Chronic abdominal vagus stimulation increased brain metabolic connectivity, reduced striatal dopamine transporter and increased mid-brain serotonin transporter in obese miniature pigs

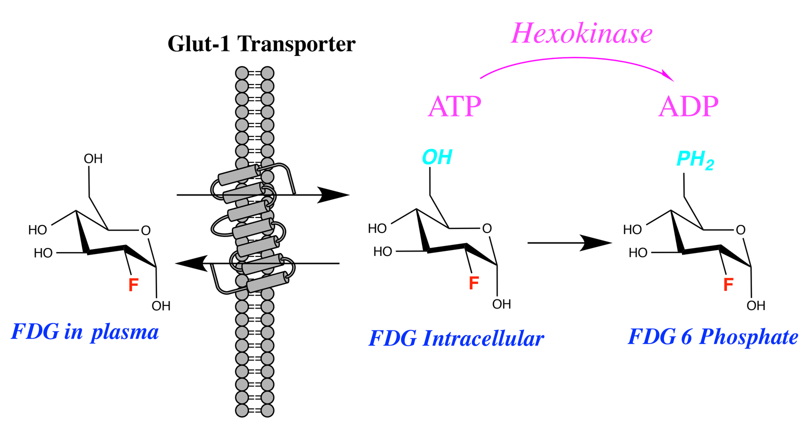
Charles-Henri Malbert[a], Mickael Genissel[b], Jean-Louis Divoux[c], Christine Henry[d]

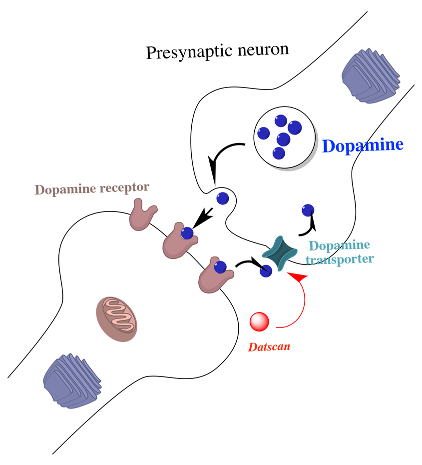
(a) Aniscan unit, Dept of Human nutrition, INRA, Saint-Gilles, France
(b) Pegase unit, Dept of animal physiology, INRA, Saint-Gilles, France
(c) Axonic, Vallauris, France
(d) Livanova, Sorin CRM, Clamart, France

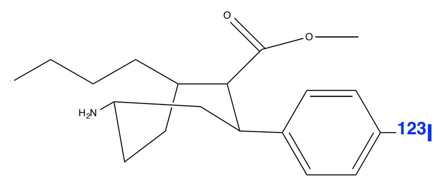
Background and aims

Changes in brain metabolism has been investigated thoroughly during unilateral cervical chronic vagal stimulation in epileptic or depressive patients. Bilateral stimulation of the abdominal vagus ($_a$VNS) has received less attention despite the reduction in body weight and an altered feeding behavior in obese animals that could be clinically relevant in obese individuals. Our study aims to examine the changes in brain glucose metabolism (CMR_{glu}) induced by $_a$VNS in obese adult miniature pigs. Dopamine (DAT) and serotonin transporters (SERT) were also quantified to further understand the molecular origins of the alterations in brain metabolism.

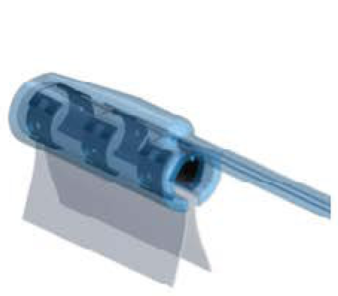
Materials and Methods

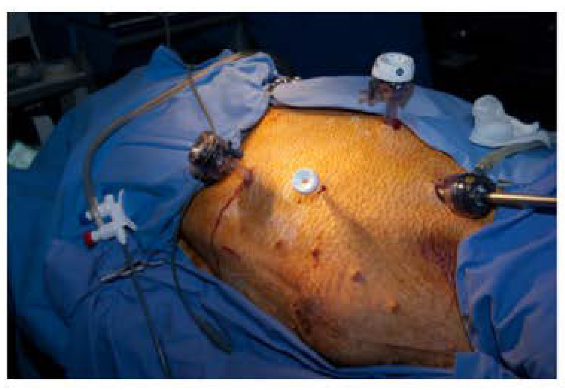


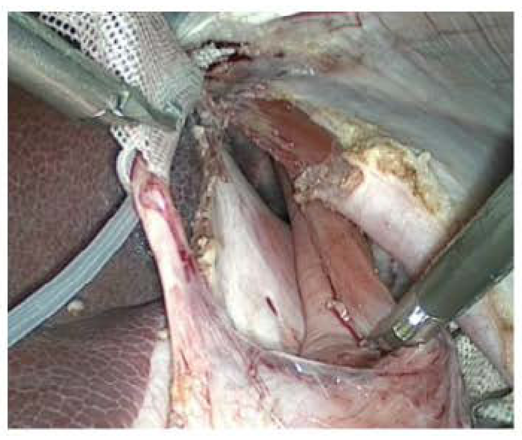




Pairs of stimulating electrodes were implanted during laparoscopy on both abdominal vagal trunks in 20 obese adult's miniature pigs. Half of the animals were permanently stimulated while the remaining were sham stimulated. Two months after the onset of stimulation, dynamic $_{18}$FDG PET and ^{123}I-ioflupane SPECT were performed. Food intake, resting energy expenditure and fat deposition were also assessed longitudinally.

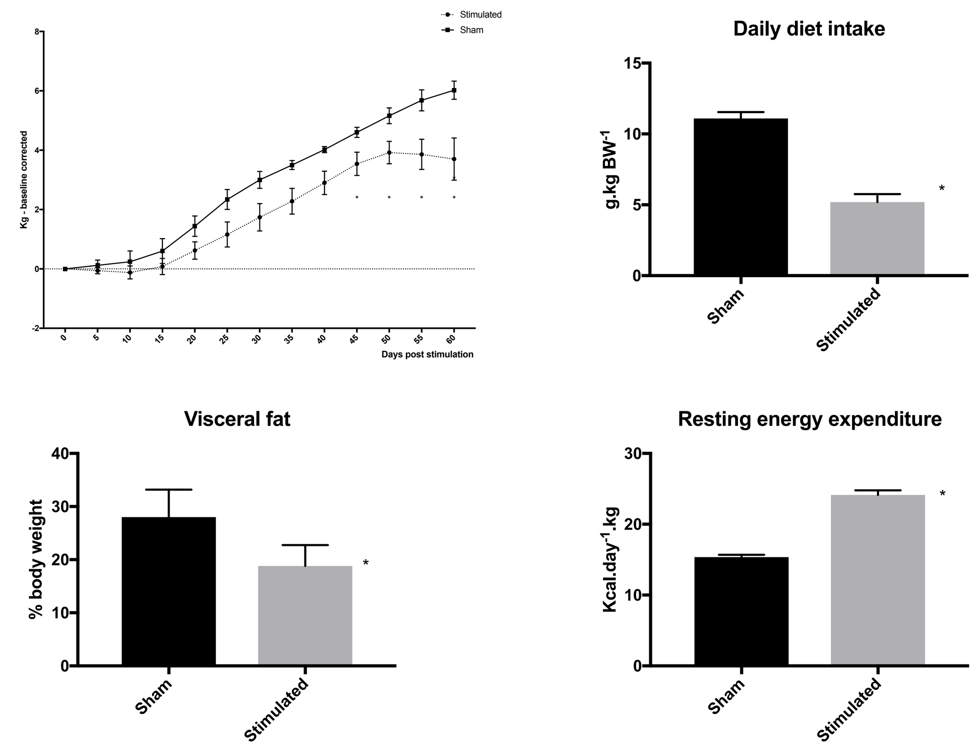




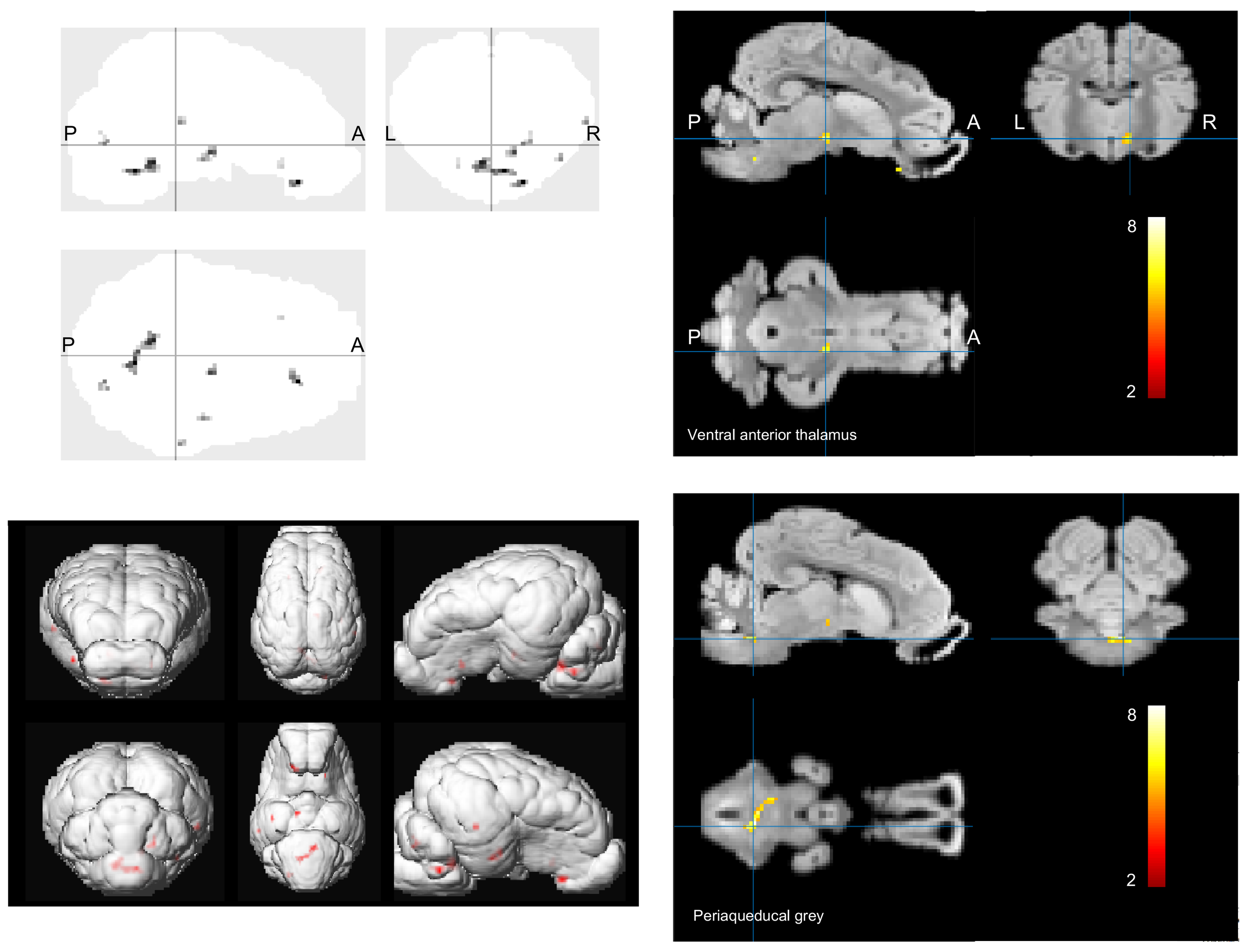


Results

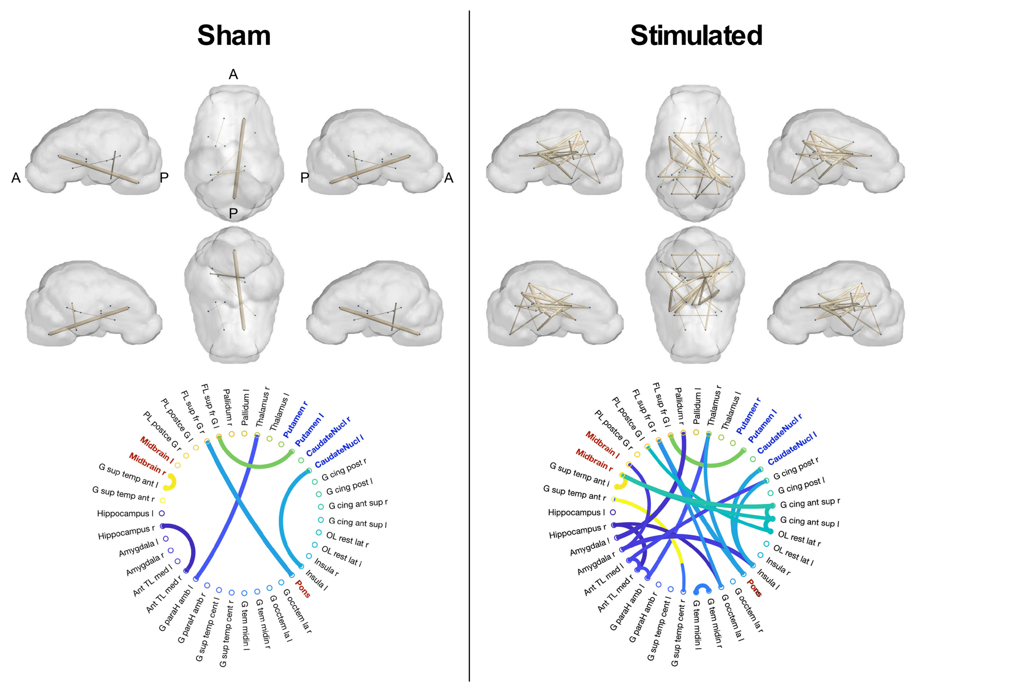
Food intake was halved and resting energy expenditure was increased by 60% in $_a$VNS group compared to sham. The gain in body weight was also 38% less in $_a$VNS group compared to sham. Brain metabolic connectivity increased between numerous structures including striatum, mid-brain, amygdala and hippocampus. On the contrary, increased CMR_{glu} were restricted to the thalamus, the periaqueducal grey and the amygdala. DAT binding potential was decreased by about one third in the striatum while SERT was about doubled in the midbrain.



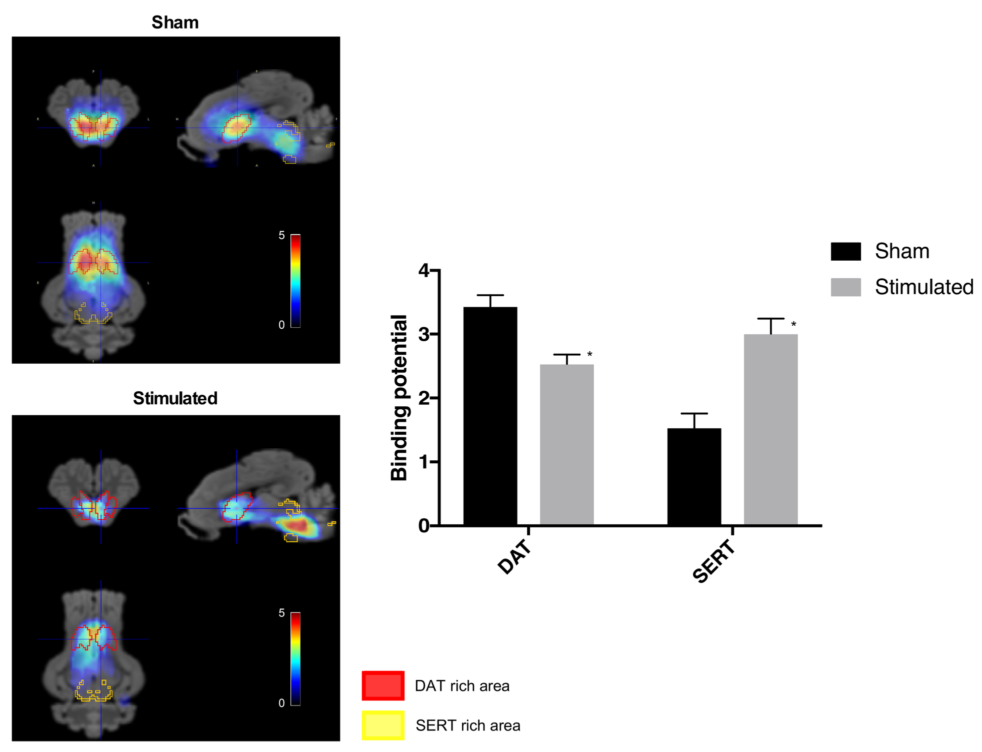
Evolution in body weight gain for sham and abdominal vagal stimulated groups (Top left panel). Note that body weight relative to the pre-operative one was significantly reduced in the stimulated group after 45 days of continuous stimulation. This reduction was a consequence of both a diminished daily food intake (Top right panel) and an increased resting energy expenditure (Bottom right panel). The decreased body weight in the stimulated group was representative of a reduced visceral fat (Bottom left panel).



Statistical parameter mapping of ^{18}FDG uptake (CMRglu) in sham and stimulated group. SPM analysis was performed using pixel-wise modeled quantitative PET images. Statistical differences were analyzed using T-test in SPM12, P<0.001 FDR and cluster level corrected. The analysis was performed with a cluster size of 100 voxels each of the cluster representing 1 mm^3. Note the activation in the thalamic and periaqueducal grey areas. Top left – Brain glass with activation in shade of grey. Top right – Thresholded activation (in color scale) depicting the ventral anterior thalamic activation. Bottom left – 3D representation of the activation matrix. Shade of red indicates activation. Bottom right - Thresholded activation (in color scale) with the image centered on the periaqueducal grey.



Metabolic connectivity analysis in the sham and stimulated groups. A. The figures showed the results of connectivity analysis performed with NetPET software using CMRglu coded voxel-vised images. Top panels - Surface renderings of the brain overlaid with network connections. Nodes and edges were coded using BrainNet viewer and edges were thresholded for P<0.001. Only nodes with attached edges were represented. Bottom panels- Correlograms representing the correlation weighted matrices thresholded at P<0.001. Nodes' abbreviations are expended in the Supplementary material table. Note the increased metabolic connectivity in stimulated compared to sham group.



Left panels – Examples of reconstructed normalized volumes obtained after the administration of ^{123}I ioflupane in sham versus stimulated animals. The colors represented pixel-wise modeled SPECT dynamic image series according to Ichise i.e. the binding potential overlaid on the MRI template of the pig brain atlas. Red VOIs corresponded to DAT-rich areas whereas yellow VOIs represented SERT-rich areas. Right panel - Binding potential for DAT and SERT in sham versus stimulated groups obtained from region-based analysis * Indicates a significant difference at P<0.001.

Conclusions

Our findings demonstrated that $_a$VNS reduced weight gain as a consequence of diminished daily food intake and increased resting energy expenditure. These changes were associated with enhanced connectivity between several brain areas. A lower striatal DAT together with a doubled mid-brain SERT were likely causative for these changes.