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THE ENSEMBLE PROJECT
Earlier detection for earlier intervention

LES CAHIERS DE LA RECHERCHE
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Cerebral palsy (CP) is caused by damage to a baby's brain. Modern medicine now permits better management of the impairments that result from this damage, in particular thanks to progress in rehabilitation/readaptation techniques, and also because we have learnt how to limit the extent of the original injury, thus preventing the development of certain disabilities. The path to repairing a damaged brain remains long, but progress is being made by limiting the consequences of the injury: better detection of the very first signs of cerebral palsy, and improved early management of babies diagnosed with a brain injury. This is the challenge for the ENSEMBLE Project, led by a multi-disciplinary group of high-level researchers from across Europe.

"The earlier, the better", the motto behind the ENSEMBLE Project

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Coordinator of the
ENSEMBLE project

What is the purpose of ENSEMBLE?

Our goal is to improve the lives of children at risk for cerebral palsy and their families through partnership between researchers and families in Europe.

We will investigate and implement automatic tools for early diagnosis and prediction of long-term outcomes in newborns at risk of cerebral palsy.

Firstly, we will improve health programs for the early detection of CP by implementing international clinical practice guidelines, thereby reducing age at diagnosis and age at referral to CP-specific early intervention programs to under age 6 months.

Secondly, to achieve the first aim, we will develop and evaluate a machine-learning prediction model of long term motor and cognitive outcomes, based on established clinical markers, including neonatal neuroimaging, neuro-monitoring, and functional assessments.

Why are early interventions so important?

Children are often diagnosed after the ideal time for early interventions, missing the opportunity to capitalise on the brain's peak capacity for neuroplasticity, which occurs in early postnatal months.

In spite of the recent fast scientific progress in early detection and intervention in CP, there is still a lack of implementation into clinical practice and service delivery. The care that children with CP receive is disproportionately dictated by where they live and how their care is financed, rather than what is warranted by their condition, and the translation of the best science into context-specific best practice is still more hope than reality.

How do you detect early signs of CP?

The current tools that can best predict CP before 5 months of age are neonatal MRI, EEG and General Movements at 3-4 months of age. Training and experience is essential for interpretation. Machine-learning strategy is a highly efficient way to create a model to combine various methods in order to reliably predict CP at an early age.

We will collect multimodal data from a unique cohort of ~1,000 newborn infants with brain injury who are at high risk of developing CP, in eight clinics in five European countries. This prediction model can provide valuable data regarding the type, severity, and prognosis for neurodevelopmental disorders. Furthermore, it will facilitate knowledge translation eventually at a larger scale, accessible for a larger network, even for less experienced physicians.

So, is training as important as data collection for the project?

Our goal is to help clinicians at various sites across Europe, who treat high-risk infants, to make an early diagnosis of CP. This is particularly important, given that assessing cerebral injury and behavioral performance can be challenging for less experienced neonatologists in modalities relevant to CP outcome.

By combining a large-scale database with interdisciplinary expertise, this project will produce an automated scoring algorithm that uses cerebral measurements (MRI, EEG) and behavioral assessments together with clinical risk factors, thus providing a personalized, accurate diagnosis, prognosis and long-term outcome for each child. For this purpose, training and data collection are equally important.

What is unique in this project?

ENSEMBLE is highly relevant for families: to get insight in the impact of early prediction of the child's development on the family.

We will study the impact of early prediction of CP on the parents' mental wellbeing and how they cope with their work, social relations, their affected child's siblings, as well as their ability to cope with the child's problems (e.g., pain, crying, difficulty in sleeping and eating) while working together in multidisciplinary team with European wellknown experts in the field of neonatology, child neurology and rehabilitation and parent/patient representatives per country and their support organisations.

The quality and motivation of the team makes ENSEMBLE a high standard project, that gives potential for additional funding. With five countries and eight neonatal units involved, we will start building a unique data collection. This should start in October 2022, once all contracts to permit the exchange of data are signed. We will agree on harmonised data collection via protocols and will share a common opinion about the quality of those data.

In the future, other professionals will also be able to utilise these data via the open-access database. More importantly, this database will also allow us to follow these children through adolescence (and beyond) and hopefully link with other CP registers in many countries ●

Artificial intelligence: Machine learning should help us to see further

What is your role in the project?

Our aim is to develop a predictive model, based on data gathered from various consultations and tests, that will allow an earlier identification of risk factors and an earlier diagnosis of cerebral palsy than is currently possible.

This tool will advance the experts' ability to interpret medical results, especially because the tool has access to more data and a wider field of reference than a specialist, who is limited to their own domain of expertise.

The tool should, therefore, make it possible to recognise more subtle indications and, in turn, this should encourage the development of new management protocols for newborns identified as being at-risk.

How can you prepare to manage the data collected by practitioners?

We are fortunate to be able to rely on the French CATI (Centre for the Acquisition and Treatment of Images) platform, created in 2010 as part of the French Alzheimer's Disease Initiative, which provides expertise in the collection and processing of brain imaging data. The 12 years of using this platform to study psychiatric disorders and diseases of ageing have taught us how best to manage these data, and to minimise variability.

Jean-François Mangin

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Today, we are extending this field of study to include neonatology and incorporate data other than MRI scans, such as electroencephalograms or movement assessment videos.

Paradoxically, standardisation of these other data is less complicated than for MRI data since this requires modification of the scanners' settings to harmonise the results. Expertise acquired from the CATI will help to define standardised protocols for the collection of data and so avoid local differences which would disrupt the tool's predictive model. One challenge is to ensure that those who carry out the examinations are sufficiently aware of the protocols, so as to reduce the variability of the data collected, without disrupting the care they give to the children.

The collection phase will initially last for three years but, if all works well, we hope to continue the efforts far beyond this: the more data we have from care, the more we can advance our knowledge.

How will the data be used?

We are aiming to produce an "expert system" that lays down guidelines to inform care decisions, just as a specialist would; imagine, for example, that one could say to a newcomer to the department: "if we observe this, we can predict that" or "if the child is born at such an age, we may expect that this will happen".

The difference is that human experts are not always able to explain their decision-making process: there can be an element of "gut feeling" that the doctor may not be able to express. Artificial intelligence can identify and describe decisions that an expert would make without necessarily

A baby wearing an electrode cap during an electroencephalogram (EEG) recording: for greater precision, up to 64 electrodes can be used. This test is totally painless for the child.

(c) University Hospital Robert-Debré APHP, team inDev Inserm/CEA

knowing how to explain them, and it can therefore progress faster than a human to whom we have to try to explain these processes. Despite this, part of what happens inside the tool may still remain obscure, and so another challenge is to clearly show what information is being used by the algorithm for its predictions. This is particularly important when it is used in a clinical setting.

The tool will allow us to go further than is currently possible. While an expert can interpret data from ten sources when making a prediction, the tool will be able to use not only this information to make predictions, but also data from all available sources, and so its predictions will be based on a field of study far wider than that of any human expert.

In this way, data collected during all clinical examinations and consultations will contribute to the prediction-making process. This phase of the project will take five years.

What other benefits can be expected?

The data used will come from examination techniques, such as EEG and MRI, that are not always available in every care setting. Our tool, therefore, will enable the dissemination of information from these techniques to every centre. It will also allow those who are not experts to access such specialist information in an understandable format.

But we can also go further and dream a little: neural networks and the methods of machine learning that underpin artificial intelligence have been around since the 1950s, but now we have more powerful computers and a better understanding of how networks work. It seems reasonable to suppose that the guidelines for patient care could be improved by allowing computers, rather than humans, to interpret raw data directly.

In seeing what humans cannot see or explain, the tool could help research evolve and reveal things that are currently unknown. Artificial intelligence could identify groups we are not aware of at present: for example, those children who would otherwise leave the neonatal unit without follow-up "because they are fine", but for whom difficulties will appear later in life, once they have been lost sight of.

We will, therefore, be able to improve upon everything that we do currently using current techniques. But algorithms do not work like humans; they need a lot of data. Will 1,000 babies be enough? Because of the multiple presentations possible with CP, will the different cases repeat enough for conclusions to be drawn? It seems unlikely that this work can be finished in five years. But we believe that the database we are creating will not just apply to cerebral palsy: it will provide insights into a wide range of babies' health conditions ●

1,000 at-risk children to be monitored in a standardised way to create the database

Pr Valérie Biran

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Which children will be included in the ENSEMBLE Project clinical trial?

This part of the project aims to create a clinical database to model cerebral palsy risk, therefore only newborn infants with a brain injury diagnosed at an early stage by an MRI scan will be included. Injuries will include white matter damage, cerebellar lesions, or periventricular leukomalacia.

We aim to include approximately 1,000 newborns, divided into the following groups:

- approximately 600 premature babies born before 36 weeks' gestation
- approximately 350 babies born at term and diagnosed with hypoxic-ischaemic encephalopathy (a lack of oxygen to the brain) who required therapeutic hypothermia
- approximately 150 babies born at term and diagnosed as having had a stroke.

What types of data will be collected?

We will collect clinical data, as well as results from examinations such as MRI or EEG scans. These data will be entered using an electronic Case Report Form (e-CRF) entry tool which will be in a standardised format and language for all centres participating in the study.

For each child, data will be entered at the different stages of the study by the named practitioner and the team who is carrying out the study at that centre. The first data will be entered retrospectively, detailing pregnancy and birth.

The eight centres participating in the study will follow the same screening and follow-up protocol. These centres all have the same level of expertise, which should avoid bias due to differences in follow-up or the management of newborns. Apart from data collection and entry for this study, routine examinations will be carried out as normal.

Will this mean that follow-up appointments are slightly different?

We have developed a follow-up program for all centres; it includes all mandatory follow-up steps, as well as additional appointments for this project . The children included in the study will, therefore, benefit from closer monitoring and follow-up than children not in the study.

The first examination will be an EEG recording carried out within the first three days after birth. There will also be an MRI scan that will be performed between 4 and 7 days postnatally for full-term babies, and at corrected term* for premature babies.

Data will be collected at 3-4 months, at 6-9 months, at 15-18 months, and at 24-27 months. All appointments and clinical data collection will occur at the same time-points for all of the children: for babies born at term this will be their real age and for preterm babies the date will be corrected based on their prematurity.

Consultations will all be conducted in the presence of the child's parents. At each visit they will be asked to complete a questionnaire that assesses their child's development based on observations from daily life and their parenting experiences.

During these consultations, General Movement Assessment (GMA) tests will be performed and, from 3-4 until 15-18 months, selected observations from the Hammersmith Infant Neurological Examination (HINE**) will also be taken to identify risk factors.

Between the different study consultations, the children will continue to receive the usual follow-up care.

** "Corrected term" is the age of a baby which is equivalent to term, or 39/40 weeks of gestation. Therefore, if a child is born 2 months prematurely, at 32 weeks' gestation, at 5 months of age postnatally, their 'corrected' age would be 3 months.*

*** The Hammersmith Infant Neurological Examination (HINE) is a tool used to assess motor functions in infants from 2 months to 2 year of age.*

What are the benefits of this approach?

First of all, the study design will allow us to compare all patients because everything we observe will be quantified .

Analysis, and subsequent modelling of the data will of course also bring additional insights.

Finally, we anticipate that families will benefit directly from their participation in the study. Their children will receive additional support, as well receiving closer monitoring than usual, due to the additional data collection appointments ●

Training programs tailored to suit regional needs will help implement new methods for the benefit of children

Pr Andrea Guzzetta

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Coordinator of the
ENSEMBLE project

Training is a big part of the project, what is its purpose?

A fundamental part of the ENSEMBLE Project concerns the translation to clinical practice of what we already know in terms of early detection and intervention in CP.

Indeed, the translation of knowledge is a crucial aspect of research as usually the time between new discoveries and their clinical implementation is way too long.

For this reason, we believe that with the ENSEMBLE model we will be able to accelerate this process at the level of the Italian and French neonatal and follow-up networks of high risk infants, by providing comprehensive training to clinicians interested in catching up with the newest advances in early detection and intervention.

Who is concerned?

Knowledge translation of early detection and intervention will target clinicians involved in the early follow-up programs of high risk infants, as well as families and the general public. We will start by surveying current practices and knowledge to tailor the knowledge translation to the actual needs of the different regional contexts.

There will be a general design based on current knowledge on best implementation practices, but training will be context specific, based on different languages and local practices and level of current implementation.

What is the content of the training?

The training will focus on three main streams:

- the early detection one will cover current knowledge on the best tools to early identify infants at high risk, including general movements assessment, structured neurological assessments and neuroimaging;
- the early surveillance stream consisting of the translation of the best tools to surveil early development in infants at high risk;
- and the early intervention stream, consisting of the spreading of the best practices of early treatment in these infants, based on recent international recommendations.

At the end of the project, how will you implement the guidelines and recommendations to promote early detection and interventions widely?

As part of the project we will monitor knowledge uptake and we will assess potential benefits against historical data. We will also assess the impact on families and we hope that the effects will be significant and inspiring for the rest of the international community ●

The view of the families supports the richness of the ENSEMBLE Project

You are an advocate of collaboration between patients, families, clinicians and researchers, why is it so important?

We know that cerebral palsy, like other disabilities, affects the whole family and has a huge impact on the family life and its organisation. Thus it is very important to include them and to listen to them to make research projects more relevant.

Families often have a different perspective and consider the issues through another lense, we learn a lot from them: what really matters, how to deal with the questions and the certainties...

What is interesting in this project is the combination of fundamental research, the use of artificial intelligence, clinical data, practic-based research focusing on the families and the long-term development of the children, and the focus on knowledge translation and implementation.

Usually, we tend to do research in silos with separate studies, but this project considers the full spectrum of the child's development; it is a major step in connecting relevant research that will hopefully make a difference.

How will you proceed to include the families' perspectives?

We will send a questionnaire to the families of the 1,000 children included in the study, we will have interviews with parents, and we have established a Family Advisory Council that will represent families within the project management and provide us with advice. There will be a central family council, plus local councils for each country participating in the project.

Questionnaires will be sent individually to families when the child is 4 months old and 2 years old. We will exchange with the Family Advisory Council on a regular basis. We will collect information in all countries, and then share the interpretation. We don't know yet how often we will exchange with the council, nor the form of feedback we will get from families, we will work it out together with them.

Dr Marjolijn Ketelaar

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Co-founder of CP-Net
in The Netherlands

We definitely need to hear their voices and their needs, for example to collect insights about the parents' experiences and wellbeing. It will help us understand what type of information and how much needs to be shared with them: families don't necessary need all the details they could have access to.

We know from other studies that parents want honest information. But this can be difficult for clinicians: sometimes it's too early to know, or honest information is too tough, where we know hope is important too.

One of our purposes is to establish recommendations about how to provide optimal individual support ●

8 CLINICAL TEAMS - 5 COUNTRIES

France, Germany, Italy, Spain, The Netherlands

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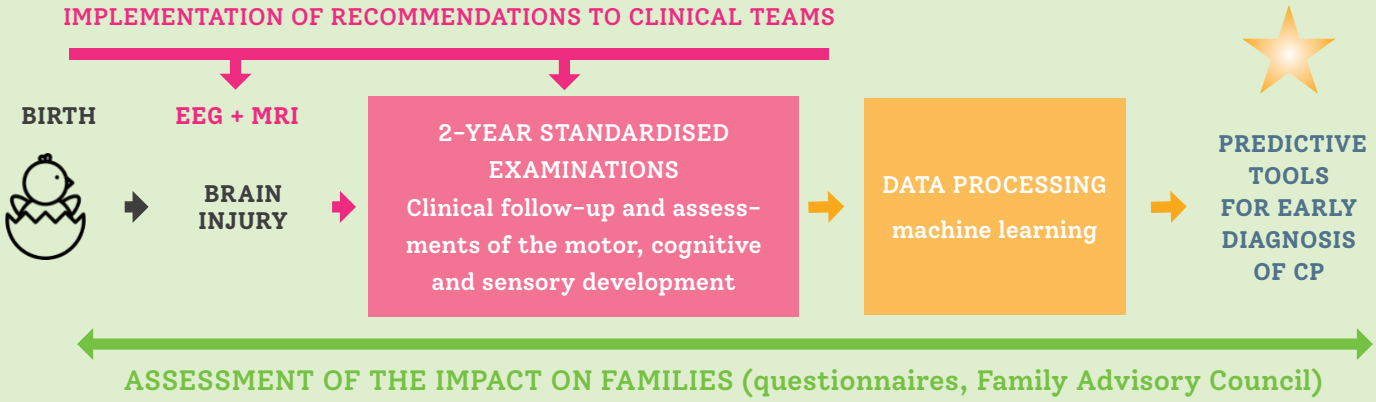

THE FAMILIES' POINT OF VIEW

Jean-Claude Graindorge

Member of the Scientific Council of the Fondation Paralysie Cérébrale
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For one of the first times, with the ENSEMBLE Project, we (the families) are witnessing where collaboration between families and research is so important. Not only were families involved in the decision to support this research work by having one of their representatives on the Foundation's scientific board, but a Family Council was also established within the project itself. All of this has given us feelings of greater involvement than in other studies.

Together with the Family Council, this work will include the views of families, those who are affected today, and those who have already been through it. For parents like me, whose child with cerebral palsy is now an adult, the feedback received from other parents confirms the idea underpinning this project: the earlier you learn about the risk or reality of cerebral palsy for your child, the better it is for the whole family. And by family we mean, of course, not only the parents, but also siblings and the whole close circle of friends.

The therapeutic benefits of early detection and treatment for the child are now well-known, and they justify this research project. But what has been less discussed are the benefits of providing early information to the family and its organisation. It must be said that this runs against the traditional attitude of medicine as "la grande muette"*.

When their child's disability is diagnosed, many families, sometimes suddenly and often despairingly go through a phase of denial, a period during which they hope that "everything will be alright". By the provision of information at an early stage we can reduce this period of denial, so often an obstacle to the prompt care that reduces the risk of difficulties and increases the child's chances and abilities. It also improves the acceptance of reality, and not only does this allow the family to organise itself earlier and better, but it also helps to reduce negative psychological effects for parents and siblings.

Early detection and information, in promoting earlier care, "lightens the load" for parents: they know that they have done the best for their child and that they can now calmly organise their family life.

** a French expression that means to be secretive or silent; it translates literally as "the great mute".*

Those Cahiers de la recherche are based on interviews. The texts of Jean-François Mangin, Valérie Biran and Jean-Claude Graindorge have been translated from French.

LABEL IDEAS L'EXIGENCE en action

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