**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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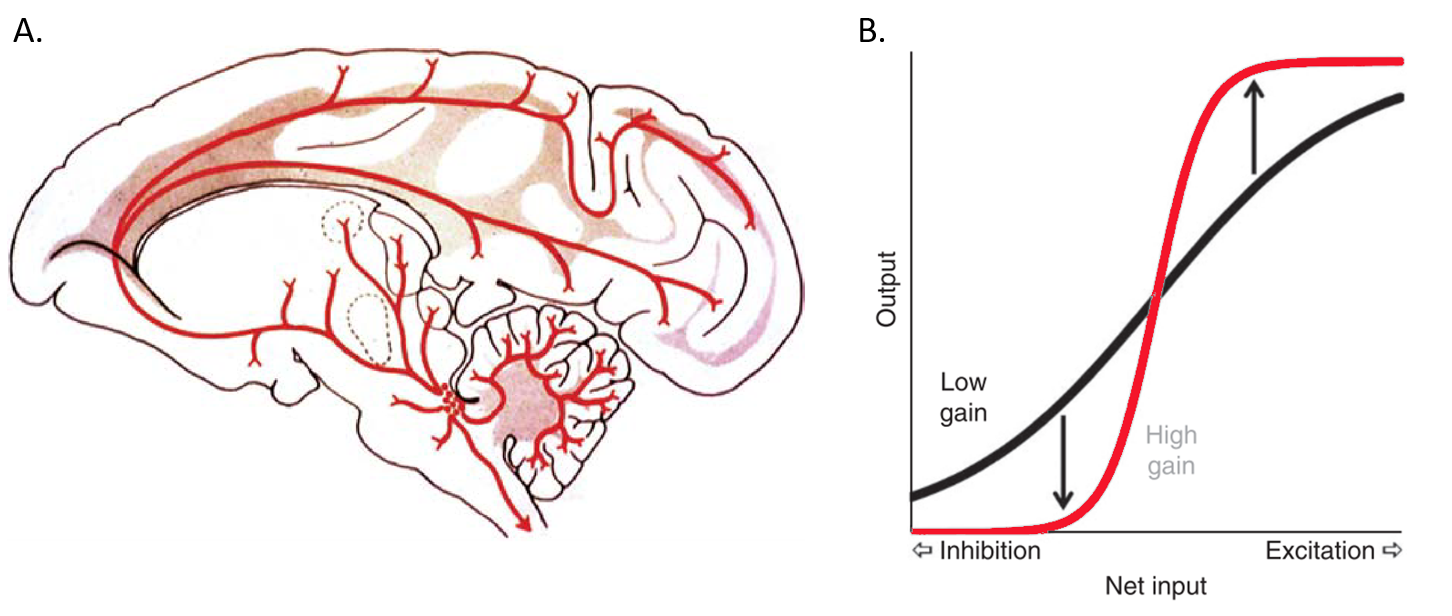
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**Abstract, including goals and proposed methods:**

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].



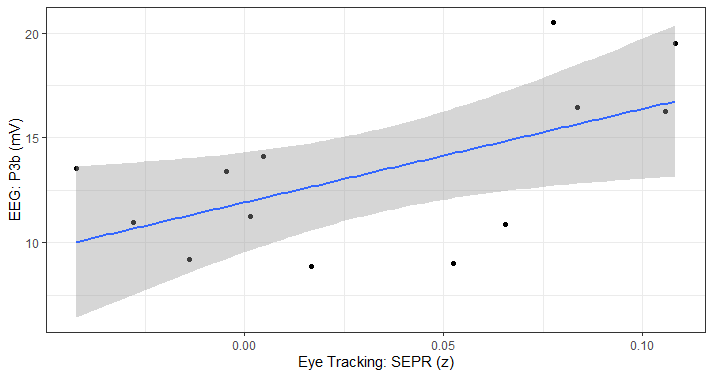
***Figure 1.*** *A. The Locus-Coeruleus (LC, red dot cluster) in the macaque brain and its projections that provide cortical norepinephrine (NE) and constitute the LC-NE system (Aston-Jones & Cohen 2005). B. Change in neural gain adaptation by phasic LC-NE activity (‘high gain’). X-axis = neuronal input,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

1. Positive associations of LC-NE activity and P3b or MMN to oddball stimuli across groups
2. Attenuated LC-NE activity (SEPR) to oddball stimuli in ASD compared to TD
3. Attenuated sensory selectivity (P3b, MMN) to oddball stimuli in ASD compared to TD
4. 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.

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