BIOGRAPHICAL SKETCH

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NAME: Joy Hirsch

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POSITION TITLE: Elizabeth Mears and House Jameson Professor of Psychiatry, Comparative Medicine, and Neuroscience

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Oregon, Portland, OR	B.S.	1967	Biology
Portland State University, Portland, OR	M.S.	1970	Exp. Psychology
Columbia University, New York, NY	Ph.D.	1977	Vision Sciences

A. Personal Statement

In my view the most exciting and important questions in contemporary neuroscience relate to real "person-to-person" interactions. Most of our day-to-day behaviors throughout the lifespan are with another person. Yet, most of what we know about the functioning human brain relates to functions that are performed in isolation. This knowledge gap between the underlying neurobiology that supports solo and interactive behaviors is resistant to change due to the paucity of techniques to investigate dyads in natural interactions. However, an emerging non-invasive "break-through" neuroimaging technology, functional near infrared spectroscopy (fNIRS), that acquires BOLD-like signals using optical methods with head mounted detectors is readily applicable to the investigation of interactive conditions. The current research directions build a body of developmental work resulting from prior funding (NIMH R01MH107513 (PI JH) 7/1/15 – 6/30/21), titled: "Mechanisms of Interpersonal Social Communication: A Dual Brain fNIRS Investigation" under the Modeling Social Behavior Funding Opportunity (PAR-13-374). The aim of this prior funding opportunity was "to support the development of innovative theories and computational, mathematical, or engineering approaches to deepen understanding of complex social behavior". This prior work advanced the field with support for the interactive brain hypothesis[1–4] purporting that both verbal interaction[1] and interactive face gaze with a real human partner[2–4] activates "interaction specialized" neural systems in the temporal parietal junction known for social and receptive processes. The constellation of findings has been reported in more than 30 peer reviewed research papers that have 1) validated the technology, 2) developed the signal processing tools, and 3) introduced paradigms for "two-person" neuroscience. These findings merge visual models of face processing and social processes and lead to "next stage" questions such as how human faces communicate information including emotion[1 - 4]. The technology for this proposal is advanced to include multi-modal acquisitions with simultaneous fNIRS, facial classifications, eye-tracking, EEG, and ratings of affect. All are operational and illustrated in prior findings and pilot data. For example, a recent publication links temporal and spatial processes in live social face processing, (Kelley M, Tiede M, Zhang X, Noah JA, Hirsch J. Spatiotemporal processing of real faces is modified by visual sensing. Neuroimage. 2025 Apr 17;312:121219. doi: 10.1016/j.neuroimage.2025.121219. Epub ahead of print. PMID: 40252877). Current investigations are focused on understanding the mechanisms that underlie interactive social and cognitive difficulties typical of Schizophrenia, and builds upon a prior grant, R01MH111629 "Neural Mechanisms of Social Interactions and Eye Contact in ASD" to develop and apply the advantages of this neuroimaging technology to understand the neural systems that underlie live face processing in ASD and those that underlie social symptomatology. Findings are consistent with a model of alternative live-face processing mechanisms where in ASD ventral stream systems are employed and in TD dorsal stream systems are employed for live face processing and eye contact[2]. Using AI models it was determined that neural activity in dorsal stream regions of ASD participants was also negatively correlated with

ADOS scores of symptom severity suggesting a relationship to social symptomatology (Zhang, X., Noah, J.A., Singh, R., McPArtland, J., Hirsch, J. (2024) Support vector machine prediction of individual Autism Diagnostic Observation Schedule (ADOS) scores based on neural responses during live eye-to-eye contact. *Sci Rep* 14, 3232 . Further a recently published machine learning paper with schizophrenia also provides another example of the predictive value of a multi-modal (Singh R, Zhang Y, Bhaskar D, Srihari V, Tek C, Zhang X, Noah JA, Krishnaswamy S and Hirsch J (2025) Deep multimodal representations and classification of first-episode psychosis via live face processing. *Front. Psychiatry 16:1518762. doi: 10.3389/fpsyt.2025.1518762)*. Current investigations aim to develop causal models of underlying neural circuitry for live social interactions and apply to neuromodulatory approaches for treatment of disorders with social symptomatology.

1. Hirsch, J.*, Noah, J.A., Zhang, X., Dravida, S., & Ono, Y. (2018). A cross-brain neural mechanism for human-to-human verbal communication. Social Cognitive and Affective Neuroscience, 13(9), 907–920. DOI: 10.1093/scan/nsy070. PMCID: PMC6137318.
2. Hirsch J, Zhang X, Noah JA, Dravida S, Naples A, Tiede M, Wolf, J, McPartland, J. (2022) Neural correlates of eye contact and social function in autism spectrum disorder. PLoS ONE 17(11): e0265798. Doi.org/10.1371/journal.pone.0265798
3. Hirsch, J., Zhang, X., Noah, J.A. & Bhattacharya, A. Neural mechanisms for emotional contagion and spontaneous mimicry of live facial expressions. Philosophical Transactions of the Royal Society B: Biological Sciences 2023 Apr 24;378(1875):20210472. doi:10.1098/rstb.2021.0472. Epub 2023 Mar 6.
4. Nan Zhao, Xian Zhang, J. Adam Noah, Mark Tiede, and Joy Hirsch. Separable Processes for Live "In-Person" and Live "Zoom-like" Faces. Imaging Neuroscience, 1: 1–17, doi.org/10.1162/imag_a_00027.

Ongoing and recently completed projects that I would like to highlight include:

NIMH R01MH111629
Hirsch (PI)
09/26/2016–06/30/2022
Neural Mechanisms for Social Interactions and Eye Contact in ASD

NIMH R01MH119430
Hirsch (PI)
03/01/2019-12/31/2023
Mechanisms of Dynamic Neural Coupling during Face-to-Face Expressions of Emotion.

B. <u>Positions and Employment</u>

2022-currrent Wu Tsai Institute, Yale University
2019-current Elizabeth Mears and House Jameson Professor of Psychiatry, Comparative Medicine, and Neuroscience, Yale School of Medicine, New Haven, CT
2015-current *ex-officio* Professor of Neuroscience, Department of Medical Physics and Biomedical Engineering, Faculty of Engineering Sciences, University College London, London, UK (In accordance with the Yale-UCL Collaborative agreement)
2013-current Professor of Neuroscience, Department of Comparative Medicine, Yale School of Medicine.

C. Contributions to Science

Five contributions are described below in chronological order.

I. Early breakthroughs in brain mapping with functional MRI leading to clinical applications

Frame of the problem. Prior to the development of neuroimaging techniques, models of brain function were inferred primarily from lesion studies, psychophysiological functions, behavioral measures, and electrophysiology**.** The discovery of the Blood Oxygen Level Dependent (BOLD) signal initiated new opportunities to directly observe neural function in relation to behavior, perception and complex cognitive and social processes. **Background:** In 1992 I relocated from Yale to MSKCC to develop neural imaging techniques that would extend models of the working intact brain to include neural processes. Specific aims included the identification of cortical regions associated with specific functions associated with motor, vision, language, hearing, memory, and complex decision making. My original goal was to "map" the underlying neural circuitry engaged during execution of essential tasks and thereby enabling their protection from possible surgical accident. Because language functions are essential quality of life functions, our laboratory also focused on understanding the neural basis for language. **Findings and Impact**. These early mapping results served to validate fMRI procedures, and pioneered the application of fMRI for basic neuroscience and clinical purposes[1]. These studies also contributed to the development of high resolution mapping of language-sensitive processes leading to our discovery that 1) late-acquired second language requires new dedicated regions in Broca's Area[2], 2) neural circuitry for language ability can be identified in patients who are minimally conscious[3], and 3) Autism Spectrum Disorder can be identified by hypoactivity in Wernicke's Area in response to spoken narratives[4].

Findings also contributed to the basis for billing codes issued by the American Medical Association to enable these procedures for clinical purposes. **Relevance to current work**: Neural mapping of functional regions has contributed to current models of functional specificity, and more advanced investigations of functional connectivity that lead to understanding the roles of integrative processes and large-system networks in complex behaviors. Our current work extends this foundation of methods, models of functional specificity, and models of functional connectivity to the investigation of neural systems that are engaged during natural interactions between two individuals using functional near infrared spectroscopy (fNIRS) as the neuroimaging technique. This background of neuroimaging for clinical questions and orientation toward "science for service" is a main theme in current investigations and a platform for mentoring students and other trainees.

1. Hirsch, J., Ruge, M.I., Kim, K.H.S., Correa, D.D., Victor, J.D., Relkin, N.R., Labar, D.R., Krol, G., Bilsky, M.H., Souweidane, M.M., DeAngelis, L.M., Gutin, P.H. An Integrated fMRI Procedure for Preoperative Mapping of Cortical Areas Associated with Tactile, Motor, Language, and VisualFunctions. *Neurosurgery,* 2000, 47(3), *711-722.*
2. Kim, K.H.S., Relkin, N.R., Lee, K.M., Hirsch, J. Distinct cortical areas associated with native and second languages. *Nature,* 1997, 388, 171-174.
3. Schiff, N.D., Rodriguez-Moreno D., Kamal, A., Kim, K.H.S., Giacino, J.T., Plum, F., Hirsch, J. fMRI Reveals Large Scale Network Activation in Minimally Conscious Patients, *Neurology*, 2005, Vol 64, 514-523.
4. Lai, G., Schneider, H., Schwarzenberger, J., Hirsch, J. Speech stimulation during functional MR imaging as a potential indicator of autism. *Radiology*, 260(2):521-530, 2011. PMID: 21628495.

II. Breakthroughs in understanding neural mechanisms of emotional control and anxiety. Frame of the problem. Effective mental processing requires that cognition be protected from emotional conflict and interference by task-irrelevant, emotionally salient, stimuli that can be either consciously perceived or not perceived. Drawing on the classical Stroop conflict task, we developed a general protocol that allowed us to disassociate the generation and monitoring of emotional conflict from its resolution. **Background:** Responses to threat related stimuli are influenced by conscious and unconscious processes, and the neural systems underlying these emotional processes related to anxiety and conflict had been largely unknown. **Findings.** Using functional MRI we discovered that activity in the amygdala and dorsolateral prefrontal cortices reflect emotional conflict[1]. By contrast, however, the resolution of emotional conflict was associated with activation of the rostral cingulate cortex[1]. Further studies revealed distinct neural circuits were engaged during the resolution of non-emotional and emotional conflict[2]. Employment of fearful faces in conscious (perceptible) and unconscious (not perceptible) conditions revealed activation in the basolateral amygdala that was specific to unconscious threat and modulated by anxiety[3]. Further, we discovered patterns of functional connectivity that decoded these subliminally perceived, task irrelevant, affective stimuli[4]. Identification of long-range and interconnected cortical systems actively engaged during subliminal fear processing contributes understanding of the processes for resolution of emotional conflict through top-down inhibition of amygdala by systems that involve the rostral cingulate cortex. **Impact.** These findings provide a biological basis for unconscious emotional vigilance characteristic of anxiety, and a means for investigating the mechanism and efficacy of treatments for anxiety and other psychiatric conditions related to emotional dysregulation such as PTSD and other effects of long-term exposure to violence and stress. For example, the emotional Stroop task has recently been selected by a national consortium study to follow emotional control mechanisms in young children exposed to traumatic events. **Relevance to current work**: This model provides a hypothesis-based approach for current investigations of emotion, conflict, and anxiety in interpersonal interactions. Further, these previous investigations are based on facial expressions which provide the background to investigate dynamic eye-gaze and communication during interactive social behavior in the proposed studies.

1. Etkin, A., Egner, T., Peraza, D.M., Kandel, E.R., Hirsch, J., Resolving emotional conflict: a model for amygdalar modulation by the rostral anterior cingulate cortex, *Neuron*, 51, 871-882, 2006.
2. Egner, T., Etkin, A., Gale, S., Hirsch, J. "Dissociable neural systems resolve conflict from emotional vs. non-emotional distractors," Cerebral Cortex, 18: 1475-1484, June 2000
3. Etkin, A., Klemenhagen, K., Dudman, J., Rogan, M., Hen, R., Kandel, E., Hirsch, J. Individual Differences in Trait Anxiety Predict the Response of the Basolateral Amygdala to Unconsciously Processed Threat, *Neuron*, 2004, Vol 44, 1043-1055.
4. Pantazatos, S.P., Talati, A., Pavlidis, P., Hirsch, J. Cortical functional connectivity decodes subconscious, task-irrelevant threat-related emotion processing, *Neuroimage,* 2012 Mar 28, 61(4):1355-1363. PMCID PMC2293600.

III. Breakthroughs in understanding the biasing of perceptual processes and decision making under conditions of uncertainty and expected utility.

Frame of the problem. Incoming visual information is often ambiguous and binary decisions have to be made with various levels of uncertainty. Neural mechanisms specialized for these functions are fundamental for cognitive function, and yet poorly understood. **Background:** One model of binary perceptual decision making is based on "predictive coding" where perceptual ambiguity is resolved by anticipating a forthcoming stimulus generating a template against which to match an observed case. Prior trial experiences have also been implicated in models of perceptual conflict processing and decision-making emphasizing task relevant information. In cases where uncertainty is not influenced by prior experience, another model proposes modulation of indigenous neural strategies sensitive to uncertainty. Finally, real-world tasks involving moving targets, such as catching a ball, are performed based on continuous decisions thought to depend upon the temporal derivative of some expected utility. We used fMRI to isolate the neural strategies for perceptual biasing in each model. **Findings.** First, perceptual decisions about faces were associated with an increase in top-down connectivity from the frontal cortex to face sensitive visual areas consistent with the matching of predicted and observed evidence for the presence of faces[1]. Second, we discovered that conflict resolution related to face distractors is mediated by amplifying neural representations of task relevant information while inhibiting representations of task irrelevant information[2]. Third, the temporal derivative, and best predictor of a motor response, was mediated by cingulate, inferior parietal lobule and ventral structures of the brain[3], and finally, we discovered a fronto-striatal-thalamic network modulated by categorization uncertainty[4]. **Impact**: Neural models of face processing are extended to include effects of decision making with uncertainty. **Relevance to current work**: The integration of face processing and decision-making with sensory and perception processes guides models of dynamic interactions between individuals where these encoding and response cycles occur rapidly and in parallel. Current investigations of two-person interactions builds upon these prior findings and models of emotion, decision-making, and face-perceptions providing a theoretical background for current work.

1. Summerfield, C., Egner, T., Greene, M., Korchlin, E., Mangels, J., Hirsch, J., Predictive Codes for Forthcoming Perception in the Frontal Cortex, *Science* (111, v.314, no.5803, 1311-1314), 2006.
2. Egner, T., Hirsch, J., Cognitive control mechanisms resolve conflict through cortical amplification of Task-Relevant information, *Nature Neuroscience*, 8 (12), 1784-1790, 2005.
3. Zhang, X., Hirsch, J., The temporal derivative of expected utility: a neural mechanism for dynamic decision-making, *NeuroImage,* 2013 Jan 15, 65:223-30. PMID 22963852.
4. Grinband, J., Hirsch, J., Ferrera, V.P., A neural representation of categorization uncertainty in the human brain, *Neuron*, 2006, 49: 757-763.

IV. Functional connectivity and long-range neural systems as units of communication disability.

Frame of the problem: We and others have shown that prefrontal regions are involved in expectation of visual features such as faces, and these early findings are expanded to models of functional connectivity that account for complex perceptual, emotional, and cognitive functions and dysfunctions**.** Here we test a related set of hypotheses that social deficits in ASD, emotion, and anxiety are associated with specific features of long-range networks. **Background:** Analyses of PsychoPhysiological Interactions, PPI; independent components analyses; dynamic causal modeling; diffusion tensor imaging, DTI; and pattern classifiers based on linear kernel Support Vector Machines, SVM, confirm that visual search processes[1], visual perceptions associated with dual states of ambiguous figures[2], as well as coding of emotional (fearful faces[3]) are well characterized by frontoparietal, fronto-occipital, and default mode networks. **Findings**: Applied to the study of communication disability in ASD, these long-range approaches reveal the novel finding that functional systems associated with speech are more effectively engaged for song than for spoken narratives although the physical projections of the structural pathways were not distinguished from controls[4]. **Impact:** These and related findings contribute to a large and rapidly expanding literature that advance understanding of global and long-range mechanisms and their respective roles in complex cognitive and communication functions as well as developmental disorders. **Relevance to current work**: This extensive background in neuroimaging, cognitive neuroscience, and clinical studies is foundational to the development of similar capabilities using fNIRS and two-person paradigms. Continuing investigations of integrative functions related to the social brain during dynamic and natural interpersonal interactions build upon and extend these segregation and connectivity models of neural systems.

1. Pantazatos, S. Yanagihara, T.K., Meitzler, T., Hirsch, J. Frontal-occipital connectivity during visual search. *Brain Connectivity*, 2012 Aug 6, 2(3):164-75*.* PMID 22708993.
2. Karten A, Pantazatos S, Khalil D, Zhang X, Hirsch J. Brain Connectivity. Dynamic Coupling between the Lateral Occipital Cortex, Default Mode and Frontoparietal Networks During Bistable Perception. Brain Connectivity, 2013. doi:10.1089/brain.2012.011. PMID 23510237.

3. Pantazatos, S.P., Talati, A., Pavlidis, P., Hirsch, J., Decoding unattended fearful faces with whole-brain correlations: an approach to identify condition-dependent large-scale functional connectivity, *PloS Comput. Biol.,* 2012 Mar, 8(3):e1002441. PMCID: PMC3315448.
4. Lai, G., Pantazatos, S.P., Schneider, H., Hirsch, J., Neural systems for speech and song in autism, *Brain*, 2012 Mar, 135(Pt 3):961-75. PMCID: PMC3286324.

V. Two-person Neuroscience: Breakthroughs in understanding the neural basis of real-time, dynamic social interactions and communication. Frame of the problem. Human-to-human interaction and communication engages interactive functions that are mediated by both verbal and non-verbal cues. Although language, auditory, and visual functions are well studied in single brains, the neural mechanisms engaged during the associated across-brain interactive processes are less frequently studied and only partially understood. A novel neuroimaging technology, functional near-infrared spectroscopy (fNIRS), enables, for the first time, tests of the Interactive Brain Hypothesis that broadly predict variation in cognitive mechanisms associated with interpersonal interaction. **Background:** Investigation of social interactions between two individuals extends the theoretical unit of behavior from a single brain to a two-brain unit, the dyad, with a novel focus on communication and interactive protocols. We have addressed challenges of dynamic and natural stimuli associated with rapid and dynamic responses by developing two-person paradigms using hyperscanning and fNIRS with full head coverage of detectors along with computational algorithms validated for isolation of functional brain systems. **Findings:** Spoken language during interaction (as opposed to without interaction) increases activity in the left temporal parietal junction, TPJ (Wernicke's Area), during listening consistent with the hypothesis that TPJ is a neural hub for verbal interactive functions[1]. Similarly in the visual system, real eye-to-eye contact in contrast to mutual eye-gaze focused on a dynamic video of a face activates right TPJ neural systems not activated with simulated faces and eyes[2]. We apply two-person fNIRS to add biological insight to neural coupling and inter brain synchrony[2]. Mechanisms for interactive visual joint-attention were found to be modulated by mutual eye-contact[3]. Findings also led to a new understanding of face processing in ASD based on ventral rather than typical dorsal pathways[4]. **Impact:** These advances provide a "proof of principle" for two-person neuroscience and document the theoretical richness associated with understanding the dynamic interactions between dyads. **Relevance to current work:** Technical and computational tools for fNIRS hyperscanning and the expertise of the investigators are uniquely aligned to support new specific aims of the current proposal.

1. Hirsch J, Tiede M, Zhang X, Noah JA, Salama-Manteau A and Biriotti M (2021) Interpersonal Agreement and Disagreement During Face-to-Face Dialogue: An fNIRS Investigation. Front. Hum. Neurosci. 14:606397. doi: 10.3389/fnhum.2020.606397.
2. Descorbeth, O., Zhang, X. , Noah, J.A., & Hirsch, J. (2020). Neural processes for live pro-social dialogue between dyads with socioeconomic disparity. Social Cognitive and Affective Neuroscience,15(8), 875–887. doi.org/10.1093/scan/nsaa120
3. Dravida S., Noah J.A., Zhang X., & Hirsch J. (2020). Joint attention during live person-to-person contact activates rTPJ, including a sub-component associated with spontaneous eye-to-eye contact. Frontiers in Human Neuroscience, 14(201). doi: 10.3389/fnhum.2020.00201. PMCID: PMC7283505
4. Zhang, X., Noah, J.A., Singh, R. et al. Support vector machine prediction of individual Autism Diagnostic Observation Schedule (ADOS) scores based on neural responses during live eye-to-eye contact. Sci Rep 14, 3232 (2024). doi.org/10.1038/s41598-024-53942-z