Early metabolic changes in the amyotrophic lateral sclerosis SOD1 mouse brain are revealed using 1H MRS rather than CASL and 18FDG PET

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INTRODUCTION
Amyotrophic lateral sclerosis (ALS) is a debilitating and fatal neurodegenerative disease of unknown etiology affecting motor-neurons of the CNS and PNS, and for which diagnostic criteria are sorely needed. Mice overexpressing G93A mutant form of human superoxide dismutase 1 (SOD1) develop a progressive limb paralysis that closely mimics the ALS. Therefore, they represent a model of choice for elucidating the biochemical/metabolic changes that may occur in affected CNS regions. The progressive nature of this disease highlights the need for longitudinal and non-invasive measurements of brain function, structure and metabolism. We have exploited the G93A SOD1 mouse model to explore regional biochemical variations in brain and brainstem during the pre- and post-symptomatic phases using 1H MRS (1,2) CASL (3) and 18FDG PET imaging (4).

METHODS
G93A-SOD1 mice were bred and genotyped as previously described (5). Based on preliminary electromyographical measurements and swimming abilities, we designated post-natal day 60 (P60) as pre-symptomatic, and P100 as mildly post-symptomatic. The mean lifespan of our animals was ~125 days. During the entire experimental period, animals were maintained under isoflurane anesthesia (0.8-1.5%) and physiological parameters were continuously monitored. At 9.4T, localized 1H MRS was applied on motor cortex, striatum and brainstem using SPECIAL (2 and references therein). Water signals with no water suppression (VOIs) in SOD1 mouse brain, striatum, and brainstem were detected with CRLB <50%. One week after P100, mice and age-matched controls (5 per group) subsequently underwent 18FDG PET imaging of the head and neck regions following a ~5MBq 18FDG intravenous bolus. Trapped, intracellular 18FDG-6-phosphate was quantitated using Standard Uptake Values (SUV): [mean ROI activity (kBq/cm3)] / [injected dose (kBq)/body weight (g)].

RESULTS AND DISCUSSION
At 9.4T, quality anatomical imaging data allowed precise localization of the volume of interests (VOIs) in SOD1 mouse brain, striatum, motor cortex and brainstem (Figure 1A). With improved field homogeneities, and satisfactory water suppression performance and sufficient scan number, localized MR spectra were processed and quantified using the LCModel (1, 2 and references therein). Water content was 80% for motor cortex, striatum and brainstem as in references 1 and 2) were detected with CRLB <50%. One week after P100, mice and age-matched controls (5 per group) subsequently underwent 18FDG PET imaging of the head and neck regions following a ~5MBq 18FDG intravenous bolus. Trapped, intracellular 18FDG-6-phosphate was quantitated using Standard Uptake Values (SUV): [mean ROI activity (kBq/cm3)] / [injected dose (kBq)/body weight (g)].

Table 1 Summary of significant metabolic changes observed at P60 and P100 (unpaired t-test).

<table>
<thead>
<tr>
<th></th>
<th>Relative increase (%, p-value)</th>
<th>Relative decrease (%, p-value)</th>
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<tbody>
<tr>
<td>P60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brainstem</td>
<td>Gln (+18, 0.017)</td>
<td>Lac (-19, 0.04)</td>
</tr>
<tr>
<td>Motor cortex</td>
<td>Ase (+51, 0.017)</td>
<td>GABA (-30, 0.003)</td>
</tr>
<tr>
<td>Striatum</td>
<td>Gln (+13, 0.02)</td>
<td>Lac (-21, 0.04)</td>
</tr>
<tr>
<td>P100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor cortex</td>
<td>Gln (+33, 0.0005)</td>
<td>Lac (-12, 0.0004)</td>
</tr>
<tr>
<td>Striatum</td>
<td>Glu (+22, 0.02)</td>
<td>Lac (-60, 0.002)</td>
</tr>
<tr>
<td>Striatum</td>
<td>PCr (+22, 0.006)</td>
<td>Lac (-44, 0.03)</td>
</tr>
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REFERENCES

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