SUPPLEMENTARY MATERIALS for the paper

**The current view on THE PARADOX OF PAIN IN AUTISM SPECTRUM DISORDERS**

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| **Supplementary table 1. General pathways of pain perception and regulation**  |
| **Nociception** (1–3). |
| **Nociceptors: activation of** the first order sensory neurons with two different types of axons\*: * rapid, myelinated ***Aδ (A-delta)*** fiber axons; acute pain transmission
* slow, ***non-myelinated C fiber*** axons with slow adaptation, pain sensitization and hyperalgesia

\*recently ultra-fast myelinated, type A pain sensitive neurons were discovered in humans |
| **From nociceptors to the brain** (1,2,4–7) |
| First-order neurons connect to the second order cells on the spinal cord. There are two main pain ascending pathways (mostly contralateral):* ***spinothalamo-cortical pathway*** that processes the discriminative aspects of pain (to the thalamus)
* ***spinoparabrachial-amygdala(-limbic) pathway*** that processes the affective-motivational aspects of pain (to PeriAqueductal Gray (PAG) matter of the midbrain, the lateral parabrachial area in the pons, amygdala and others nuclei)
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| **The high-level processing of pain**  (8–17)  |
| Second-order neurons connect to third-order neurons, which project to upper brain areas: ***“the pain matrix”:*** the *primary somatosensory cortex* (*S1):* direct somatotopic input from the thalamus; *the secondary somatosensory cortex (S2), the insula, cingulate, orbitofrontal and prefrontal cortices, and the amygdala:* * nociceptive information simultaneously reaches sensory, motor and limbic regions of the brain, with a specific hierarchy in their activation:

***-first order brain area: ‘the nociceptive matrix’:*** sensory (*the primary somatosensory cortex*, *the* *posterior insula, adjacent suprasylvian operculum, and posterior parietal regions)* and motor-orienting *(the posterior midcingulate and supplementary motor area)* * + bodily pain perception and rapid pre-motor and orienting response; manipulation may induce pain or selective loss of nociception, may be unconsciously activated

***-second order brain area: ‘the salience matrix’:*** *posterior parietal, prefrontal and anterior insular areas:* * + transition from the ‘nociceptive matrix’ activation to conscious pain perception

***-third-order brain areas:*** *anterolateral and orbitofrontal, ventral tegmental and perigenual /limbic* areas:* + initial pain experience modified by cognitive, affective and motivational factors
	+ impact of autobiographical memory and self-reference integration, s*elf-consciousness,* proper pain perception and localization, emotional components of pain perception, pain expectation and expression
 |
| **Chronic pain** (18) |
| Pain chronification leads to increase in connectivity between somatosensory brain areas and the self-representational Default Mode Network brain regions (*the medial prefrontal cortex*, *posterior cingulate cortex*, *inferior parietal cortex* and *precuneus*)(19–21), misbalance between pain pathways and embodiment of pain (18). |
| **Pain regulation** (1,4,6,22,23)  |
| In the ***corticofugal pathway*** the pain-associated brain areas project descending axons towards the rostral ventromedial medulla, the dorsolateral pontomesencephalic tegmentum, and PAG towards the *dorsal horn of spinal cord.* Pain down-regulation may be inhibitory and excitatory:* Descending projections from *S1, cingulate and insular* cortex facilitate sensory transmission, provoking pain hypersensitivity and/or maintaining chronic pain
* *ventro-medial prefrontal cortex,* possesses antinociceptive effects via down-regulation of other pain-sensitive brain areas and modulates of ascending pain signals via *PAG*-dependentpathway

***PAG*** receives inputs from thalamus, hypothalamus and cortex and sends direct and indirect projections to *reticular formation, several structures of midbrain, thalamus, and ventral tegmental area and substantia nigra*. Stimulation of PAG produces profound analgesia by anti-nociceptor inputs to *nucleus raphe magnus*, which projecting to the spinal cord and block there pain stimuli transmission, but it may also facilitate nociceptive signal transduction. |

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| **Supplementary table 2. Abbreviations used in the paper text** |
| ASD | Autism spectrum disorder |
| CFCS | the Child Facial Action Coding System for children |
| CNS | central nervous system |
| CPM | Conditioned Pain modulation |
| CT fibers | C-tactile fibers |
| DMN | default mode network |
| DNIC | Diffuse Noxious Inhibitory Controls |
| ECS | Endocannabinoid system |
| ESDDA | Simplified Pain Evaluation Scale for Dyscommunicative Autism Spectrum Disorders |
| FLACC-R | Faces, Legs, Activity, Cry and Consolability – Revised  |
| GABA | Gamma-aminobutyric acid |
| HRV | heart rate variability |
| MNS | Mirror Neuron System |
| NCCPC-R | Noncommunicating Children’s Pain Checklist  |
| PAG | PeriAqueductal Gray |
| PL-BPRS | Pre-Linguistic Behavioral Pain Reactivity Scale |
| SF-MPQ | short-form McGill Pain Questionnaire |
| SIB | Self-injury behaviour |
| S1  | the primary somatosensory cortex |
| S2 | the secondary somatosensory cortex |

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