Multimodal neurometabolic investigation of the effects of zolpidem on leukoencephalopathy-related apathy

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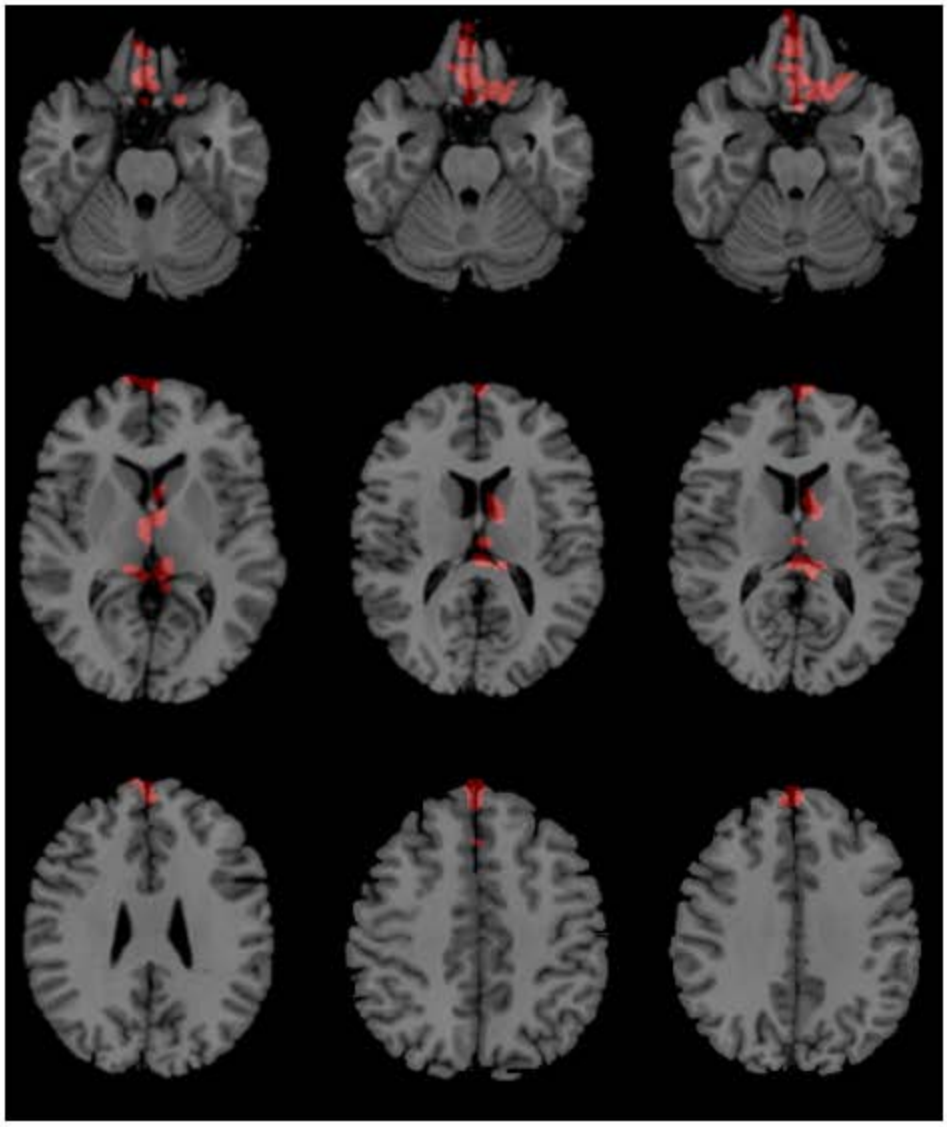
A



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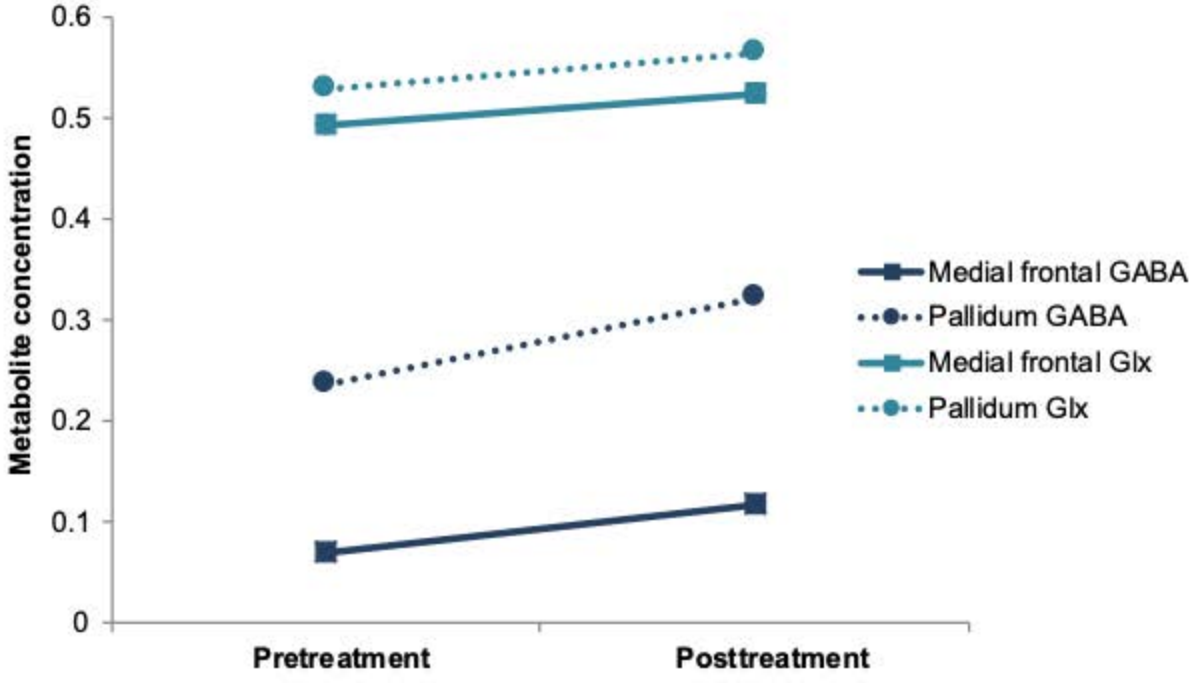
Metabolite concentration
0.6
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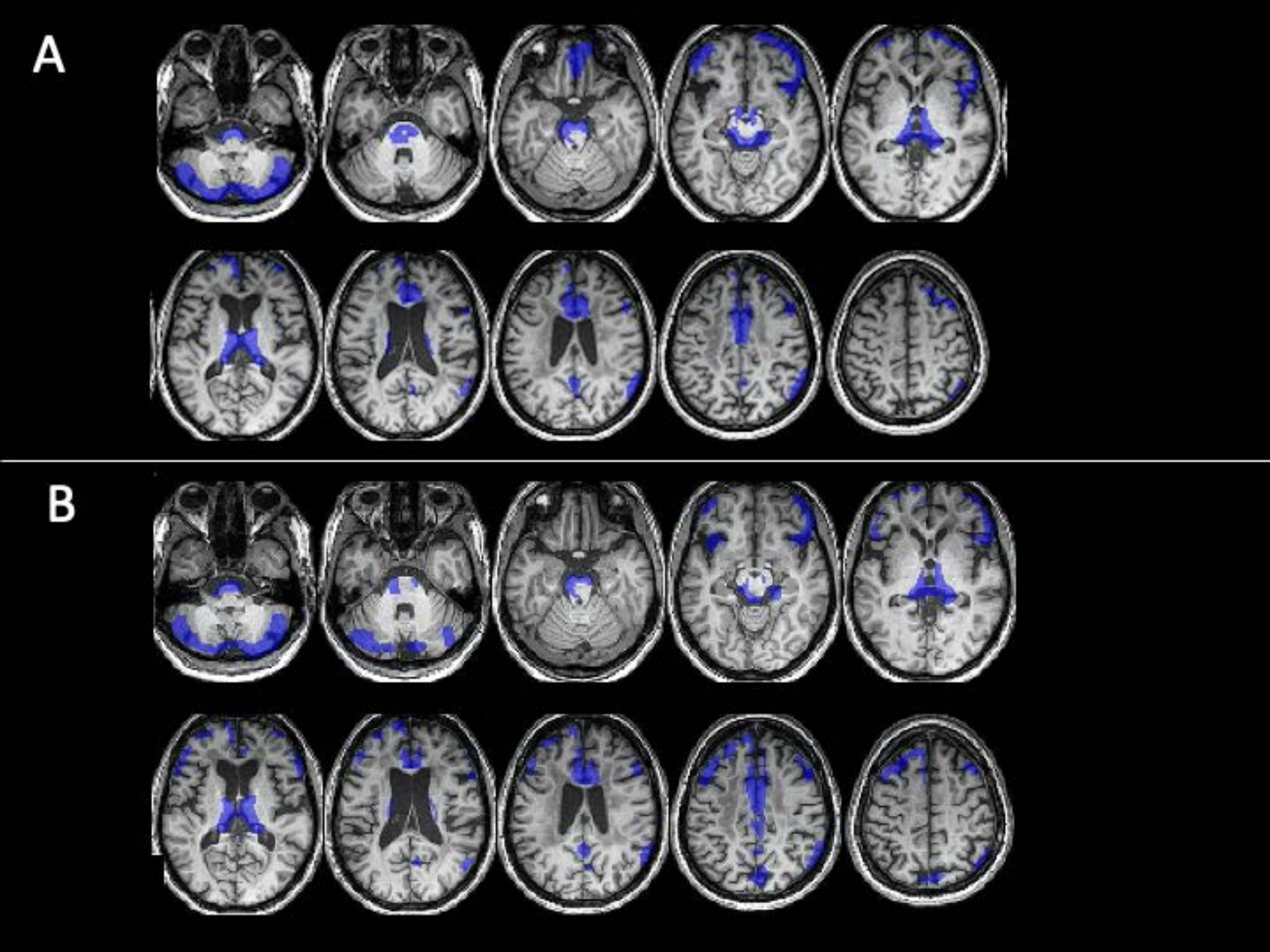
Pretreatment
Posttreatment
Medial frontal GABA
Pallidum GABA
Medial frontal Glx
Pallidum Glx


A
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Multimodal neurometabolic investigation of the effects of Zolpidem on leukoencephalopathy-related apathy

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Running title: Zolpidem in leukodystrophy-related apathy

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Abstract

Background: The symptomatic effect of Zolpidem on apathy has been reported in neurological disorders such as strokes and post-anoxic brain injuries, but not in white matter disease of the brain.

Methods: We studied a 38-year-old patient presenting with severe apathy related to a genetic leukoencephalopathy but marked improvement of apathy after taking 10 milligrams of Zolpidem. To understand what may mediate such a clinical effect, we undertook a multimodal neurometabolic approach using ^{18}F Fluorodeoxyglucose (FDG)-PET metabolism and a dedicated magnetic resonance spectroscopy (MRS) sequence for GABA and glutamine/glutamate metabolism.

Results: Pre-Zolpidem FDG-PET showed hypometabolism in the orbitofrontal cortex, dorsolateral cortex and basal ganglia compared to healthy controls. Post-Zolpidem, FDG-PET displayed increased metabolism in the orbitofrontal cortex together with improvement in the emotional and auto-activation domains of apathy. There was no improvement in the cognitive domain of apathy, and no change in metabolism in the dorsolateral frontal cortex. Post-Zolpidem, MRS showed increased GABA and glutamine+glutamate levels in the frontal cortex and pallidum.

Conclusion: Our multimodal neurometabolic study suggests that the effects of Zolpidem on apathy are related to increased metabolism in the orbitofrontal cortex and basal ganglia secondary to GABA modulation. Zolpidem may improve apathy in other white-matter disorders.

Abbreviations

FDG: ^{18}F Fluorodeoxyglucose; MRS: magnetic resonance spectroscopy; ALSP: axonal spheroids and pigmented glia; Glx: glutamine+glutamate; tCr: total creatine.

Introduction

Apathy is defined as a quantitative reduction of goal-directed activity (1–3). Each dimension of apathy, namely cognitive, affective-emotional and auto-activation/self-initiating impairment seems to be related to distinct lesions of the prefrontal cortex and basal ganglia: respectively, dorsolateral, ventral (orbitofrontal/inferior) and medial prefrontal cortex regions as well as their corresponding projections to the basal ganglia (1). Apathy should rather be seen as a "network-related" cerebral dysfunction, involving white matter or multifocal lesions, than a focal disorder (4–7).

Zolpidem, a GABAergic non-benzodiazepine hypnotic, was found to enhance arousal and neuropsychiatric functions in some patients with stroke (8) or post-anoxic brain injuries, (9,10). Zolpidem can also alleviate catatonic syndromes (11–15). Zolpidem effects have never investigated in white matter disorders.

Here, we studied a patient with a genetic white matter disease characterized by severe apathy, who experienced marked improvement after Zolpidem. We undertook a multimodal approach using ^{18}F Fluorodeoxyglucose (FDG)-PET metabolism and a dedicated magnetic resonance spectroscopy (MRS) sequence for GABA and glutamine/glutamate metabolism, pre and post-Zolpidem, to understand what may mediate this effect.

Methods

Patient description and pharmacological intervention

The patient was 33 when she developed attentional difficulties and apathy. Her condition rapidly worsened with marked walking impairment, severe cognitive disturbances and spasticity. Brain MRI showed patchy asymmetric white matter hyperintensities on fluid-attenuated inversion recovery sequence, and lesions with increased diffusivity on diffusion weighted imaging sequence (data not shown). She was diagnosed with multiple sclerosis, but diagnosis was reconsidered due to the very atypical and rapid evolution. Axonal spheroids and pigmented glia (ALSP) was suspected and confirmed by *CSF1R* gene sequencing, which identified a heterozygous c.2342C>T (p.A781V) pathogenic variant (16). At age 38, she could only walk a few steps with help due to frontal disturbances. She had marked pyramidal syndrome but no muscle deficit. She had dementia with evidence of frontal dysfunction.

The patient was enrolled in a study on frontotemporal lobar degeneration approved by Inserm ethical committee (Inserm RBM 02-059). FDG-PET and MRS were performed before (after a wash-out of more than 12 hours) and one hour after taking orally 10 milligrams of Zolpidem. FDG-PET was used for the therapeutic evaluation of Zolpidem, with a low total radiation dose (4.6 mSv), and data use was approved by the French authority for the protection of privacy and personal data in clinical research (CNIL, approval No. 2111722). Written informed consent was obtained from the patient and her caregiver for clinical investigation including repeat FDG-PET and MRS, video and publication.

FDG-PET

A 10 minutes acquisition was performed with a hybrid PET/CT system (Biograph mCT Flow - Siemens Healthcare) 30 min after the intravenous injection of FDG (2 MBq/Kg). PET volumes were co-registered, spatially normalized in the Montreal Neurological Institute (MNI) space using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/), smoothed and normalized in intensity. Two-sample T-tests were used to compare the patient's metabolism to normal controls, with a general liner model with age and gender as covariates. The primary cluster-defining threshold was p=0.001, with the cluster-level extent threshold set at p = 0.05 for false discovery rate correction.

A z-score mapping implemented in BrainVisa software (http://brainvisa.info) was used to extract areas with differences in metabolism before and after Zolpidem. Relative difference was computed into z-scores as described (17,18). Clusters < 100 voxels (8ml) and voxels with absolute values < 1.5 z-score were excluded before displaying z-score maps onto anatomical MRI.

Magnetic Resonance Spectroscopy

MRS was performed on a 3-Tesla Siemens Prisma fit scanner (Siemens Medical Solutions, Erlangen, Germany). Single volume MEGA-Point-Resolved Spectroscopy (MEGA-PRESS, TR = 2000 ms, TE = 68 ms, averages = 48) was used to acquire data in a 17 x 35 x 15 mm^3 and 15 x 20 x 20 mm^3 volumes of interest in the medial frontal cortex and pallidum respectively. Consecutive application of spectral editing pulses at 1.9 ppm (MEGA-ON) and 7.5 ppm (MEGA-OFF) was performed for enhanced detection of low-concentrated metabolites including GABA and Glx (glutamine + glutamate). The difference of the ON and OFF spectra revealed the GABA and Glx signals that usually overlap with higher concentrated metabolites. Quantification of the spectra was done using LCModel (19). The ratio of GABA/total creatine (tCr) and Glx/tCr were reported.

Results

Clinical evaluation

Behavioral examination before Zolpidem revealed major apathy involving all three dimensions, with executive dysfunction, affective indifference, emotional flattening, anhedonia, and lack of initiative to undertake spontaneous actions or elaborate about future projects (Supplementary Video, Part 1). Cognitive examination was limited due to severe distractibility and slowing of thoughts. She scored 17/30 on the Mimi Mental State Examination, 2/18 on the Frontal Assessment Battery and 10/30 on the Montreal Cognitive Assessment.

One hour after taking 10 mg of Zolpidem, the patient was more alert, responsive and able to communicate more fluently (Supplementary Video, Part 2). There was a marked increase in the emotional and social content of her conversation. She did elaborate on some future projects such as doing an around the world travel with her family. Neuropsychological scores otherwise remained unchanged and a severe executive deficit persisted. Patient's participation to clinical examination clearly improved, including her ability to walk. There was also a marked increase in spontaneous motor expression, with increased and more rapid facial and bodily movements. The effect of Zolpidem was reproductive over days and lasted for about four hours.

FDG-PET

Pre-Zolpidem cerebral FDG-PET showed hypometabolism in the bilateral cerebellum, the pons, orbitofrontal cortex, thalamus, cingulate, and dorsolateral prefrontal cortex compared to a cohort of healthy controls (Figure 1A).

Post-Zolpidem cerebral FDG-PET showed increased metabolism in the orbitofrontal cortex, the median prefrontal cortex, the caudate nucleus and the thalamus compared to pre-Zolpidem acquisitions (Figure 2). Post- Zolpidem metabolism in the orbitofrontal cortex was not significantly decreased compared to healthy controls (Figure 1B).

Magnetic resonance spectroscopy

Post-Zolpidem, we observed increased ratios of GABA/tCr and Glx/tCr in the medial frontal cortex and pallidum compared to pre-Zolpidem (Figure 2B).

Discussion

We report the marked clinical response to Zolpidem of a patient with severe apathy in the context of a white-matter disease. Our multimodal neurometabolic study revealed that Zolpidem increased metabolism in the orbitofrontal cortex and basal ganglia, and increased GABA and Glx levels in the medial prefrontal cortex and pallidum.

ALSP is one of the most common leukodystrophies and is a model of microglia dysfunction (20). Neuropsychiatric manifestations of ALSP include cognitive decline, apathy, and other behavioral changes resembling behavioral-variant frontotemporal dementia (16). ALSP predominantly affects the white matter, in particular the frontal subcortical white matter and corpus callosum (20,21). FDG-PET in ALSP patients showed diffuse hypometabolism predominantly affecting the frontal and parietal lobes (21,22).

Pre-Zolpidem FDG-PET in our patient displayed significant hypometabolism in brain regions involved in motivation and goal-directed behaviors, namely the orbitofrontal cortex, medial prefrontal cortex and basal ganglia. Post-Zolpidem FDG-PET showed increased metabolism in these regions. These results are consistent with the three-dimensional model of apathy (1) as, post-Zolpidem, our patient showed emotional-affective and auto-activation improvement contrasting with persisting severe executive disturbance. This response was paralleled by increased FDG-PET metabolism in the orbitofrontal cortex, median prefrontal cortex and basal ganglia but no change in the dorsolateral frontal regions. It has been hypothesized that, in some leukodystrophies, frontal neuropsychiatric symptoms might reflect a “disconnection syndrome” secondary to white matter alterations rather than a cortical dysfunction (23,24). Apathy is frequent in other white matter diseases, such as small vessel diseases (25) and multiple sclerosis (26).

Zolpidem increased GABA and Glx in our two MRS regions of interest, the medial frontal cortex and the pallidum. In healthy controls, decreased GABA/Cr ratio in response to Zolpidem has been reported previously in the thalamus but with no effect on Glx (27). The binding of Zolpidem in healthy controls, in which the glutamatergic/GABAergic balance is not impaired, leads to cortical inhibition. Conversely, increased GABA/Cr ratio has been reported in the thalamus and anterior cingulate of patients with major depressive disorder after Zolpidem administration (28). Hence, the effect of Zolpidem seems to be influenced by changes in receptor configurations and how the glutamatergic / GABAergic balance is affected by neuropsychiatric disorders.

Zolpidem can improve cognitive function in some patients with post-hypoxic brain injuries, which also affect the white matter (29). One common hypothesis is that the cortical disconnection related to white matter alterations induces allosteric changes in GABA receptors, which may become hypersensitive in order to keep their function even with low GABAergic tone. In line with this

hypothesis, a ^{18}F Flumazenil PET study showed increased GABA receptors activity in the frontoparietal regions in a patient with hypoxic brain injury (30). Zolpidem may enhance cortical function by reversing this functional diaschisis, as suggested by our MRS findings. Zolpidem is specific for GABA1-receptors containing the α1 subunit, which are predominantly expressed in the thalamus and the striatum (31–34). Zolpidem binding may inhibit the internal pallidum, which would in turn disinhibit thalamus and activate thalamo-cortical projections and result in a "deep brain stimulation-like" effect (35,36).

This study has several limitations. It was not placebo-controlled and was performed on a single subject. The severe frontal cognitive impairment made it difficult to provide a more detailed clinical examination, for example social cognition evaluations that require a preserved working memory and attention. Although we cannot draw definite conclusions about the mode of action of Zolpidem on apathy, our multimodal approach suggests that its effects are related to increased metabolism in the orbitofrontal cortex and basal ganglia secondary to GABA modulation.

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Figure Legends

Figure 1 - Pre- and post-Zolpidem FDG-PET

In blue are shown regions with significant hypometabolism in the patient compared to a cohort of healthy controls ($p<0.05$ after cluster correction). A- Pre-Zolpidem. B- Post-Zolpidem.

Figure 2 – Post-Zolpidem neurometabolic response

A. FDG-PET. In red are shown regions with significant post-Zolpidem increased metabolism compared to the pre-Zolpidem acquisition. B. MR-Spectroscopy. GABA/Cr and Glx/Cr ratios in the medial frontal and pallidum before and after 10 mg of Zolpidem. Metabolite concentrations are in μmol/g. *Cr: total creatine; Glx: glutamine+ glutamate.*

Video legend

Part 1 – Before Zolpidem

Part 2 – One hour after 10 mg of Zolpidem.