BIOGRAPHICAL SKETCH

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NAME: Müller, Ralph-Axel

eRA COMMONS USER NAME (credential, e.g., agency login): RMUELLER

POSITION TITLE: Professor

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
J.W. Goethe University, Frankfurt/Main (Germany)	M.A.	05/1984	Linguistics
J.W. Goethe University, Frankfurt/Main (Germany)	Ph.D.	01/1991	Neurolinguistics

A. Personal Statement

My work has been in the field of developmental cognitive neuroscience since the early 1990s, specifically through the use of neuroimaging techniques (PET and later fMRI) to study typical development and developmental disorders. I have been involved in imaging research on autism spectrum disorder (ASD) for about 20 years, being among the first ASD investigators to publish in the field of functional activation imaging as well as in functional connectivity MRI. My more recent work has expanded to additional MRI modalities including diffusion tensor imaging and tractography, anatomical volumetrics, and MR spectroscopy, specifically with the aim of more comprehensive characterization of local cortical and distributed network abnormalities in ASD. Aside from those cited in Section C, further relevant publications (selected from a total of 86 peer-reviewed journal publications) are:

a. Cardinale, RC, Shih, P, Fishman, I, Ford, LM & Müller, R-A. Pervasive rightward asymmetry shifts of functional networks in autism spectrum disorder: An fMRI study using independent component analysis. *JAMA Psychiatry* 70, 975-82 (2013). http://www.ncbi.nlm.nih.gov/pubmed/23903586
b. Keehn, B, Shih, P, Brenner, L, Townsend, J & Müller, R-A. Functional connectivity for an "island of sparing" in autism spectrum disorder: An fMRI study of visual search. *Human Brain Mapping* 34, 2524-2537 (2013). http://www.ncbi.nlm.nih.gov/pubmed/22495745
c. Abbott, A.E., Nair, A., Keown, C.L., Datko, M.C., Jahedi, A., Fishman, I. & Müller, R.-A. (2015) Patterns of atypical functional connectivity and behavioral links in autism differ between default, salience, and executive networks. *Cerebral Cortex.* E-pub. http://www.ncbi.nlm.nih.gov/pubmed/26351318
d. Carper, R.A., Treiber, J.M., Yandall DeJesus, S. & Müller, R.-A. (in press) Reduced Hemispheric Asymmetry of White Matter Microstructure in Autism Spectrum Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. E-pub. http://www.sciencedirect.com/science/article/pii/S0890856716317373

B. Positions and Honors

1994 - 1995 Research Fellow, PET Center, Children's Hospital of Michigan, Detroit
1995 - 1998 Assistant Professor of Pediatrics, Wayne State University Medical School, Detroit
1998 - 2010 Research Scientist, Dept. of Cognitive Science, University of California at San Diego
2001 - 2004 Assistant Professor, Dept. of Psychology, San Diego State University
2001 - Doctoral faculty, Clinical Psychology, SDSU & UCSD
2002 - Doctoral faculty, Language & Communicative Disorders, SDSU & UCSD
2004 - 2008 Associate Professor, Dept. of Psychology, San Diego State University
2008 - Professor, Dept. of Psychology, San Diego State University
2013- Doctoral faculty, Computational Science, SDSU & Claremont University
2015 - Associate Editor, *Autism Research*

C. Contributions to Science

(1) **Brain plasticity and reorganization in children**: Work originating from my doctoral dissertation was motivated by dissatisfaction with the dominant school of linguistic thinking (based on N. Chomsky and J. Fodor) that viewed language as an autonomous mind/brain 'module', fully predetermined by genetic

information. In an extensive review of relevant cognitive neuroscience literature[a] I showed that such thinking was deeply flawed because it disregarded known experience-driven principles of neuroplasticity. In 1994, I began to directly test functional brain plasticity in children with early brain damage, using positron emission tomography. My studies were among the first to demonstrate functional reorganization of language and motor functions into the right hemisphere, following early left hemisphere damage.[b,c] These studies were also among the first human neuroimaging studies showing greater plasticity and reorganization following early, compared to later, lesion onset.[d]

a. Müller, R-A. Innateness, autonomy, universality? Neurobiological approaches to language. *Behavioral and Brain Sciences* 19, 611-631 (1996). http://dx.doi.org/10.1017/S0140525X00043405
b. Müller, R-A, Chugani, HT, Muzik, O, Rothermel, RD & Chakraborty, PK. Language and motor functions activate calcified hemisphere in patients with Sturge-Weber syndrome: a positron emission tomography study. *Journal of Child Neurology* 12, 431-437 (1997). http://www.ncbi.nlm.nih.gov/pubmed/9373799
c. Müller, R-A, Rothermel, RD, Behen, ME, Muzik, O, Mangner, TJ & Chugani, HT. Differential patterns of language and motor reorganization following early left hemisphere lesion: a PET study. *Archives of Neurology* 55, 1113-1119 (1998). http://www.ncbi.nlm.nih.gov/pubmed/9708962
d. Müller, R-A, Rothermel, RD, Behen, ME, Muzik, O, Chakraborty, PK & Chugani, HT. Language organization in patients with early and late left hemisphere lesion: a PET study. *Neuropsychologia* 37, 545-57 (1999). http://www.ncbi.nlm.nih.gov/pubmed/10340314

(2) **Sensorimotor roots of aberrant plasticity in autism**: Since 1998, I have continued my studies of developmental disorders and brain plasticity in children using functional MRI and other MRI techniques, with increasing focus on autism spectrum disorder (ASD). Much of the work done since then has been dedicated to the study of potential sensorimotor bases of sociocommunicative impairment in ASD. Mine were the first fMRI studies to show atypical brain organization for simple[a] and more complex motor functions.[b,c] These studies were also among the first to document a high level of inter-individual variability of functional maps in ASD. Recent machine learning diagnostic classification work from my group,[d] which achieved higher prediction accuracy than any previous functional connectivity MRI (fcMRI) machine learning study of ASD, has again highlighted the importance of anomalous sensorimotor functioning. Specifically, this study showed that atypical connectivity of somatosensory and motor regions (especially postcentral gyri) was most informative for correct diagnostic classification (ASD vs. typically developing).

a. Müller, R-A, Pierce, K, Ambrose, JB, Allen, G & Courchesne, E. Atypical patterns of cerebral motor activation in autism: a functional magnetic resonance study. *Biological Psychiatry* 49, 665-76 (2001). http://www.ncbi.nlm.nih.gov/pubmed/11313034
b. Müller, R-A, Kleinhans, N, Kemmotsu, N, Pierce, K & Courchesne, E. Abnormal variability and distribution of functional maps in autism: an FMRI study of visuomotor learning. *American Journal of Psychiatry* 160, 1847-62 (2003). http://www.ncbi.nlm.nih.gov/pubmed/14514501
c. Müller, R-A, Cauich, C, Rubio, MA, Mizuno, A & Courchesne, E. Abnormal activity patterns in premotor cortex during digit sequence learning in autistic patients. *Biological Psychiatry* 56, 323-332 (2004). http://www.ncbi.nlm.nih.gov/pubmed/15336514
d. Chen, CP, Keown, CL, Jahedi, A, Nair, A, Pflieger, ME, Bailey, BA & Müller, R-A. Diagnostic classification of intrinsic functional connectivity highlights somatosensory, default mode, and visual regions in autism. *Neuroimage: Clinical* 8, 238-245 (2015). http://www.ncbi.nlm.nih.gov/pubmed/26106547

(3) **Overconnectivity in ASD linked to symptomatology**: Since the mid-2000s, my group's fMRI work has expanded into network connectivity. My group was among the first to use functional connectivity MRI (fcMRI) in ASD.[a] One prominent contribution of our work was to correct the long-standing misperception of general underconnectivity in ASD as a firm finding. While our initial work (e.g., ref.[b]) was considered either unbelievable or heretical, our studies have made strong contributions to a changing view of connectivity in ASD that goes beyond simple underconnectivity (see below). In more recent studies,[c,d] we were able to show that atypical neurofunctional organization in ASD is characterized by reduced local functional differentiation (specialization), linked to measures of cortical thickness, and atypical diffuse (out-of-network) overconnectivity, associated with symptom severity.

a. Villalobos, ME, Mizuno, A, Dahl, BC, Kemmotsu, N & Müller, R-A. Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism. *Neuroimage* 25, 916-925 (2005). http://www.ncbi.nlm.nih.gov/pubmed/15808991

b. Mizuno, A, Villalobos, ME, Davies, MM, Dahl, BC & Müller, R-A. Partially enhanced thalamo-cortical functional connectivity in autism. *Brain Research* 1104, 160-74 (2006). http://www.ncbi.nlm.nih.gov/pubmed/16828063
c. Shih, P, Keehn, B, Oram, JK, Leyden, KM, Keown, CL & Müller, R-A. Functional differentiation of posterior superior temporal sulcus in autism: A functional connectivity magnetic resonance imaging study. *Biological Psychiatry* 70, 270-7 (2011). http://www.ncbi.nlm.nih.gov/pubmed/21601832
d. Fishman, I, Datko, M, Cabrera, Y, Carper, RA & Müller, R-A. Reduced integration and differentiation of the imitation network in autism: A multimodal fcMRI and DWI study. *Annals of Neurology* 78, 958-69 (2015). http://www.ncbi.nlm.nih.gov/pubmed/26418284

(4) **The dual impairment model of ASD**: Prompted by an extensive series of findings from my lab showing either mixed patterns of functional under- and overconnectivity or even exclusive and widespread overconnectivity in ASD (presented in a total of 15 independent peer-reviewed publications since 2006; e.g. ref.[a]), we proposed a *dual impairment model*, which reconciles under- and overconnectivity findings found in the literature as reflections of impaired constructive and regressive neurodevelopmental mechanisms resulting in reduced 'network sculpting'.[b] Several of these studies have shown links between functional overconnectivity and symptom severity. For example, in one study examining local density of functional connections we found that local overconnectivity in striate and extrastriate visual cortices was significantly correlated with social behavioral impairment and repetitive behavior scores on the Autism Diagnostic Observation Schedule in children and adolescents with ASD.[c] In another study, we found that overconnectivity ('cross-talk') between mirror neuron system and theory of mind network was correlated with social impairment based on scores from the Autism Diagnostic Interview.[d]

a. Khan, AJ, Nair, A, Keown, CL, Datko, MC, Lincoln, AJ & Müller, R-A. Cerebro-cerebellar resting state functional connectivity in children and adolescents with autism spectrum disorder. *Biological Psychiatry* 78, 625-34 (2015). http://www.ncbi.nlm.nih.gov/pubmed/25959247
b. Müller, R-A, Shih, P, Keehn, B, Deyoe, JR, Leyden, KM & Shukla, DK. Underconnected, but how? A survey of functional connectivity MRI studies in autism spectrum disorders. *Cerebral Cortex* 21, 2233-43 (2011). http://www.ncbi.nlm.nih.gov/pubmed/21378114
c. Keown, CL, Shih, P, Nair, A, Peterson, N & Müller, R-A. Local functional overconnectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. *Cell Reports* 5, 567-72 (2013). http://www.ncbi.nlm.nih.gov/pubmed/24210815
d. Fishman, I, Keown, CL, Lincoln, AJ, Pineda, JA & Müller, R-A. Atypical Cross Talk Between Mentalizing and Mirror Neuron Networks in Autism Spectrum Disorder. *JAMA Psychiatry* 71, 751-60 (2014). http://www.ncbi.nlm.nih.gov/pubmed/24740586

(5) **Methodological advances in connectivity science of ASD**: My group has also made methodological contributions advancing autism connectivity research. A major contribution to the field was our ability to attribute many previous inconsistencies in the ASD functional connectivity literature to differences between *co-activation* and *intrinsic* fcMRI. Following a meta-analysis of the fcMRI literature (ref. 4b), we tested the emerging methodological patterns empirically in three independent ASD and TD datasets that were analyzed along competing pipelines.[a] Rather startlingly, this study showed that an identical dataset may yield under- or overconnectivity findings depending on crucial data processing and analysis choices. Focus on task-driven signal correlations in regions of interest tended to yield underconnectivity effects in ASD groups, whereas focus on intrinsic (spontaneous, non task-related) low-frequency signal fluctuations tended to yield overconnectivity, in particular outside domain-specific regions of interest. A related methodological issue concerns the links between functional and anatomical assays of connectivity. Our group has been among the first to use multimodal techniques in the investigation of connectivity in ASD, by combining diffusion tensor imaging (DTI) and fcMRI. In several recent studies,[c-d] we were able to show that fcMRI and DTI effects in thalamo-cortical connectivity and connectivity of primary motor cortex do not always coincide and that, in particular DTI is relatively insensitivity to architectural differences associated with functional overconnectivity.

a. Nair, A, Keown, CL, Datko, M, Shih, P, Keehn, B & Müller, RA. Impact of methodological variables on functional connectivity findings in autism spectrum disorders. *Human Brain Mapping* 35, 4035-48 (2014). http://www.ncbi.nlm.nih.gov/pubmed/24452854

b. Nair, A, Treiber, JM, Shukla, DK, Shih, P & Müller, R-A. Thalamocortical connectivity in autism spectrum disorder: A study of functional and anatomical connectivity. *Brain* 136, 1942-55 (2013). http://www.ncbi.nlm.nih.gov/pubmed/23739917
c. Nair, A., Keown, C.L., Datko, M., Shih, P., Keehn, B. & Müller, R.A. (2014) Impact of methodological variables on functional connectivity findings in autism spectrum disorders. *Human Brain Mapping, 35*(8), 4035-48. http://www.ncbi.nlm.nih.gov/pubmed/24452854
d. Carper, RA, Solders, S, Treiber, JM, Fishman, I & Müller, R-A. Corticospinal tract anatomy and functional connectivity of primary motor cortex in autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry* 54, 859-67 (2015). http://www.ncbi.nlm.nih.gov/pubmed/26407496

Google Scholar Publication Listing:
https://scholar.google.com/citations?user=HDqmYiUAAAAJ&hl=en&oi=ao
https://scholar.google.com "Ralph-Axel Müller" [public profile]

D. Research Support

Current

R01 MH101173 — Total direct cost: $2,588,440
Role: PI — Effort: 4.8 CY months
NIMH — 8/2014-7/2019
"Integrity and Dynamic Processing Efficiency of Networks in ASD"
This project implements functional MRI, magnetoencephalography, and diffusion tensor imaging to examine the temporal dynamics and anatomical substrates of functional connectivity for visual, lexico-semantic, executive, and motor processing in adolescents with autism spectrum disorder and typically developing adolescents.

R01MH103494 — Total direct cost: $2,500,000
Role: PI — Effort: 4.2 CY months
NIMH — 5/1/2015 - 4/30/2020
"The Autistic Brain Over 45: The Anatomic, Functional, and Cognitive Phenotype"
A longitudinal examination of neuroanatomical, neurofunctional, and cognitive aging in 45-65 year olds with Autism Spectrum Disorder. MRI methods include anatomical, diffusion, and functional connectivity approaches.

R01 MH107802-01 (PI: Fishman) — Total Direct Costs: c. $1,700,000
Role: Co-investigator — Effort: 1.2 CY months*
NIMH — 9/01/2015 – 08/31/2020
"Multimodal Imaging of Early Neural Signature in Autism Spectrum Disorder"
The major goals longitudinal multimodal imaging study are to fully characterize the function, as well as macro- and micro-structure of cortical networks in 18-24 month old toddlers who exhibit first behavioral signs of ASD as compared to age-matched typically developing (TD) peers, and to examine changes in brain network organization from the age of the first symptom onset through the full symptom manifestation at age 4-5 years.

Note: If present proposal is funded, PI will reduce his effort slightly on the above grants and the present one and funding will instead be applied to additional postdoctoral support.

Recently Completed

1R21 MH102558-01 — Total direct cost: $275,000
Role: PI (Co-PI: T. Liu) — Effort: 1.8 CY months
NIMH — 6/2014-5/2016
"FMRI and EEG approaches to the 'resting state' in ASD"
This project uses combined EEG and functional MRI, acquired at high temporal resolution, to investigate potential differences in cognitive condition during the resting state in adolescents with autism spectrum disorder and matched typically developing participants.

1K01 MH097972-01A1 — Total direct cost: $598,951
Role: Mentor (PI: Inna Fishman) — [No salaried effort]
NIMH — 09/05/2012 – 05/31/2016
"Multimodal Imaging of Social Brain Networks in ASD"

This mentored career award aims to outfit a new investigator with expertise necessary for examining the neural bases of social impairments in autism, specifically focusing on the integrity of connections among distributed brain regions in autism.

1R01 MH081023 — Total direct cost: $1,364,001
Role on project: PI — Effort: 4.8 CY months
NIMH — 2/2009-1/2015

"Linking local activity and functional connectivity in autism"
This project investigates potential links between impaired local cortical architecture and atypical functional and anatomical connectivity in autism, using functional MRI, functional connectivity MRI, and diffusion-tensor imaging.

Grant AR093335 — Total direct cost: $490,233
Role: Subcontract P.I. (PI: Jaime Pineda, UCSD)
CDMRP — 6/2010 – 7/2013

"Improving Synchronization and Functional Connectivity in Autism Spectrum Disorders Through Plasticity Induced Rehabilitation Training"
This project used biofeedback to train children with autism spectrum disorders (ASD) to learn mu suppression during a variety of observation tasks, with the goal of determining whether significant training in mu suppression correlates with behavioral, neuropsychological, and neurological improvement.