DONDERS INSTITUTE

Newsletter 29

15 December 2016

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RELIABLE IN-DEPTH CHARACTERISATION OF THE DISEASE

Regaining speech

VITORIA PIAI'S DREAM JOB AT DONDERS

Imaging and stimulating adaptive brain plasticity

DONDERS LECTURE

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Radboud University Radboudumc

Parkinson's cohort study kicks off

This is an innovative big data project designed to help understand the debilitating disease Parkinson's. The Donders Institute, ParkinsonNet and Verily Life Sciences have together initiated the Personalized Parkinson Project, a study involving 650 Parkinson's patients, to examine the disease and its progression over the course of two years.

"New insights are urgently needed," says Parkinson's specialist Bas Bloem. "The symptoms, rate of progression, and treatment response vary considerably among patients with Parkinson's disease. Currently, we don't understand what causes these differences and therefore we cannot yet offer patients the best possible treatment plan: one that is tailored to their individual needs." Bloem is Professor of Neurological Movement Disorders at Radboud University Medical Center and Founder of ParkinsonNet. "We are therefore scaling up our efforts to phenotype Parkinson's disease on a scale that guarantees a reliable in-depth characterisation of the disease."

The study will use state-of-the-art techniques, including sophisticated molecular analyses of spinal fluids and microbiota, and advanced brain imaging. One innovative aspect is that a life sciences research and engineering organisation related to Google – Verily Life Sciences – is providing wearable devices with sensors to measure data, such as vital signs and activity levels, in the home situation. Research data will be securely stored and shared with using an advanced method called Polymorphic Encryption and Pseudonymisation (PEP), which was developed by the Digital Security Group at Radboud University, led by Prof. Bart Jacobs.

NATIONAL AND INTERNATIONAL COLLABORATION

The Personalized Parkinson Project will use ParkinsonNet's unique infrastructure to find and monitor 650 patients for this intensive study, which will be performed by leading researchers at the Donders Institute. ParkinsonNet is an innovative health care network that facilitates Parkinson-specific specialisation, interdisciplinary collaboration, and the exchange of knowledge. The Dutch association for Parkinson's patients will also be closely involved. "The purpose of our study is to share data. Researchers from all participating Dutch hospitals will be given the opportunity to carry out their own studies on Parkinson's disease using the data collected. Parkinson's researchers in other countries can also be granted access to this data after submitting a research proposal," Bloem explains. "I'm sure this broad approach to secure privacy-friendly information sharing will help accelerate research on the disease."

A ROYAL START

Bas Bloem, who is well known nationally and internationally for his meticulous, inspiring work on the innovation of care for people with Parkinson's disease, came into contact with Verily Life Sciences while he was accompanying the Dutch King and Queen on a trade mission to the United States. Bas Bloem's ParkinsonNet is a well know Dutch export product in which Verily were immediately interested, so that's how the partners became acquainted. A royal start, one could say.

"We have studied Parkinson's in a more traditional way for such a long time. We've learned a lot, but we still know too little about the personal differences in terms of the course of the disease. There are good prospects that this big data approach will help us find new ways of understanding and predicting these personal differences."

Iris Roggema

Rick Helmich conducting an fMRI experiment.

650X2 FMRI SCANS

Rick Helmich is a resident in Neurology at the Radboud University Medical Centre. As an experienced fMRI researcher he'll be joining the Parkinson's cohort study. He is particularly interested in tremor – the well-known shaky limbs symptom that many, but not all, Parkinson's patients experience.

He's currently investigating why an increase in stress levels can increase tremor and he hypothesises that noradrenaline is involved. His earlier work showed that tremor is rooted in different brain circuits than other Parkinson's symptoms. These distinct areas – thalamus, motor cortex and cerebellum – are all sensitive to noradrenaline. Helmich wants to find out how this works and he hopes that his findings will lead to a new tremor therapy, be it pharmaceutical, stress reduction training, or a combination of both. "Some patients have told me that the popular self-help therapy mindfulness reduces their tremor," he says. "Actually this was what put me on the track of studying the effects of stress."

Helmich has been studying movement disorders since his scientific internship on dystonia during medical school and he has focused his work on Parkinson's ever since. "It's an interesting disease because it affects cognitive skills, motor skills and emotions. It is also an interesting model for studying the role of dopamine, since all Parkinson's patients have depleted dopamine. The diseased brain teaches us a lot about how the healthy brain works." And, speaking as a clinical neurologist now – it's nice to be able to alleviate symptoms with medication, which we can't do with some other neurological diseases."

One of the things that fascinate Helmich is that the visible appearance of a clinical symptom in a patient doesn't always give you any clues about the effectiveness of therapy, or about the progression of the disease. "Why does patient X's tremor go away when it is treated with the drug levodopa? And why doesn't it help the same tremor in patient Y at all?"

This is one of the issues the study hopes to tackle with Verily's help, Helmich says. "The scale is really unprecedented. Usually you include around twenty patients in an fMRI study. Now we will scan 650 subjects, and repeat this after a two-year interval. This allows us to really take personal differences into account, instead of averaging them out. I really hope to find an indicator that correctly predicts which therapy will work for which patient."Because the Personalized Parkinson Project will also involve looking at proteins in the brain fluids – indicators of cellular decay – and include full DNA profiling of every subject, combined with daily measurements at home, it will considerably expand the scope of research on this enigmatic disease. This will surely lead to a deeper understanding of the neurology, and hopefully to better therapies.

Regaining speech

“Language is extremely important for humans and the plasticity of the brain is fascinating. This is why I want to figure out what our brain is capable of, despite damage in its language areas. I want to investigate how we can boost plasticity to help patients function optimally in terms of language. And I believe therapies should focus on the remaining potential of the brain.”

Vitoria Piai is back at the Donders Institute for what she calls her ‘dream job’. After two years at the University of California in Berkeley she has returned to Nijmegen as an aspiring Principal Investigator in the Neuropsychology of Language – a new position that is shared by the university and the medical centre.

“I have always felt a strong connection to the Donders Institute and the Radboud community, so I am very happy to be back,” Piai explains. “The language research here is leading worldwide, but the mentality here also attracts me. Since I’m a pretty active person, I love to be involved in many projects

simultaneously. The research climate in Nijmegen allows me to work that way – something that proved to be a lot harder in Berkeley. Here, facilities are shared and discussing and collaborating are the norm. When I walk into the coffee room, there is always someone there to share my thoughts with."

"By applying my fundamental and methodological background in linguistics and neuroscience in new projects with clinical populations, I aim to analyse and hopefully boost the language skills of people who suffer from stroke, epilepsy, dementia, or Parkinson's disease, for example. In due course, this will improve the societal relevance of brain research on language, which tends to be fundamental."

DREAMING OF LINGUISTICS

Ever since she was a child, Piai knew she wanted to become a scientist. "I remember reading an article in the newspaper when I was about twelve. A scientist answered the question whether English would ever be the world's lingua franca. "Never!" he said, and went on to explain how languages evolve and spread. I remember thinking "Wow, that's so cool!" So I checked what kind of scientist he was and, based on that, I decided to become a linguist. During my Bachelor's degree course, I analysed the foundations of languages. But I always thought: those grammar rules do not actually exist in our brain... How does it work, in real life? So later on, I switched to cognitive neuroscience, and I still work on these questions in my current work. The rules I learned in linguistics continue to help me, though. For example when learning new languages, something I really enjoy." Piai speaks Portuguese, English, Dutch, Swedish, Italian, French, Spanish, and some Polish.

VITORIA PIAI

Vitoria Piai, who was born in Brazil, studied Linguistics and Portuguese Language and Culture at Utrecht University. In 2007, she came to Radboud University for the Cognitive Neuroscience Master's programme. She subsequently obtained her PhD degree cum laude at the Donders Institute. During that period, she was awarded a Frye Stipendium: an annual stipend for ten promising female researchers at Radboud University. A few years later, in 2013, Piai obtained a two-year Rubicon Fellowship, which enabled her to work at the Helen Wills Neuroscience Institute at the University of California, Berkeley (USA). Her current position as an aspiring Principal Investigator in the Neuropsychology of Language is part of the Language in Interaction consortium that is funded by the Dutch national Gravitation programme.

At the time of this interview, Vitoria Piai is busy settling in. Her office is filled with moving boxes and she's just back from a meeting with a contractor who's going to do some work on her new house, near Nijmegen. Once that's arranged, Piai's time will mostly be taken up by ethical approvals for patient studies. One of the projects she's preparing focuses on patients with a brain tumour in language areas, in the left hemisphere. Such tumours are removed while the patient is awake to ensure that language is not affected. "I test these patients' language skills live, during the surgery," she says. "This is fascinating, but it's also quite bizarre!" Based on skills measured during or just after the operation, Piai hopes to make a prognosis for the same skills months later.

"My interest in possible applications for patients is something that is always at the back of my mind. With my work, I want to discover new things, but I also want to be able to do something for the patients."

AHA MOMENT

Although working with patients is rewarding, it can also be quite difficult. "There is so little evidence about the actual effects of certain therapies, and I think it's better to be honest than to give patients false hope. I strongly believe that therapies should focus on the remaining potential of the brain."

Piai currently has an article in peer review showing how the amount of damage in the corpus callosum – the 'information highway' between the two hemispheres – predicts how much information can travel from left to right. Once this highway is broken, Piai believes there's not much point pursuing therapies designed to stimulate the patient's right hemisphere to compensate for the loss of language function. "This strengthens my point that information on the mechanisms of plasticity is necessary for good therapies."

When Piai encountered patients for the first time in her research career, during her time in Berkeley, it was a revelation. "You could say it was love at first sight. Now I knew why I was doing this work. For that reason, I believe it's important for students to get acquainted with multiple facets of research early on. My ultimate aim is to integrate my fundamental and clinical work as well as possible. But I also want to make others think about how they could do that in their own research. So I also aim to offer students the opportunity for that 'aha moment' as early as possible."

Iris Kruijen

Go to our website to check out the latest news and events

Meanwhile at www.ru.nl/donders

SOME RECENT HEADLINES

- **Donders brain-powered racer wins silver**
  The Donders Brain Computer Interface (BCI) team made it to the second position in the BCI race during the first Cybathlon for athletes with disabilities at ETH in Zurich.
- **Radboud Science Award 2016**
  Christian Doeller wins the 2016 Radboud Science Award. The award will give him the opportunity to translate his research into teaching materials for primary school education.
- **Dr Moritz Helmstaedter appointed Professor of Neural Networks**
  Moritz Helmstaedter has – by special appointment – become Professor of Neural Networks at the Radboud University Faculty of Science as from 1 September 2016.
- **Roshan Cools joins Academia Europaea**
  Professor of Cognitive Neuropsychiatry, Roshan Cools, has been elected as a member of the Behavioural Sciences Section of the Academia Europaea.
- **€1.5 million for research on noisy sensory information in the brain**
  Janneke Jehee received an ERC Starting Grant to investigate how people make decisions on the basis of noisy sensory information

SOME RECENT HIGH-IMPACT PUBLICATIONS

- **The memory factory of the brain**
  Christian Doeller and his colleagues have shown that the hippocampus plays a central role in combining fragments of information into one coherent memory. (*Nature Communications*)
- **Need to remember something? Exercise four hours later!**
  A new study by Guillen Fernandez and colleagues suggests an intriguing strategy to boost your memory of what you've just learned: hit the gym four hours later. (*Current Biology*)
- **Smart biostatistics identifies ten new genes for intellectual disability**
  Researchers at Radboudumc and the Donders Institute have discovered ten new genes that are involved in the development of intellectual disability. (*Nature Neuroscience*)
- **Study charts development of emotional control in teens**
  Karin Roelofs and her colleagues describe how the ability to control emotions moves from one brain area to another as teens mature into adults, offering an opportunity to understand how disorders related to emotional control start. (*The Journal of Neuroscience*)
- **Depressed? Computers can help**
  Indira Tendolkar and colleagues have developed – in close collaboration with several universities in the USA – a new computerized treatment for depression called CBM-Memory, which is now made available to psychiatric clinics in the German-Dutch border region.
- **The brain networks of psychopathic criminals function differently**
  Robbert-Jan Verkes and his colleagues have shown that a strong focus on reward combined with a lack of self-control appear to be linked to the tendency to commit an offence. (*Social Cognitive and Affective Neuroscience*)

PhD defences

- 1 July 2016, DS 226*. **Lartseva, A.**, *Reading emotions: how people with Autism Spectrum Disorders process emotional language.*
- 8 July 2016, 234. **Witteveen, J.**, *Neurodevelopmental mechanisms underlying brain disorders – from loss-of-gene function to behavioural endophenotypes.*
- 31 Augustus 2016, DS 233. **Lindner, T.**, *Selective Visualization of intracranial arteries by means of Arterial Spin Labelled Magnetic Resonance Imaging.*
- 31 Augustus 2016, DS 219. **Bosga-Stork, I.**, *A longitudinal study of preparatory handwriting: Developing efficiency in motor control.*
- 22 September 2016, DS 232. **Van Holstein, M.**, *Neural circuitry and neurochemistry of motivated cognitive control. A cross-species approach.*
- 22 September 2016, DS 240. **Francx, W.**, *On neural networks related to ADHD as a continuous disorder.*
- 28 September 2016, DS 227. **Synhaeve, N.**, *Determinants of long-term functional prognosis after stroke in young adults.*
- 3 October 2016, DS 242. **Oldehinkel, M.**, *Investigation of cortico-striatal network dysfunction in ADHD using applications of resting-state fMRI.*
- 4 October 2016, DS 243. **Tuladhar, A.**, *The disconnected brain: mechanisms of clinical symptoms in cerebral small vessel disease.*
- 14 October 20176, DS 239. **Voet, N.**, *Aerobic exercise and cognitive behavioural therapy in facioscapulohumeral muscular dystrophy: a model-based approach.*
- 17 October 2016, DS 237. **Lam, K.**, *Understanding action-related language: sensorimotor contributions to meaning.*
- 19 October 2016, DS 241. **Van Dinteren, F.**, *Finding a new balance: change in cortical activations during the lifespan.*
- 4 November 2016, DS 236. **Walvoort, S.**, *The neuropsychology of alcohol use disorder: a multimethod evaluation of cognition and illness insight.*
- 8 November 2016, DS 248. **Kos, A.**, *Regulation of cortical neuronal development by microRNA-controlled gene networks.*
- 23 November 2016, DS 244. **Zimmermann, M.**, *A cerebral mechanism for translating action goals into action plans.*
- 28 November 2016, DS 246. **Thijssen, S.**, *Path Integral Control.*
- 1 December 2016, DS 249. **Piray, P.**, *Compute to learn. Neural implementation of computations underlying associative learning and decision making.*
- 5 December 2016, DS 235. **Bergsma, A.**, *The upper limb in neuromuscular disorders – from basic function to daily life performance.*
- 8 December 2016, DS 247. **Herpers, P.**, *Callous-unemotional traits in a cross-disorder perspective.*
- 13 December 2016, DS 251. **Post da Silveira, A.**, *Word stress in second-language word recognition and production.*
- 19 December 2016, DS 255. **Albers, B.**, *Sensory (re)weighting in spatial orientation.*
- 19 December 2016, DS 260. **Navarro Schröder, T.**, *Grids and gradients: structure and function for space in the brain.*
- 21 December 2016, DS 245. **Rensen, Y.**, *Life is not a fairy tale. Understanding (the relationship between) intrusions and confabulations.*

*Donders series number

DONDERS
TOOLKIT

Tool-kit courses on the Essentials of Neuroimaging, Advanced MRI/ fMRI, Advanced MEG/EEG and Transcranial Brain Stimulation. **See www.ru.nl/donders/toolkit for information, dates and updates.**

With 2500 visitors attending lectures and demonstrations, the Donders Open Day on September 24th was a great success.

DONDERS LECTURE 2 FEBRUARY 2017

Imaging and stimulating adaptive brain plasticity

Prof. Heidi Johansen-Berg (Oxford University) will open the 2017 Donders lecture series in February. She will talk about her work on how the brain changes with learning, experience, and as a result of damage. Her work is both fundamental and clinical.

The work being done by Heidi Johansen, who heads the Plasticity Group at the Oxford Centre for Functional FMRI of the Brain, is shedding light on how the healthy brain responds to change. Her group is assessing whether taking up exercise could slow the effects of ageing on the brain and is testing new methods for rehabilitation after stroke and This year they published a study in the journal *Science Translational Medicine* which suggests that electrical brain stimulation could benefit stroke patients by boosting the effects of rehabilitation therapy. This is an exciting message because there is a great deal of frustration about people not reaching their true recovery potential, due to the high cost of programmes and the limited availability of therapists.

Another line of research is developing new methods that help unravel the underlying biological phenomena of the measures that are derived from structural MRI. Structural methods have been powerful in indicating when and where changes occur in both grey and white matter during learning and recovery, but what has changed precisely? That is what the group led by Johansen aims to resolve. Ivan Toni, Professor of Cognitive Psychology, invited Prof. Johansen because her work is a prime example of how to combine excellent fundamental with clinical neuroscience, translating neurobiological evidence from animal models into human clinical interventions, and combining different methodologies in order to understand the mechanisms of neural plasticity.

DIARY

- 2 February 2017, **Donders Lecture** by **Heidi Johansen-Berg** on *Imaging and stimulating adaptive brain plasticity*. Linnaeus Building, 16.00-17.15
- 9 March 2017, **Donders Lecture** by **Ken Harris** on *The large-scale organization of neural activity*. Linnaeus Building, 16.00-17.15
- 22 June 2017, **Donders Lecture** by **Alcino Silva** on *Strategies and principles underlying the integration and planning of experiments in neuroscience in an age of information overload*. Linnaeus Building, 16.00-17.15

Anyone who is interested is welcome.

THE MACHINE

A new light-sheet microscope

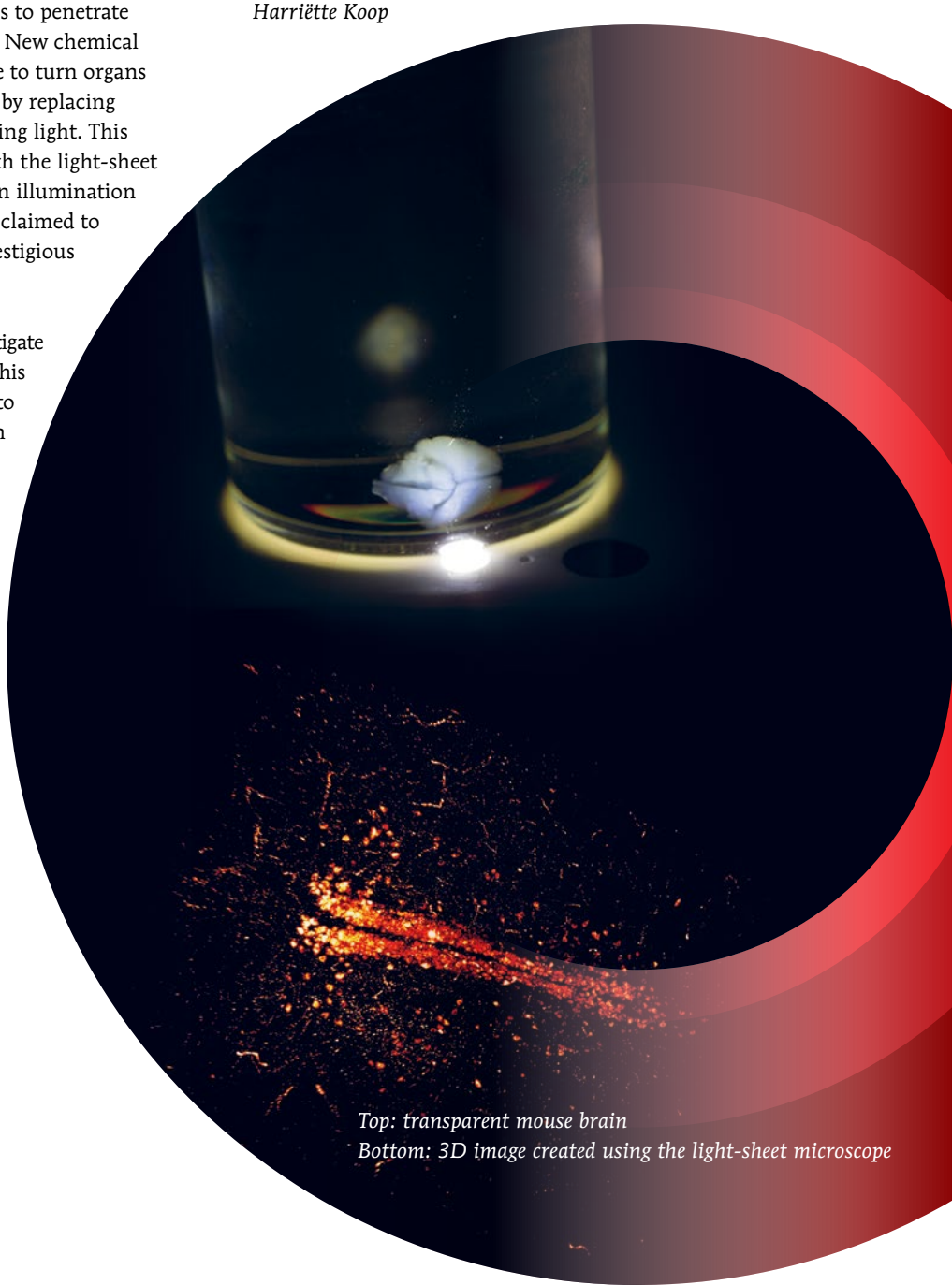
The installation of a light new microscope in the Trigon building at Donders promises the end of cut and paste brain images. The brain is a 3D organ, but neuroscientists generally look at it in a 2D way. To research the molecular physiology of the brain, one has to cut it into slices, measure the individual slices under a microscope and then put all the parts back together. Fortunately, this laborious approach has become superfluous with the arrival of the new light-sheet microscope at the Donders Institute. For the first time, it is now possible to image an intact brain. "To image a whole brain would normally take weeks. Now it can be done in an hour," says Nael Nadif Kasri, Assistant Professor in the Molecular Neurophysiology group at the Donders Institute.

To image a whole brain without cutting it open, the beam used by a light microscope needs to penetrate all the way through the brain sample. New chemical techniques are now making it possible to turn organs into transparent, glass-like structures by replacing lipids that normally reflect the incoming light. This clearing technique works perfectly with the light-sheet microscope, which uses 'selective plain illumination microscopy' (SPIM) and has been proclaimed to be the 'Method of the Year' by the prestigious journal Nature Methods.

Molecular neuroscientists tend to investigate small brain areas in great detail. With this new equipment, they will also be able to look at long-range connections between whole brain areas, as scientists working in the field of neuroimaging typically do. "This machine will merge these two worlds," Nael proudly points out. New knowledge can now be acquired about the brain circuits involved in stress or how brain circuits are affected in autism.

All researchers at Radboud University and the University's Medical Centre can use the light-sheet microscope, which is located in the Trigon Building of the Donders Institute. In addition to the brain, organoids and whole organisms can also be imaged. In January 2017, Nael expects the microscope to be up and running with everything needed in place: a station to clear the organs as well as the expertise required to analyze the hundreds of gigabytes of information that will become available with the microscope.

Harriëtte Koop



Top: transparent mouse brain
Bottom: 3D image created using the light-sheet microscope

DONDERS INSTITUTE Newsletter

The Donders Newsletter is published twice a year by the Donders Institute for Brain, Cognition and Behaviour, which brings together research groups at Radboud University and the Radboudumc as well as the Max Planck Institute for Psycholinguistics. Its purpose is to keep you informed of developments within the Donders Institute and the field of neuroscience.

Editors: Iris Kruijen, Nathalie Bovy and Mike Gould
Editorial Board: Nathalie Bovy, Marcel van Gerven, Harriette Koop, Iris Kruijen, Robert Oostenveld, Iris Roggema and Bert de Vries
Text: Iris Kruijen, Iris Roggema, Harriëtte Koop
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