that this effect was driven by a significant difference between LF and PW ( $*p* = .003$ ), with PW eliciting higher activation ( $M = 0.090$ ) compared to LF ( $M = -0.091$ ). The mean difference of  $-0.181$  (95% CI  $[-0.29, -0.07]$ ) suggests a small-to-moderate effect size, reinforcing the robustness of this finding.

Crucially, the lack of significant effects for variables x, y, and z indicates that stimulus conditions in this paradigm did not modulate these neural or behavioral measures. This selective sensitivity suggests that Value may index a specific aspect of reading-related processing, such as phonological decoding, lexical access, or attentional engagement, that is differentially recruited depending on task demands.

These findings align with prior neurocognitive models of reading development [3][14], which propose that children’s reading networks become increasingly specialized with experience. The heightened response to PW may reflect greater reliance on dorsal stream mechanisms (e.g., grapheme-phoneme conversion) or increased executive demands. In contrast, the lack of differentiation between HF and LF could indicate more automated processing for these conditions. The significant LF vs. PW contrast, in particular, suggests that subtle variations in stimulus properties (e.g., lexical frequency, phonological complexity) may selectively engage distinct neural subsystems in developing readers.

C. Both

The comparative analysis of brain activation patterns during reading tasks reveals a striking similarity between healthy children and adults, with nearly identical mean

activation values for both high-frequency ( $M_{\text{children}} = 17.76$  vs.  $M_{\text{adults}} = 17.79$ ) and low-frequency words ( $M_{\text{children}} = 17.06$  vs.  $M_{\text{adults}} = 17.04$ ). This suggests that, by the time children reach the studied age range, their neural processing of familiar lexical items closely mirrors that of mature readers, supporting the view that core reading networks become functionally specialized relatively early in development.

However, a notable divergence emerges in pseudoword processing, where children show slightly higher activation ( $M = 18.43$ ) than adults ( $M = 17.43$ ). This discrepancy may reflect the increased cognitive effort required for children to decode novel phonological forms, implicating less automatized grapheme-phoneme conversion mechanisms or greater reliance on compensatory attentional and executive resources. The absence of such a gap for real words underscores the idea that while children achieve adult-like efficiency in recognizing familiar words earlier, their neural systems for processing unfamiliar orthographic patterns remain under refinement.

These findings align with neurodevelopmental models of literacy [3], which posit that the ventral visual word form system stabilizes early for known words. In contrast, dorsal stream pathways supporting phonological assembly continue to mature. The results highlight both the remarkable plasticity of the developing reading brain and the late consolidation of effortful decoding processes, offering insights for educational strategies and interventions targeting phonological skill development. Future research should explore whether these small but meaningful differences in pseudoword processing reflect developmental delays or normative variability in reading acquisition.

No systematic link between stimulus lexicality and anterior/posterior VOTC subdivisions has been found. While prior work associates anterior regions with lexical-semantic processing [2], our null results align with critiques of rigid functional parcellation [18]. The high individual variability in our sample may reflect the dynamic nature of word recognition [49], where task demands and stimulus properties interact to shape activation patterns.

#### D. Limitations and Future Directions

Several limitations should be noted. First, there may be limited statistical power, which is relevant to both age groups. With more participants, the overall dominance of variability may diminish, and anticipated correlations may arise [23]. Second, uncontrolled confounders (e.g., attention) may contribute to variability; future work could integrate eye-tracking [29] or higher-resolution imaging [30]. Finally, spatial resolution may have been insufficient to detect fine-grained functional subdivisions; advanced methods like depth-weighted MEG [35] could clarify these dynamics. Moreover, combining MEG with other neuroimaging techniques (e.g., DWI) is necessary to determine whether the boundary between VWFA-1 and VWFA-2 aligns with a white-matter tract, thereby explaining the functional differences between them.

## VI. CONCLUSION AND FUTURE WORK

Overall, this paper aimed to pinpoint exactly how lexicality affects the activation of the VWFA. The present study provides novel insights into neural activation patterns during lexical processing in healthy adults and children. A significant correlation between high-frequency word recognition and pseudoword processing was revealed, suggesting overlapping yet distinct neural mechanisms for lexical access. Notably, in adults, stimulus intensity showed a nonlinear modulation along the z-axis, with intermediate stimuli eliciting weaker activation than both high-frequency and low-frequency conditions. As for children, a significant correlation between neural activation and stimulus type was observed, along with a more robust reaction to pseudowords.

As the first investigation of Russian lexicality effects using this paradigm, the results lay the groundwork for future research in several critical directions. Firstly, high-resolution neuroimaging techniques could further dissect the observed z-axis dynamics, particularly in clinical populations with language-processing deficits, which, for now, may be obscured by MEG's spatial limits. Secondly, cross-linguistic comparisons, especially with languages exhibiting different orthographic depth, are essential to determine whether these effects are language-specific or generalize across typologically diverse systems, or how these patterns emerge in children [7]. Such studies would not only refine neurocognitive models of reading but also inform targeted interventions for dyslexia and aphasia across all ages in multilingual contexts.

This work advances the understanding of lexical representation while highlighting the need for expanded stimulus sets and more diverse participant samples in future research. The methodological and empirical contributions of this study could serve as a foundation for both clinical applications and theoretical developments in the cognitive neuroscience of language.

## REFERENCES

- [1] L. Cohen et al., "The visual word form area, Spatial and temporal characterization of an initial stage of reading in normal subjects and posterior split-brain patients," *Brain*, vol. 123, no. 2, pp. 291–307, 2000.
- [2] L. Cohen et al., "Language-specific tuning of visual cortex? Functional properties of the visual word form area," *Brain*, vol. 125, no. 5, pp. 1054–1069, 2003.
- [3] S. Dehaene, L. Cohen, M. Sigman, and F. Vinckier, "The neural code for written words, A proposal," *Trends Cogn. Sci.*, vol. 9, no. 7, pp. 335–341, 2010.
- [4] L. S. Glezer, X. Jiang, and M. Riesenhuber, "Adding words to the brain's visual dictionary, Novel word learning selectively sharpens orthographic representations in the VWFA," *J. Neurosci.*, vol. 35, no. 12, pp. 4965–4972, 2015.
- [5] B. Gagl et al., "The lexical categorization model, A computational account of visual word recognition," *Psychol. Rev.*, vol. 129, no. 3, pp. 564–592, 2022.
- [6] S. J. Joo and S. Caffarra, "Automaticity in the reading circuitry," *Trends Cogn. Sci.*, vol. 25, no. 8, pp. 721–735, 2021.
- [7] S. Caffarra, M. Lizarazu, N. Molinaro, and M. Carreiras, "Word and object recognition during reading acquisition, MEG evidence," *Dev. Cogn. Neurosci.*, vol. 25, pp. 198–210, 2017.

- [8] M. Schurz *et al.*, “Top-down and bottom-up influences on the left ventral occipito-temporal cortex during visual word recognition, An analysis of effective connectivity,” *Hum. Brain Mapp.*, vol. 31, no. 9, pp. 1299–1317, 2010.
- [9] M. Kronbichler *et al.*, “The visual word form area and the frequency with which words are encountered, Evidence from a parametric fMRI study,” *NeuroImage*, vol. 21, no. 3, pp. 946–953, 2004.
- [10] S. Caffarra, J. D. Yeatman, M. Lizarazu, and M. Carreiras, “Development of the visual white matter pathways mediates development of electrophysiological responses in visual cortex,” *NeuroImage*, vol. 243, 118436, 2021.
- [11] C. J. Price, “A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading,” *NeuroImage*, vol. 62, no. 2, pp. 816–847, 2012.
- [12] A. Hultén, J. M. Schoffelen, J. Uddén, N. H. Lam, and P. Hagoort, “How the brain makes sense beyond the processing of single words, An MEG study,” *NeuroImage*, vol. 186, pp. 586–594, 2019.
- [13] Y. N. Yoncheva, J. Wise, and B. McCandliss, “Hemispheric specialization for visual words is shaped by attention to sublexical units during initial learning,” *Brain Lang.*, vol. 145–146, pp. 23–33, 2015.
- [14] S. Brem *et al.*, “Brain sensitivity to print emerges when children learn letter–speech sound correspondences,” *Proc. Natl. Acad. Sci.*, vol. 107, no. 17, pp. 7939–7944, 2010.
- [15] A. Martin, M. Schurz, M. Kronbichler, and F. Richlan, “Reading in the brain of children and adults, A meta-analysis of 40 fMRI studies,” *Hum. Brain Mapp.*, vol. 36, no. 5, pp. 1963–1981, 2015.
- [16] L. K. Blackburne *et al.*, “Neural correlates of letter reversal in children and adults,” *PLoS One*, vol. 9, no. 5, e98386, 2014.
- [17] B. D. McCandliss, L. Cohen, and S. Dehaene, “The visual word form area, Expertise for reading in the fusiform gyrus,” *Trends Cogn. Sci.*, vol. 7, no. 7, pp. 293–299, 2003.
- [18] C. J. Price and J. T. Devlin, “The myth of the visual word form area,” *NeuroImage*, vol. 19, no. 3, pp. 473–481, 2003.
- [19] M. Vigneau, G. Jobard, B. Mazoyer, and N. Tzourio-Mazoyer, “Word and non-word reading, What role for the visual word form area?” *NeuroImage*, vol. 27, no. 3, pp. 694–705, 2005.
- [20] A. Haug *et al.*, “Self-regulation of visual word form area activation with real-time fMRI neurofeedback,” *NeuroImage*, vol. 264, 119732, 2022.
- [21] R. Chauhan *et al.*, “The visual word form area (VWFA) is part of both language and attention circuitry,” *Neuropsychologia*, vol. 178, 108414, 2023.
- [22] O. N. Lyashevskaya and S. A. Sharov, *Frequency Dictionary of Modern Russian Language*. Moscow, Russia, Azbukovnik, 2009.
- [23] Y. Akinina *et al.*, “Russian normative data for 375 action pictures and verbs,” *Behav. Res. Methods*, vol. 48, no. 4, pp. 1281–1315, 2016.
- [24] E. Keuleers and M. Brysbaert, “Wuggy, A multilingual pseudoword generator,” *Behav. Res. Methods*, vol. 42, no. 3, pp. 627–633, 2010.
- [25] V. Arutiunian *et al.*, “Age-related changes in 40 Hz Auditory Steady-State Response and sustained Event-Related Fields in typically developing children, A MEG study,” *Hum. Brain Mapp.*, vol. 43, no. 17, pp. 5370–5383, 2022.
- [26] V. P. Lelik, M. D. Dyachkova, and S. V. Dorofeeva, “Tools for assessing speech and language development in preschool and early school-aged children, A literature review,” *Current Pediatrics*, vol. 23, no. 3, pp. 131–144, 2024.
- [27] S. N. Tseitlin *et al.*, *A Study of Children’s Acquisition of the Russian Writing System in Typical and Atypical Development*, Russian Foundation for Basic Research, Rep. No. 97-06-80333, 1997.
- [28] S. V. Dorofeeva *et al.*, “Assessing the validity of the standardized assessment of reading skills in Russian and verifying the relevance of available normative data,” *Russ. J. Cogn. Sci.*, vol. 6, no. 1, pp. 4–24, 2019.
- [29] J. Peirce *et al.*, “PsychoPy2, Experiments in behavior made easy,” *Behav. Res. Methods*, vol. 51, no. 1, pp. 195–203, 2019.
- [30] A. M. Dale, B. Fischl, and M. I. Sereno, “Cortical surface-based analysis, I. Segmentation and surface reconstruction,” *NeuroImage*, vol. 9, no. 2, pp. 179–194, 1999.
- [31] F. Tadel *et al.*, “Brainstorm, A user-friendly application for MEG/EEG analysis,” *Comput. Intell. Neurosci.*, 2011, Art. no. 879716.
- [32] S. Taulu and J. Simola, “Spatiotemporal signal space separation method for rejecting nearby interference in MEG measurements,” *Phys. Med. Biol.*, vol. 51, no. 7, pp. 1759–1768, 2006.
- [33] R. A. Seymour, G. Rippon, and K. Kessler, “The detection of phase amplitude coupling during sensory processing,” *Front. Neurosci.*, vol. 14, 570, 2020.
- [34] M. X. Huang, J. C. Mosher, and R. M. Leahy, “A sensor-weighted overlapping-sphere head model and exhaustive head model comparison for MEG,” *Phys. Med. Biol.*, vol. 44, no. 2, pp. 423–440, 1999.
- [35] F.-H. Lin *et al.*, “Assessing and improving the spatial accuracy in MEG source localization by depth-weighted minimum-norm estimates,” *NeuroImage*, vol. 31, no. 1, pp. 160–171, 2006.
- [36] M. S. Hämäläinen and R. J. Ilmoniemi, “Interpreting magnetic fields of the brain, Minimum norm estimates,” *Med. Biol. Eng. Comput.*, vol. 32, no. 1, pp. 35–42, 1994.
- [37] V. Arutiunian *et al.*, “Language deficits in Russian-speaking children with developmental language disorder,” *J. Speech Lang. Hear. Res.*, vol. 66, no. 1, pp. 154–169, 2023.
- [38] T. A. Stroganova *et al.*, “Left hemispheric deficit in the sustained neuromagnetic response to periodic click trains in children with ASD,” *Mol. Autism*, vol. 11, 100, 2020.
- [39] R Core Team, *R, A Language and Environment for Statistical Computing*. Vienna, Austria, R Foundation for Statistical Computing, 2019.
- [40] D. Bates, M. Mächler, B. Bolker, and S. Walker, “Fitting linear mixed-effects models using lme4,” *J. Stat. Softw.*, vol. 67, no. 1, pp. 1–48, 2015.
- [41] H. Wickham, *ggplot2, Elegant Graphics for Data Analysis*. New York, Springer-Verlag, 2016.
- [42] C. Sievert, *Interactive Web-Based Data Visualization with R, plotly, and shiny*. Chapman and Hall/CRC, 2020.
- [43] H. Wickham *et al.*, *dplyr, A Grammar of Data Manipulation*, R package version 1.1.4, 2023. Available: <https://dplyr.tidyverse.org>.
- [44] A. Kassambara, *ggpubr, ‘ggplot2’-Based Publication Ready Plots*, R package version 0.6.0, 2023.
- [45] C. Wilke, *ggridges, Ridgeline Plots in ‘ggplot2’*, R package version 0.5.6, 2024.
- [46] Y. Xie, *knitr, A General-Purpose Package for Dynamic Report Generation in R*, R package version 1.50, 2025.
- [47] M. Yablonski, K. Rastle, J. S. H. Taylor, and M. Ben-Shachar, “The transition from vision to language, Distinct patterns of functional connectivity for subregions of the visual word form area,” *Cereb. Cortex*, vol. 33, no. 4, pp. 1234–1256, 2023.
- [48] Bouhali *et al.*, “Anatomical connections of the visual word form area,” *J. Neurosci.*, vol. 34, no. 46, pp. 15402–15414, 2014.
- [49] A. L. White, J. Palmer, and G. M. Boynton, “Engaging in word recognition elicits highly specific modulations in visual cortex,” *J. Neurosci.*, vol. 43, no. 5, pp. 742–756, 2023.
- [50] J. Raven, “The Raven’s progressive matrices: change and stability over culture and time,” *Cogn. Psychol.*, vol. 41, no. 1, pp. 1–48, 2000.
- [51] A. Delorme and S. Makeig, “EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics,” *J. Neurosci. Methods*, vol. 134, no. 1, pp. 9–21, 2004.

# Brain to Bedside: Using Neuroscience to Cultivate Empathy in Medicine

Tia Chakraborty  
 Inpatient Neurology  
 Corewell Health West  
 Grand Rapids, Michigan, USA  
 Michigan State University  
 East Lansing, Michigan, USA  
 email: Tia.chakraborty@corewellhealth.org

Michael DeWilde  
 Koeze Business Ethics Initiative  
 Seidman College of Business  
 Grand Valley State University  
 Grand Rapids, Michigan, USA  
 email: dewildem@gvsu.edu

**Abstract**—Much has been written about the "empathy-deficit" among medical students, residents, and physicians, and the resulting (negative) effects on patients. While various proposals to counter the erosion of empathy throughout medical education and practice have been offered, to our knowledge no one has looked to map what we know about how the brain processes various kinds of empathy (affective, cognitive, etc.) to particular kinds of pedagogy (role play, simulation, didactic, etc.). For example, in cognitive empathy crucial brain regions involved include the ventral TemporoParietal Junction (TPJ), Superior Temporal Sulcus (STS), temporal poles, medial PreFrontal Cortex (mPFC) and precuneus/posterior cingulate. The TPJ has shown to mediate transient mental inferences about others such as about their goals, desires, and beliefs, while the mPFC facilitates attribution of more enduring traits about self and others. Our research indicates that to strengthen this trait narrative medicine and mindfulness training work better than, say, role play, which is better suited to the neural processes associated with affective empathy. In this review, we examine the neuroanatomical and chemical bases of empathy and discuss how these insights might well inform medical curricula. Integrating neuroscience and pedagogy allows for empathy to be cultivated in ways that are both scientifically grounded and clinically sustainable.

**Keywords** - Empathy; Narrative medicine; Neuroscience; Compassion.

## I. INTRODUCTION

Empathy, or the capacity to resonate with, understand, and respond to the mental and emotional states of others, is a multidimensional construct with critical relevance to neuroscience, clinical care, and medical education. Understanding these dimensions may lay the foundation for enhancing the delivery of compassionate and quality medical care.

Empathy is a fundamental component of connecting with others. Physicians have been consistently shown to drop in empathy scores as they move through medical school and into practice. Despite recent attention, empathy is still often an overlooked and deprioritized element of medical training, with consistently low empathy scores in physicians from training into practice [1]-[3], attached to the conventional thought that empathy is intrinsic rather than a teachable skill [4]. Yet, different aspects of empathy have been shown to be teachable, and it is a crucial ability to hone for building trust between patients and providers. Once built, this trust can

serve as the catalyst for effective shared decision-making and improved patient outcomes [5]-[12].

Types of empathy include affective (resonance), cognitive (Theory of Mind (ToM)), and empathetic concern (compassion). Here, we elaborate on these types, examine the neuroanatomical and chemical bases of empathy, and discuss how these insights may inform medical curricula. Integrating neuroscience and pedagogy allows for empathy to be cultivated in ways that are both scientifically grounded and clinically sustainable.

We conducted a narrative review about empathy, neural correlates of empathy, and proposed approaches to teaching empathy leveraging these correlations. We searched for pertinent scientific literature without restricted dates, focusing on rigorous meta-analyses, review papers, and randomized controlled trials with an emphasis on recent studies with higher impact that presented robust evidence-based findings.

## II. FOUNDATIONS IN NEUROSCIENCE

Most areas of the supratentorial (cerebrum), and to a lesser extent the infratentorial (brainstem, cerebellum) brain have been shown to be utilized in empathy, with heavy involvement of limbic and paralimbic networks in frontal, temporal, and parietal lobes. Neural networks are mediated by a mirror neuron system in which action perception is coupled to action execution through two main cortical networks. The first of these networks is formed by the parietal and premotor cortices, and the second by the Anterior Cingulate Cortex (ACC) and insula [13].

### A. Neural Circuits

Mirror neurons may form the cellular basis for empathy. Initially found in rats and macaque monkeys, these neurons pave the way for perception-action coupling (understanding-based simulation) [14], [15]. Mirror neuron systems span sensorimotor and emotional neural networks, and may also include the basal ganglia and cerebellum [16]. The sensorimotor regions involved are the ventral PreMotor cortex (PMv), primary Motor cortex (M1), Inferior Parietal Lobe (IPL), Anterior Intraparietal Area (AIP) dorsal and mesial PreMotor cortices (Pmd, PMm), PreFrontal Cortex (PFC), and the secondary Somatosensory cortex (SII). Emotional neural networks span limbic and paralimbic centers including the Anterior Cingulate Cortex (ACC), amygdala, and Anterior Insula (AI).

The perception of emotion in others activates mirror neurons in the Inferior Frontal Gyrus (IFG, Brodmann's Area BA 45/44/6) and Inferior Parietal Lobe (IPL, BA 39, 40) in coordinating first-hand emotional experiences, eliciting a corresponding automatic motor response [17]. The IFG identifies goals or intentions of actions by their resemblance to stored representations of these actions [13]. The amygdala facilitates recognition of facial emotions in others [18].

Conceptual frameworks distinguish empathy as affective (resonance), cognitive (Theory of Mind (ToM)), and as empathetic concern (compassion). These domains are dynamically interactive, with partially overlapping neural substrates [15][17][19][20]. Affective empathy is the capacity to emotionally react to another's mental state, and usually involves the interrelated unconscious processes of emotional recognition, contagion, and shared pain [21]. The IPL and IFG have been consistently shown to be activated in emotional contagion, and AI and ACC in the shared pain network [15][17][22].

Cognitive or ToM empathy refers to the capacity to use cognitive processes to take the perspective of others, make inferences, and predict the emotional and mental states of others. Rather than centering around emotion, ToM infers knowledge about another's beliefs, thoughts or emotions. Crucial brain regions involved include the ventral TemporoParietal Junction (vTPJ), Superior Temporal Sulcus (STS), temporal poles, medial PreFrontal Cortex (mPFC), and precuneus/posterior cingulate [17][23]. The TPJ has shown to mediate transient mental inferences about others such as about their goals, desires, and beliefs, while the mPFC facilitates attribution of more enduring traits about self and others [17].

Empathetic concern is defined as a compassionate response elicited by witnessing someone else in need [24]. This empathy type is regarded as a complementary social emotion related to feelings of concern and support. Neural networks implicated include the Ventral Striatum (VS) including the nucleus accumbens, Ventral Tegmental Area (VTA), medial OrbitoFrontal Cortex (mOFC) and the subgenual Anterior Cingulate (sgACC). Congruently with these activations in reward- and affiliation-associated networks, compassion generates positive affect towards others' suffering [23][25][26].

Though we distinguish these types of empathy, it's plausible that the empathetic response incites them synchronously, with different components being evoked to different extents depending on the context. In fMRI brain studies, distinct but sometimes overlapping neural pathways have been found to correspond to both affective and cognitive empathy, providing evidence for the separate but related forms empathy can take [27].

### B. Neurochemical Modulators

The neuropeptide oxytocin is synthesized in the hypothalamus and released both centrally in the brain and peripherally into the bloodstream. Oxytocin plays a foundational role in social bonding, attachment, and trust [28]. Mechanistically, oxytocin downregulates amygdala

activity, thereby lowering social threat perception and enhancing social approach behaviors [29]. This neurochemical modulation supports cooperation, affiliation, and the capacity for emotional attunement to others. Oxytocin has been shown to be particularly linked to affective empathy [18].

Empirical studies using the Multifaceted Empathy Test have shown that intranasal oxytocin enhances self-assessed emotional empathy but not cognitive empathy [18]. Other work shows that individuals with higher endogenous oxytocin levels report greater dispositional empathy, and polymorphisms in the oxytocin receptor gene correlate with higher empathy and stress reactivity [28]. Together, these findings suggest that oxytocin's influence on empathy may primarily operate through emotional resonance, trust formation, and reduced social anxiety [29].

Dopamine is a catecholamine neurotransmitter central to motivation, reinforcement learning, and the valuation of reward. In social cognition, dopamine links ToM empathy with motivational systems that drive prosocial action [30]. High dopaminergic activity facilitates the rewarding nature of social interactions, particularly those involving understanding or helping others [31]. Lackner et al. found that dopaminergic functioning was associated with ToM development in preschoolers, suggesting a role for dopamine in early empathic cognition [30]. Genetic studies have also shown that variation in dopamine receptor genes modulate cognitive empathy and prosocial behavior [31]. Thus, dopamine supports the cognitive processes underlying cognitive empathy and links these cognitive processes to the reward system, reinforcing social behavior.

Serotonin (5-HT) modulates social emotion and behavioral regulation by influencing mood, impulsivity, and sensitivity to social feedback. 5-HT plays a central role in regulating emotional resonance or the capacity to share another's emotional state while maintaining self-regulation. Tryptophan depletion studies show that low serotonin availability amplifies social emotional responses such as guilt or anger depending on personality traits [32]. Thus, serotonin supports adaptive empathy by modulating emotional reactivity and maintaining balance between self and other emotional states.

Cortisol, the primary stress hormone, can disrupt the coupling between emotional resonance and regulatory control. High cortisol levels reduce activity in brain regions related to empathy for pain and emotional processing [33]. Conversely, endogenous opioids, particularly the  $\mu$ -opioid system, mediate empathic concern, social bonding, and soothing responses. Opioid antagonism reduces empathic concern and diminishes affiliative behavior, supporting the view that endogenous opioids underpin the calming, nurturing dimensions of compassionate empathy [34].

### III. LINKING NEUROSCIENCE AND CURRICULUM DESIGN

A neuroscience-informed pedagogy purposefully aligns educational interventions with neural circuits and neurochemical systems that support empathy, social cognition, and prosocial motivation (Figure 1). When mapped onto empathy neural architectures, targeted curricula

can build and refine specific capacities, producing not only behavioral improvement but also measurable neuroplastic change [35]. Correlating neural networks of empathy to didactic approaches and training enhances communication while protecting against empathic fatigue and burnout.

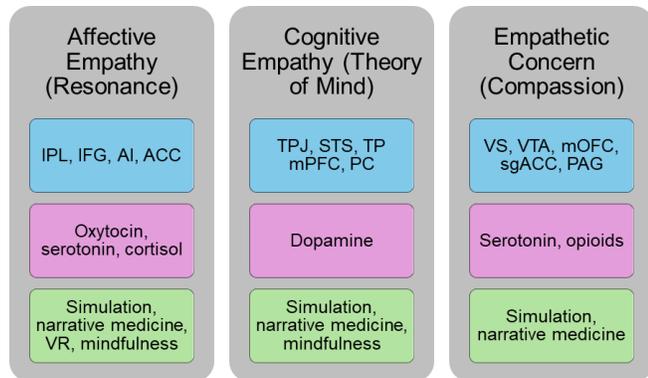


Figure 1. Overview of Neural Correlates of Empathy and Didactic Approaches; Abbreviations: Inferior Frontal Lobe (IPL); Inferior Frontal Gyrus (IFG); Anterior Insula (AI); Temporal Poles (TP); Precuneus/Posterior Cingulate (PC); PeriAquaductal Gray region (PAG).

#### IV. EDUCATIONAL STRATEGIES IN MEDICINE

Empathy requires the capacity to both share another’s emotional experience (affective empathy) and understand another’s internal state (cognitive empathy). Contemporary models emphasize three interacting components: affective sharing that supports interpersonal resonance, self–other distinction that preserves separateness, and cognitive flexibility that allows sustained attention to another while regulating self-oriented distress [15][36]. These components rely on partially dissociable but interacting neural systems, suggesting that successful empathy education integrates affective, cognitive, and compassionate processes and their regulation rather than privileging any single domain [17].

##### A. Principles of Curriculum Design

Effective empathy education aligns with neurodevelopmental principles of experience-dependent plasticity. Engaging in new experiences, memory training, and neurofeedback are known to enhance synaptic efficiency and functional connectivity within distributed socioemotional networks [37][38]. Spiral curriculum design, characterized by repeated engagement with core concepts at increasing levels of complexity, may support long-term potentiation within prefrontal-limbic pathways, including the medial PFC, ACC, and AI, which collectively contribute to empathic ability and emotion regulation [39]-[43].

Deliberate practice further leverages dopaminergic reinforcement learning mechanisms, wherein feedback-based learning strengthens behavior through reward prediction error signaling in the ventral striatum and its functional coupling with the frontal cortex [44][45]. These mechanisms have been implicated in the consolidation of complex social behaviors, including perspective-taking and prosocial decision-making [46].

Formative assessment can support neuroplastic integration by promoting reflective retrieval, a process that engages hippocampal–vmPFC circuitry and strengthens memory traces for context-specific behavioral scripts [47], [48]. The use of quantitative tools such as the Jefferson Scale of Physician Empathy and performance-based assessments including OSCEs remain directly unlinked to specific areas of neural activation. Yet existing knowledge about the recruitment of the TPJ and AI during perspective-taking and socioemotional evaluation tasks highlights the potential for such tools to be utilized in pedagogy [8][49][50].

##### B. Role-Play and Simulation

Simulation-based empathy training engages all categories of empathy circuits. Peer role-play activates regions associated with action observation and embodiment, including the IFG, IPL, and insula, core components of the mirror neuron and interoceptive systems [17][51][52]. However, peer simulations may generate limited affective salience, potentially constraining neuromodulatory engagement.

In contrast, interactions with Standardized Patients (SPs) may elicit more authentic social-emotional processing, engaging the ACC and AI, correlating with neuroendocrine markers of affiliative behavior including oxytocin release [18][53]. Though Bagacean et al. found no differences in empathy between peer- and SP-mediated role-play, the study had a low sample size and noted more appropriate communication skills with SPs [54].

High-fidelity simulations can evoke strong autonomic and limbic responses, recruiting the amygdala, insula, PeriAquaductal Gray (PAG), and brainstem autonomic nuclei involved in caregiving and threat-response integration [55] [56]. These emotionally salient experiences may enhance learning retention through dopaminergic reinforcement within the ventral striatum, a mechanism consistent with evidence that emotionally arousing learning episodes are preferentially consolidated in memory [57].

##### C. Narrative Medicine

Narrative medicine fosters narrative competence by engaging neural networks implicated in social imagination, autobiographical memory, and moral reasoning [58]. Functional neuroimaging demonstrates that reading and reflecting on stories activates the Default Mode Network (DMN), including the mPFC, TPJ, PCC, and angular gyrus, which substantially overlaps with ToM circuitry [59]-[62].

Narrative engagement has also been associated with activation of mesolimbic dopaminergic pathways, linking story comprehension to reward valuation and emotional meaning [63]-[65]. Reflective writing in narrative medicine supports emotional regulation, catharsis, and meaning making [58][66]. There are no direct empirical studies linking reflective emotional processing to serotonergic or endogenous opioid activity. However, adjacent research shows that emotional regulation and stress-processing, processes engaged during reflective writing, are modulated by these neurotransmitter systems [67]-[69].

Additionally, narrative that elicits empathy can enhance oxytocin-mediated social bonding, reinforcing prosocial motivation and affiliative trust [70]. Therefore, narrative medicine incorporates the neural architecture underlying empathic understanding.

#### D. Mindfulness and Reflective Practice

Mindfulness meditation strengthens prefrontal regulation of emotional and autonomic systems. Neuroimaging studies consistently demonstrate increased activation and functional connectivity in the dorsolateral PFC, ACC, and insula as well as reduced amygdala reactivity, reflecting enhanced interoceptive awareness and emotional regulation [71][72]. Mindfulness practices are also associated with neurochemical shifts, including enhanced GABAergic tone and reductions in cortisol and sympathetic arousal [73][74]. Emerging evidence suggests that mindfulness may also modulate dopaminergic tone in reward-related regions, including the ventral striatum, supporting intrinsic motivation and sustained prosocial engagement [75][76].

#### E. Digital and Immersive Technologies

There are varying views on the ability of VR as a tool to teach empathy [77]. On one hand, digital empathy interventions may recruit overlapping neural systems through immersive and emotionally salient experiences. VR simulations may enhance embodied perspective-taking by engaging the AI, ACC, TPJ, with measurable increases in affective resonance and variable impact on cognitive empathy [78]-[82]. On the other hand, VR has been critiqued as being an oversimplification of the complexities of empathy. Ethical concerns using VR and lack of rigorous research have been cited [77].

Neuroendocrine evidence indicates some immersive VR interventions can increase salivary oxytocin, and neuroimaging studies of interactive virtual environments show engagement of striatal-midbrain reward circuitry consistent with dopamine-mediated reinforcement learning. Together, these findings present a possible pathway by which immersive VR could strengthen empathy learning through heightened experiential salience [83][84]. Artificial-intelligence-driven conversational agents that provide real-time feedback on empathic markers such as facial expression, gaze, and tone may engage social learning circuits involving mPFC–striatal coupling, paralleling mechanisms observed in human social feedback processing [85]-[87].

Collectively, these digital approaches may offer scalable platforms that reflect the multisystem neural architecture of empathy, integrating affective resonance, cognitive perspective-taking, and motivational reinforcement into adaptive learning environments. More research is needed to examine causal relationships between these technologies and empathy.

#### F. Shielding Against Empathetic Distress

Balint groups and structured reflective dialogue add a social dimension, engaging oxytocin-mediated affiliative circuits and vmPFC–amygdala pathways implicated in

empathic concern and emotional homeostasis [40][88]-[90]. These group-based reflections may help buffer stress-related neuroendocrine responses and mitigate empathic fatigue in clinicians. Compassion training may also help mitigate burnout from providing empathy and strengthen resilience through increased activations in networks spanning the ventral striatum, pregenual ACC, and mOFC [91]. Teaching the techniques of “empathetic communication” has shown promise, as way of guiding physicians to say the right thing even if their feelings are not aligned.

#### V. CONCLUSION

Empathy is supported by robust neural networks including the mirror neuron system, limbic, and paralimbic pathways and is modulated by neurochemicals implicated in emotional and behavioral regulation. Mapping didactic methods to this neural architecture may effectively bridge current gaps in the delivery of empathic medical care, underscoring that empathy is not static.

A multitude of evidence shows empathy, in all its forms, can be taught, reinforced, and sustained. Simulation, narrative medicine, mindfulness, and digital tools provide evidence-based methods for cultivating empathy in the practice of clinical medicine. Future research assessing the efficacy of these methods is necessary to improve upon ways of teaching the vital skillset of empathy to ultimately improve patient outcomes while enriching provider experiences.

#### REFERENCES

- [1] L. M. Bellini and J. A. Shea, Mood change and empathy decline persist during three years of internal medicine training, *Acad. Med.*, 80(2), pp. 164-7, 2005.
- [2] D. Chen et al., A cross-sectional measurement of medical student empathy, *J. Gen. Intern. Med.*, 22(10), pp. 1434-8, 2007.
- [3] M. Neumann et al., Empathy Decline and Its Reasons: A Systematic Review of Studies With Medical Students and Residents, *Academic Medicine*, 86(8), 2011.
- [4] S. Thangarasu, G. Renganathan, and P. Natarajan, Empathy Can Be Taught, and Patients Teach it Best, *J. Med. Educ. Curric. Dev.*, 8, pp. 23821205211000346, 2021.
- [5] S. Patel et al., Curricula for empathy and compassion training in medical education: A systematic review, *PLoS One*, 14(8), pp. e0221412, 2019.
- [6] K. Berg et al., Medical students' self-reported empathy and simulated patients' assessments of student empathy: an analysis by gender and ethnicity, *Acad. Med.*, 86(8), pp. 984-8, 2011.
- [7] J. Noordman et al., Training residents in patient-centred communication and empathy: evaluation from patients, observers and residents, *BMC Med. Educ.*, 19(1), pp. 128, 2019.
- [8] M. Hojat et al., Physicians' empathy and clinical outcomes for diabetic patients, *Acad. Med.*, 86(3), pp. 359-64, 2011.
- [9] H. Bukowski et al., Medical student empathy and breaking bad news communication in a simulated consultation, *Patient Educ. Couns.*, 105(5), pp. 1342-1345, 2022.
- [10] S. Lelorain et al., The association of physician empathy with cancer patient outcomes: A meta-analysis, *Psychooncology*, 32(4), pp. 506-515, 2023.

- [11] K. A. Bonvicini et al., Impact of communication training on physician expression of empathy in patient encounters, *Patient Educ. Couns.*, 75(1), pp. 3-10, 2009.
- [12] H. Riess et al., Empathy Training for Resident Physicians: A Randomized Controlled Trial of a Neuroscience-Informed Curriculum, *Journal of General Internal Medicine*, 27(10), pp. 1280-1286, 2012.
- [13] G. Rizzolatti, M. Fabbri-Destro, and L. Cattaneo, Mirror neurons and their clinical relevance, *Nat. Clin. Pract. Neurol.*, 5(1), pp. 24-34, 2009.
- [14] V. Gallese, Before and below 'theory of mind': embodied simulation and the neural correlates of social cognition, *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, 362(1480), pp. 659-69, 2007.
- [15] J. Decety and P. L. Jackson, The functional architecture of human empathy, *Behav. Cogn. Neurosci. Rev.*, 3(2), pp. 71-100, 2004.
- [16] L. Bonini et al., Mirror neurons 30 years later: implications and applications, *Trends. Cogn. Sci.*, 26(9), pp. 767-781, 2022.
- [17] S. G. Shamay-Tsoory, The neural bases for empathy, *Neuroscientist*, 17(1), pp. 18-24, 2011.
- [18] R. Hurlmann, Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans, *J. Neurosci.*, 30(14), pp. 4999-5007, 2010.
- [19] J. Levy et al., The Neural Basis of Empathy and Empathic Behavior in the Context of Chronic Trauma, *Front Psychiatry*, vol. 10, pp. 562, 2019.
- [20] S. W. Mercer and W. J. Reynolds, Empathy and quality of care, *Br. J. Gen. Pract.*, vol. 52 (Suppl), pp. S9-12, 2002.
- [21] A. Abu-Akel et al., Oxytocin increases empathy to pain when adopting the other- but not the self-perspective, *Soc. Neurosci.*, 10(1), pp. 7-15, 2015.
- [22] B. C. Bernhardt and T. Singer, The neural basis of empathy, *Annu. Rev. Neurosci.*, vol. 35, pp. 1-23, 2012.
- [23] K. Preckel, P. Kanske, and T. Singer, On the interaction of social affect and cognition: empathy, compassion and theory of mind, *Current Opinion in Behavioral Sciences*, vol. 19, pp. 1-6, 2018.
- [24] L. W. Niezink et al., Empathic concern: Distinguishing between tenderness and sympathy, *Motiv. Emot.*, 36(4), pp. 544-549, 2012.
- [25] H. Kawamichi et al., Helping behavior induced by empathic concern attenuates anterior cingulate activation in response to others' distress, *Soc. Neurosci.*, 11(2), pp. 109-22, 2016.
- [26] H. Kawamichi et al., Activation of the reward system during sympathetic concern is mediated by two types of empathy in a familiarity-dependent manner, *Social Neuroscience*, 8(1), pp. 90-100, 2013.
- [27] Y. Fan et al., Is there a core neural network in empathy? An fMRI based quantitative meta-analysis, *Neurosci. Biobehav. Rev.*, 35(3), pp. 903-11, 2011.
- [28] S. M. Rodrigues et al., Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans, *Proc. Natl. Acad. Sci. USA*, 106(50), pp. 21437-41, 2009.
- [29] Y. Geng et al., Oxytocin Enhancement of Emotional Empathy: Generalization Across Cultures and Effects on Amygdala Activity, *Frontiers in Neuroscience*, vol. 12, 2018.
- [30] C. L. Lackner, L. C. Bowman, and M. A. Sabbagh, Dopaminergic functioning and preschoolers' theory of mind, *Neuropsychologia*, 48(6), pp. 1767-74, 2010.
- [31] S. Ben-Israel et al., Dopamine D4 receptor polymorphism and sex interact to predict children's affective knowledge, *Front. Psychol.*, vol. 6, pp. 846, 2015.
- [32] J. W. Kanen et al., Serotonin depletion amplifies distinct human social emotions as a function of individual differences in personality, *Transl. Psychiatry*, 11(1), pp. 81, 2021.
- [33] Z. Tang et al., Stress-induced cortisol response predicts empathy for pain: The role of task-based connectivity between the insula and sensorimotor cortex during acute stress, *Neurobiol. Stress*, vol. 33, pp. 100682, 2024.
- [34] L. Nummenmaa and L. Tuominen, Opioid system and human emotions, *British Journal of Pharmacology*, 175(14), pp. 2737-2749, 2018.
- [35] O. M. Klimecki et al., Functional neural plasticity and associated changes in positive affect after compassion training, *Cereb. Cortex*, 23(7), pp. 1552-61, 2013.
- [36] J. Decety and C. Lamm, Human empathy through the lens of social neuroscience, *Scientific World Journal*, vol. 6, pp. 1146-63, 2006.
- [37] A. May, Experience-dependent structural plasticity in the adult human brain, *Trends. Cogn. Sci.*, 15(10), pp. 475-82, 2011.
- [38] M. Krylova et al., Progressive modulation of resting-state brain activity during neurofeedback of positive-social emotion regulation networks, *Sci. Rep.*, 11(1), pp. 23363, 2021.
- [39] J. Zaki and K. N. Ochsner, The neuroscience of empathy: progress, pitfalls and promise, *Nat. Neurosci.*, 15(5), pp. 675-80, 2012.
- [40] A. Etkin, T. Egner, and R. Kalisch, Emotional processing in anterior cingulate and medial prefrontal cortex, *Trends Cogn. Sci.*, 15(2), pp. 85-93, 2011.
- [41] R. M. Harden, What is a spiral curriculum? *Med. Teach.*, 21(2), pp. 141-3, 1999.
- [42] C. Herry and R. Garcia, Prefrontal cortex long-term potentiation, but not long-term depression, is associated with the maintenance of extinction of learned fear in mice, *J. Neurosci.*, 22(2), pp. 577-83, 2002.
- [43] H. Tang et al., Prefrontal cortical plasticity during learning of cognitive tasks, *Nat. Commun.*, 13(1), pp. 90, 2022.
- [44] W. Schultz, Dopamine reward prediction error coding, *Dialogues Clin. Neurosci.*, 18(1), pp. 23-32, 2016.
- [45] M. J. Frank and E. D. Claus, Anatomy of a decision: striato-orbitofrontal interactions in reinforcement learning, decision making, and reversal, *Psychol. Rev.*, 113(2), pp. 300-326, 2006.
- [46] P. L. Lockwood et al., Neurocomputational mechanisms of prosocial learning and links to empathy, *Proc. Natl. Acad. Sci. USA*, 113(35), pp. 9763-8, 2016.
- [47] A. R. Preston and H. Eichenbaum, Interplay of hippocampus and prefrontal cortex in memory, *Curr. Biol.*, 23(17), pp. R764-73, 2013.
- [48] L. R. Squire et al., Memory consolidation, *Cold. Spring. Harb. Perspect. Biol.*, 7(8), pp. a021766, 2015.
- [49] T. R. A. Kral et al., Neural correlates of empathic accuracy in adolescence, *Social Cognitive and Affective Neuroscience*, 12(11), pp. 1701-1710, 2017.
- [50] I. Mutschler et al., Structural basis of empathy and the domain general region in the anterior insular cortex, *Front. Hum. Neurosci.*, vol. 7, pp. 177, 2013.
- [51] G. Rizzolatti and C. Sinigaglia, The mirror mechanism: a basic principle of brain function, *Nature Reviews Neuroscience*, 17(12), pp. 757-765, 2016.
- [52] C. Keysers, J. H. Kaas, and V. Gazzola, Somatosensation in social perception, *Nature Reviews Neuroscience*, 11(6), pp. 417-428, 2010.
- [53] J. A. Bartz et al., Social effects of oxytocin in humans: context and person matter, *Trends. Cogn. Sci.*, 15(7), pp. 301-9, 2011.

- [54] C. Bagacean et al., Simulated patient and role play methodologies for communication skills and empathy training of undergraduate medical students, *BMC Med. Educ.*, 20(1), pp. 491, 2020.
- [55] D. Mobbs et al., When fear is near: threat imminence elicits prefrontal-periaqueductal gray shifts in humans, *Science*, vol. 317(5841), pp. 1079-83, 2007.
- [56] J. B. Panksepp and G. P. Lahvis, Rodent empathy and affective neuroscience, *Neurosci. Biobehav. Rev.*, vol. 35(9), pp. 1864-75, 2011.
- [57] D. Shohamy and R. A. Adcock, Dopamine and adaptive memory, *Trends. Cogn. Sci.*, 14(10), pp. 464-72, 2010.
- [58] R. Charon, *Narrative Medicine: Honoring the Stories of Illness*, Oxford University Press, 2006.
- [59] R. A. Mar, The neural bases of social cognition and story comprehension, *Annu Rev Psychol*, vol. 62, pp. 103-34, 2011.
- [60] E. Simony et al., Dynamic reconfiguration of the default mode network during narrative comprehension, *Nature Communications*, 7(1), pp. 12141, 2016.
- [61] R. N. Spreng, R. A. Mar, and A. S. N. Kim, The Common Neural Basis of Autobiographical Memory, Prospection, Navigation, Theory of Mind, and the Default Mode: A Quantitative Meta-analysis, *Journal of Cognitive Neuroscience*, 21(3), pp. 489-510, 2009.
- [62] A. Obando Yar, C. Moret-Tatay, and J. V. Esteve Rodrigo, The science of story characters: a neuroimaging perspective on antagonists in narrative engagement, *Frontiers in Human Neuroscience*, vol. 19, 2025.
- [63] C. T. Hsu, M. Conrad, and A. M. Jacobs, Fiction feelings in Harry Potter: haemodynamic response in the mid-cingulate cortex correlates with immersive reading experience, *Neuroreport*, 25(17), pp. 1356-61, 2014.
- [64] B. H. Schott et al., Mesolimbic Functional Magnetic Resonance Imaging Activations during Reward Anticipation Correlate with Reward-Related Ventral Striatal Dopamine Release. *The Journal of Neuroscience*, 28(52), pp. 14311, 2008.
- [65] O. Kobo, Y. Yeshurun, and T. Schonberg, Reward-related regions play a role in natural story comprehension, *iScience*, 27(6), pp. 109844, 2024.
- [66] J. Y. Lim et al., A systematic scoping review of reflective writing in medical education, *BMC Medical Education*, 23(1), pp. 12, 2023.
- [67] P. Salvan et al., Serotonin regulation of behavior via large-scale neuromodulation of serotonin receptor networks, *Nature Neuroscience*, 26(1), pp. 53-63, 2023.
- [68] K. Nakamoto and S. Tokuyama, Stress-Induced Changes in the Endogenous Opioid System Cause Dysfunction of Pain and Emotion Regulation, *International Journal of Molecular Sciences*, 24(14), pp. 11713, 2023.
- [69] J. A. Higginbotham et al., Endogenous opioid systems alterations in pain and opioid use disorder, *Frontiers in Systems Neuroscience*, vol. 16, 2022.
- [70] P. J. Zak, Why inspiring stories make us react: the neuroscience of narrative, *Cerebrum*, pp. 2, 2015.
- [71] Y.-Y. Tang, B. K. Hölzel, and M. I. Posner, The neuroscience of mindfulness meditation, *Nature Reviews Neuroscience*, 16(4), pp. 213-225, 2015.
- [72] B. K. Hölzel et al., Mindfulness practice leads to increases in regional brain gray matter density, *Psychiatry Res.*, 191(1), pp. 36-43, 2011.
- [73] C. C. Streeter et al., Effects of yoga on the autonomic nervous system, gamma-aminobutyric-acid, and allostasis in epilepsy, depression, and post-traumatic stress disorder, *Med. Hypotheses*, 78(5), pp. 571-9, 2012.
- [74] D. S. Black and G. M. Slavich, Mindfulness meditation and the immune system: a systematic review of randomized controlled trials, *Ann. NY Acad. Sci.*, 1373(1), pp. 13-24, 2016.
- [75] U. Kirk et al., Mindfulness training modulates value signals in ventromedial prefrontal cortex through input from insular cortex, *Neuroimage*, vol. 100, pp. 254-62, 2014.
- [76] T. W. Kjaer et al., Increased dopamine tone during meditation-induced change of consciousness. *Brain Res Cogn Brain Res*, 13(2), pp. 255-9, 2002.
- [77] S. Seinfeld et al., Editorial: Virtual reality and empathy, *Front. Psychol.*, vol. 13, pp. 1089006, 2022.
- [78] N. S. Schutte and E. J. Stilić, Facilitating empathy through virtual reality. *Motivation and Emotion*, 41(6), pp. 708-712, 2017.
- [79] M. Guy et al., The sense of embodiment in Virtual Reality and its assessment methods, *Frontiers in Virtual Reality*, vol. 4, 2023.
- [80] Z. Abdulkarim et al., Neural Substrates of Body Ownership and Agency during Voluntary Movement, *J. Neurosci.*, 43(13), pp. 2362-2380, 2023.
- [81] L. Trevena, J. Paay, and R. McDonald, VR interventions aimed to induce empathy: a scoping review, *Virtual Reality*, 28(2), pp. 80, 2024.
- [82] A. L. Martingano, F. Hererra, and S. Konrath, Virtual reality improves emotional but not cognitive empathy: A meta-analysis, *Technology, Mind, and Behavior*, 2(1), pp. 7-21, 2021.
- [83] J. Kätsyri et al., Just watching the game ain't enough: striatal fMRI reward responses to successes and failures in a video game during active and vicarious playing. *Front Hum Neurosci*, vol. 7, pp. 278, 2013.
- [84] T. Shima et al., Augmented-reality-based multi-person exercise has more beneficial effects on mood state and oxytocin secretion than standard solitary exercise, *Physiology & Behavior*, vol. 283, pp. 114623, 2024.
- [85] L. Herschbach et al., Evaluation of an AI-Based Chatbot Providing Real-Time Feedback in Communication Training for Mental Health Care Professionals: Proof-of-Concept Observational Study, *J. Med. Internet Res.*, vol. 27, pp. e82818, 2025.
- [86] A. Axelsson, H. Buschmeier, and G. Skantze, Modeling Feedback in Interaction With Conversational Agents—A Review, *Frontiers in Computer Science*, vol. 4, 2022.
- [87] J. Poore et al., Prediction-error in the context of real social relationships modulates reward system activity, *Frontiers in Human Neuroscience*, vol. 6, 2012.
- [88] M. Heinrichs, B. von Dawans, and G. Domes, Oxytocin, vasopressin, and human social behavior, *Front. Neuroendocrinol.*, 30(4), pp. 548-557, 2009.
- [89] H. L. Urry et al., Amygdala and Ventromedial Prefrontal Cortex Are Inversely Coupled during Regulation of Negative Affect and Predict the Diurnal Pattern of Cortisol Secretion among Older Adults, *The Journal of Neuroscience*, 26(16), pp. 4415, 2006.
- [90] M. Yazdankhahfard, F. Haghani, and A. Omid, The Balint group and its application in medical education: A systematic review, *J. Educ. Health Promot.*, vol. 8, pp. 124, 2019.
- [91] O. M. Klimecki et al., Differential pattern of functional brain plasticity after compassion and empathy training, *Soc. Cogn. Affect. Neurosci.*, 9(6), pp. 873-9, 2014.