Project title:

Biological mechanisms of sensory selectivity in autism spectrum condition: Pupillary responses as index of locus coeruleus norepinephrine (LC-NE) system activity in event-related potential (ERP) to oddball stimuli

Name and details of lead and senior investigators, and all co-investigators:

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Abstract, including goals and proposed methods:

A central function of the brain is sensory processing, i.e. the translation of input to neural representations. Sensory processing serves as a pre-attentive input filter by amplifying the neural representations of salient stimuli and weakening the neural representations of irrelevant stimuli, also known as sensory selectivity [1]. Sensory selectivity raised research interest with the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) that introduced altered sensory reactivity as ASD symptom.

Sensory selectivity has primarily been investigated by electroencephalography (EEG). Event-related potentials (ERPs) can be recorded during an oddball task that infrequently presents deviating and thus salient stimuli ("oddballs") in a series of frequent stimuli. The resulting P3b component is associated with contextual updating [2], whereas the resulting Mismatch Negativity (MMN) is associated with auditory change detection [3]. In ASD, altered sensory selectivity has been indicated in meta-analyses by attenuated P3b amplitude to visual/auditory oddballs and MMN to non-speech auditory oddballs [3, 4]. In addition, some studies reported attenuated neurophysiological habituation to frequent stimuli [5, 6]. Together, these findings suggest decreased sensory selectivity to salient stimuli and increased sensory selectivity to frequent stimuli in ASD.

Sensory selectivity is regulated by neurotransmitters released via brainstem neuro-modulatory systems [7]. A key mechanism is neural gain adaptation, which is a change in the input-output relationship of neuronal firing [8]. The Locus-Coeruleus-Norepinephrine (LC-NE) system induces a decrease of spontaneous and an increase of input-driven neuronal firing via norepinephrine (NE, figure

1) [9]. This unique effect on neural gain adaptation is specific to LC- NE activity as it increases the signal-to-noise ratio in synaptic transmission ('high gain') [11, 12]. High gain is expected to cause a positive feedback loop of NE and glutamate release in local circuits that amplifies sensory processing of salient stimuli [4]. Thus, LC-NE activity causes high gain in response to salient stimuli, which provides an underlying mechanism of sensory selectivity on the cortical neuronal level [13].

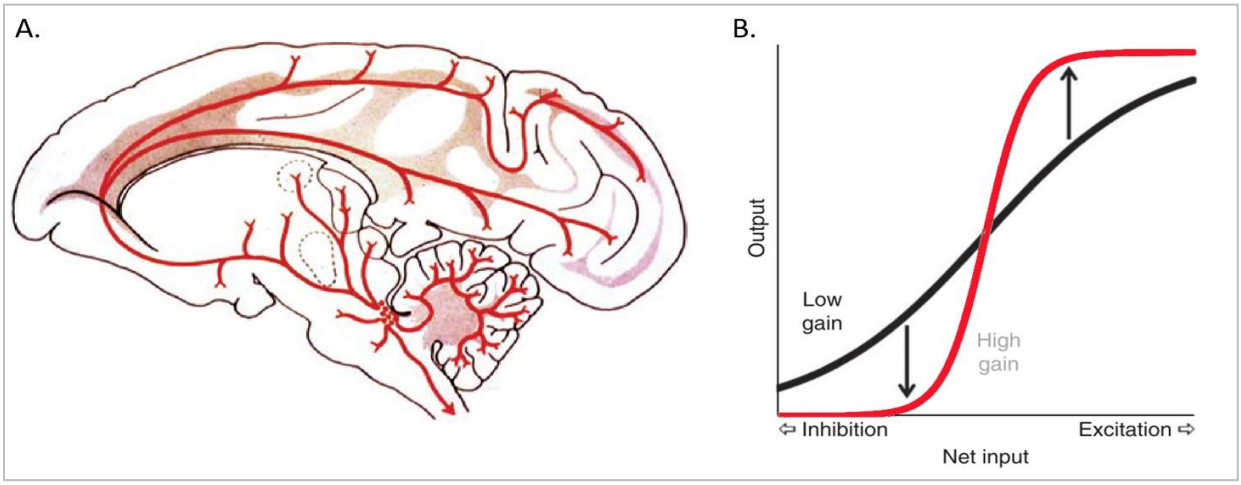

Figure 1. *A. The Locus-Coeruleus (LC, red dot cluster) in the macaque brain and its projections that provide cortical norepinephrine (NE) and constitute the LC-NE system (Aston-Jones & Cohen 2005). B. Change in neural gain adaptation by phasic LC-NE activity ('high gain'). X-axis = neuronal input, Y-axis: neuronal output (Eldar et al. 2013).*

LC-NE activity is indexed by pupillary responses in video-based eye tracking [10-12]. Previous research of my research group showed altered pupillary responses in ASD were associated with quantitative autism phenotypes like an attenuated preference for biological motion [13], a different memory retrieval [14], and slower reaction times in orienting attention [15]. In addition, an independent research group showed attenuated pupillary responses to oddballs in children with ASD [16]. These pupillometry findings suggest a different adaptation of LC-NE activity in ASD that might further explain atypical sensory selectivity in ASD [17].

The overall aim of the proposed study is thus to assess effects of LC-NE phasic activity on sensory selectivity in a group comparison of ASD and neurotypical controls. In the EU-AIMS LEAP sample, we want to utilize the combined eye-tracking and electroencephalography (EEG) data during the auditory oddball task. We will apply stimulus-evoked pupillary responses (SEPR) to oddballs as index of LC-NE activity. In addition, we utilize principal component analysis to decompose pupillary responses into distinct response factors that might represent differential underlying neurophysiological processes that modulate LC-NE activity [18, 19]. We will further apply P3b and MMN as index of sensory selectivity. In linear mixed model, we will estimate effects of LC-NE activity on sensory selectivity on the per trial level. We hypothesize:

a) Positive associations of LC-NE activity and P3b or MMN to oddball stimuli across groups
b) Attenuated LC-NE activity (SEPR) to oddball stimuli in ASD compared to TD
c) Attenuated sensory selectivity (P3b, MMN) to oddball stimuli in ASD compared to TD
d) LC-NE activity explains group differences in sensory selectivity

In preliminary data on combined pupillometry and EEG (n=10), we showed the feasibility on the association of LC-NE activity (SEPR) and sensory selectivity (P3b) on per-trial level in a Posner-type orienting task (see figure 2).

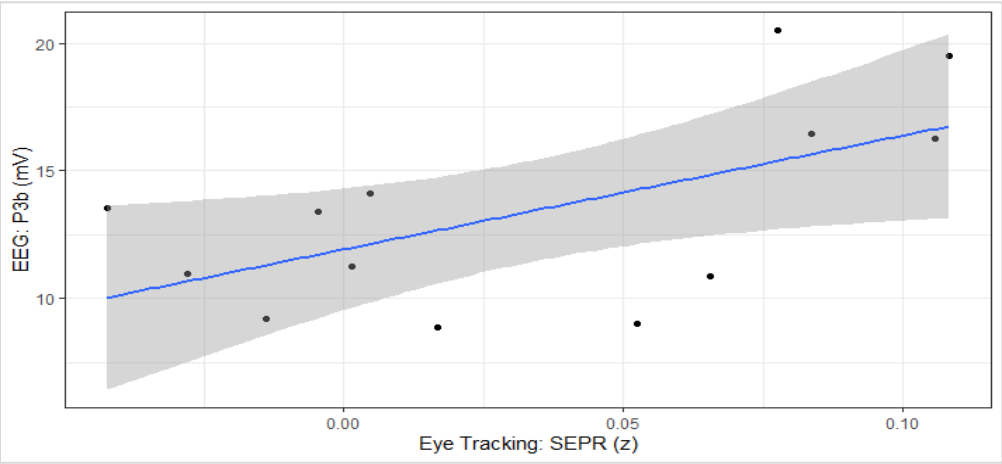

Figure 2. Scatterplot of Stimulus-evoked Pupillary Response (SEPR) and P3b amplitude per subject. Blue line indicates linear fit and grey shade indicates error margin.

Measures / Data requested

- Eye-tracking data of the mismatch negativity / oddball task
- Electroencephalography data of the mismatch negativity / oddball taks
- Demographic / Phenotype data of the EU-AIMS LEAP sample (Wave 1)

Type of project

- Post-doc research project

Approximate Start / End data

- Start date: end of 2022
- End date: end of 2023

Brief data management plan to ensure that downloaded AIMS-LEAP data will be securely stored

All data downloaded from the Pasteur server will be securely stored within our on-premise science net. In line with the European Data Protection Directive (DSGVO), personally identifiable information (PII) will be strictly separated from the research data and can only be linked by a personal identification code (PIC). PII including PIC codes is stored on a separate network located in the clinical net of the University Hospital that fulfills the highest data protection requirements according to European standards. Research data is stored in a pseudonymized way in the science net of the department, which is physically separate from the clinical net. Research databases are professionally administrated by a database manager and fulfil DSGVO standards. Data can only be accessed by research staff directly associated with the project (primary investigators, doctoral researchers) and is backup-ed automatically.

Literature

1. Mather, M., et al., *Norepinephrine ignites local hotspots of neuronal excitation: How arousal amplifies selectivity in perception and memory.* Behavioral and Brain Sciences, 2016. **39**: p. e200-e200.
2. Polich, J., *Updating P300: an integrative theory of P3a and P3b.* Clinical neurophysiology, 2007. **118**(10): p. 2128-2148.
3. Schwartz, S., B. Shinn-Cunningham, and H. Tager-Flusberg, *Meta-analysis and systematic review of the literature characterizing auditory mismatch negativity in individuals with autism.* Neuroscience & Biobehavioral Reviews, 2018. **87**: p. 106-117.
4. Cui, T., et al., *P300 amplitude and latency in autism spectrum disorder: a meta-analysis.* European Child & Adolescent Psychiatry, 2016: p. 1-14.
5. Guiraud, J.A., et al., *Differential habituation to repeated sounds in infants at high risk for autism.* Neuroreport, 2011. **22**(16): p. 845-849.
6. Kolesnik, A., et al., *Increased cortical reactivity to repeated tones at 8 months in infants with later ASD.* Translational psychiatry, 2019. **9**(1): p. 1-11.
7. Jacob, S.N. and H. Nienborg, *Monoaminergic neuromodulation of sensory processing.* Frontiers in neural circuits, 2018. **12**: p. 51.
8. Ferguson, K.A. and J.A. Cardin, *Mechanisms underlying gain modulation in the cortex.* Nature Reviews Neuroscience, 2020. **21**(2): p. 80-92.
9. Thiele, A. and M.A. Bellgrove, *Neuromodulation of attention.* Neuron, 2018. **97**(4): p. 769-785.
10. Megemont, M., J. McBurney-Lin, and H. Yang, *Pupil diameter is not an accurate real-time readout of locus coeruleus activity.* eLife, 2022. **11**: p. e70510.
11. Joshi, S., et al., *Relationships between Pupil Diameter and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex.* Neuron, 2016. **89**(1): p. 221-234.
12. Murphy, P.R., et al., *Pupil diameter covaries with BOLD activity in human locus coeruleus.* Human brain mapping, 2014. **35**(8): p. 4140-4154.
13. Polzer, L., C.M. Freitag, and N. Bast, *Pupillometric measures of altered stimulus-evoked locus coeruleus-norepinephrine activity explain attenuated social attention in preschoolers with autism spectrum disorder.* Autism Research, 2022. **n/a**(n/a).
14. Bast, N., et al., *Arousal-modulated memory encoding and retrieval in adults with autism spectrum disorder.* Autism Research, 2022. **15**(9): p. 1609-1620.
15. Bast, N., et al., *Atypical Arousal Regulation in children with Autism but not with ADHD as indicated by pupillometric measures of Locus Coeruleus Activity.* Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2021.
16. Zhao, S., Y. Liu, and K. Wei, *Pupil-Linked Arousal Response Reveals Aberrant Attention Regulation among Children with Autism Spectrum Disorder.* Journal of Neuroscience, 2022.
17. Bast, N., L. Poustka, and C.M. Freitag, *The locus coeruleus - norepinephrine system as pacemaker of attention - A developmental mechanism of derailed attentional function in autism spectrum disorder.* European Journal of Neuroscience, 2018. **47**(2): p. 115-125.
18. Bast, N., et al., *Pupil Dilation Progression Modulates Aberrant Social Cognition in Autism Spectrum Disorder.* Autism Research, 2019.
19. Wetzel, N., et al., *Infant and adult pupil dilation in response to unexpected sounds.* Developmental psychobiology, 2016. **58**(3): p. 382-392.