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INTRINSIC ACTIVITY

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*MEETING ABSTRACT*

## A2.5

### Neuronal activation patterns following interoceptive stimulation: role of high trait anxiety

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**Background:** Emotions are influenced by one's internal state of bodily arousal via interoception. It is reported that interoception is altered in anxiety disorders which are the most prevalent psychiatric disorders with approximately 25% of the population being affected during their lifetime. For example, the subjective and physiological responses to $CO_2$ inhalation are elevated in subjects with high trait anxiety compared to those with normal anxiety [1]. Yet, although altered interoception is increasingly recognized as an important component of anxiety-related disorders, its underlying neural mechanisms remain insufficiently understood. In the present study, we aimed to elucidate whether differences in trait anxiety levels determine the engagement of the anxiety network in response to $CO_2$ challenge.

**Methods:** Mice selectively bred for high (HAB) and normal (NAB) anxiety-related behavior of both sexes were habituated to the test arena and exposed for 10 minutes to either $CO_2$-enriched (10%) or synthetic atmospheric air on the next day. Locomotor activity and anxiety-related parameters were analyzed during the test period. Using immunohistochemistry, neuronal activation patterns were assessed by mapping the expression of the immediate early genes c-Fos and Zif268 in the cortex, hypothalamus and amygdala of HABs and NABs.

**Results:** Relative to chamber or air control conditions, $CO_2$ reduced locomotor activity and increased anxiety-related parameters in the test arena. These behavioral effects were associated with altered expression of c-Fos and/or Zif268 in the central and basolateral amygdala, key brain areas of the anxiety neurocircuitry. HAB mice displayed behavioral hyperresponsivity to the test challenges and increased neuronal activation of hypothalamic nuclei including the paraventricular hypothalamus. Furthermore, we obtained the first evidence that neuronal activation of the insula and hypothalamus, along the rostro-caudal axis, differed between HAB and NAB mice. Sex differences in behavior and neuronal activation patterns were also revealed.

**Discussion:** Here, we demonstrate that the $CO_2$-induced anxiogenic effects in mice were associated with altered neuronal activation of the amygdala, particularly of the central amygdala, the major output nucleus that plays a pivotal role in promoting anxiety-related behavioral responses. These data support the translational value of the paradigm in assessing negative valence. The observed greater effect of $CO_2$ on behavioral responses in the high anxiety HAB mice is in line with human studies showing that anxious individuals are hypersensitive to $CO_2$. Altered engagement of the hypothalamic stress centers and the insula is suggested to represent neuronal correlates of behavioral hypersensitivity to $CO_2$ of anxiety-prone subjects. Detailed characterization of affected neurons is ongoing.

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**Keywords:** anxiety – hypercapnia – interoception – mouse model

**Reference:**

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