Associated with document Ref. Ares(2018)3866948 - 20/07/2018 H2020 MGA MSCA ITN — Multi: v5.0

EUROPEAN COMMISSION
Research Executive Agency

Director

GRANT AGREEMENT

NUMBER — 813986 — Syn2Psy

This **Agreement** ('the Agreement') is **between** the following parties:

on the one part,

the **Research Executive Agency (REA)** ('the Agency'), under the powers delegated by the European Commission ('the Commission'),

represented for the purposes of signature of this Agreement by Head of Unit, Research Executive Agency , Excellent Science Department, Marie Sklodowska-Curie Innovative Training Networks, Klaus-Guenther BARTHEL,

and

on the other part,

1. 'the coordinator':

CENTRO DE NEUROCIENCIAS E BIOLOGIACELULAR ASSOCIACAO (CNC), established in UNIVERSIDADE DE COIMBRA, LARGO DE POMBAL, COIMBRA 3004 517, Portugal, VAT number: PT502510439, represented for the purposes of signing the Agreement by Sílvia Marisa ESTEVES DE SOUSA

and the following other beneficiaries, if they sign their 'Accession Form' (see Annex 3 and Article 56):

2. **CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS (CNRS)**, established in RUE MICHEL ANGE 3, PARIS 75794, France, VAT number: FR40180089013,

3. **ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE (EPFL)**, established in BATIMENT CE 3316 STATION 1, LAUSANNE 1015, Switzerland, VAT number: CHE116075613TVA,

4. **IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE (Imperial)**, established in SOUTH KENSINGTON CAMPUS EXHIBITION ROAD, LONDON SW7 2AZ, United Kingdom, VAT number: GB649926678,

5. **THE UNIVERSITY OF EDINBURGH (UEDIN)**, established in OLD COLLEGE, SOUTH BRIDGE, EDINBURGH EH8 9YL, United Kingdom, VAT number: GB592950700,

6. **H. LUNDBECK AS (H. LUNDBECK AS)**, established in OTTILIAVEJ 7-9, VALBY 2500, Denmark, VAT number: DK56759913,

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Unless otherwise specified, references to ‘beneficiary’ or ‘beneficiaries’ include the coordinator.

The parties referred to above have agreed to enter into the Agreement under the terms and conditions below.

By signing the Agreement or the Accession Form, the beneficiaries accept the grant and agree to implement it under their own responsibility and in accordance with the Agreement, with all the obligations and conditions it sets out.

The Agreement is composed of:

Terms and Conditions

Annex 1 Description of the action

Annex 2 Estimated budget for the action

2a Additional information on the estimated budget

Annex 3 Accession Forms

Annex 4 Model for the financial statements

Annex 5 Not applicable

Annex 6 Not applicable

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CHAPTER 1 GENERAL

ARTICLE 1 — SUBJECT OF THE AGREEMENT

This Agreement sets out the rights and obligations and the terms and conditions applicable to the grant awarded to the beneficiaries for implementing the action set out in Chapter 2.

CHAPTER 2 ACTION

ARTICLE 2 — ACTION TO BE IMPLEMENTED

The grant is awarded for the action entitled '**Synaptic Dysfunction in Neuropsychiatric Disorders**' — '**Syn2Psy**' **('action')**, as described in Annex 1.

ARTICLE 3 — DURATION AND STARTING DATE OF THE ACTION

The duration of the action will be **48 months** as of 1 March 2019 ('**starting date of the action**').

ARTICLE 4 — ESTIMATED BUDGET AND BUDGET TRANSFERS

4.1 Estimated budget

The '**estimated budget**' for the action is set out in Annex 2.

It contains the estimated eligible costs and the forms of costs, broken down by beneficiary and budget category (see Articles 5, 6).

4.2 Budget transfers

The estimated budget breakdown indicated in Annex 2 may be adjusted by transfers of amounts between beneficiaries.

This does not require an amendment according to Article 55, if the action is implemented as described in Annex 1.

However, no more than 40% of the maximum grant amount (see Article 5.1) may be allocated to beneficiaries located in the same country or to any one international European interest organisation or international organisation.

CHAPTER 3 GRANT

ARTICLE 5 — GRANT AMOUNT, FORM OF GRANT, REIMBURSEMENT RATES AND FORMS OF COSTS

5.1 Maximum grant amount

The '**maximum grant amount**' is **EUR 3 885 134.40** (three million eight hundred and eighty five thousand one hundred and thirty four EURO and forty eurocents).

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5.2 Form of grant, reimbursement rate and form of costs

The grant reimburses **100 %** of the action's eligible costs (see Article 6) ('**reimbursement of eligible costs grant**') (see Annex 2).

The estimated eligible costs of the action are EUR **3 885 134.40** (three million eight hundred and eighty five thousand one hundred and thirty four EURO and forty eurocents).

Eligible costs (see Article 6) must be declared under the following form ('**form of costs**'):

(a) for **costs for recruited researchers** (living, mobility and family allowances): on the basis of the amount(s) per unit set out in Annex 2 ('**unit costs**') and

(b) for **institutional costs** (research, training and networking costs and management and indirect costs): on the basis of the amount per unit set out in Annex 2 (**unit costs**).

5.3 Final grant amount — Calculation

The '**final grant amount**' depends on the actual extent to which the action is implemented in accordance with the Agreement's terms and conditions.

This amount is calculated by the Agency — when the payment of the balance is made (see Article 21.4) — in the following steps:

Step 1 – Application of the reimbursement rate to the eligible costs

Step 2 – Limit to the maximum grant amount

Step 3 – Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

5.3.1 Step 1 — Application of the reimbursement rates to the eligible costs

The reimbursement rate (see Article 5.2) is applied to eligible costs (unit costs; see Article 6) declared by the beneficiaries and approved by the Agency (see Article 21).

5.3.2 Step 2 — Limit to the maximum grant amount

If the amount obtained following Step 1 is higher than the maximum grant amount set out in Article 5.1, it will be limited to the latter.

5.3.3 Step 3 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations — Reduced grant amount — Calculation

If the grant is reduced (see Article 43), the Agency will calculate the reduced grant amount by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the maximum grant amount set out in Article 5.1.

The final grant amount will be the lower of the following two:

- the amount obtained following Steps 1 and 2 or
- the reduced grant amount following Step 3.

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5.4 Revised final grant amount — Calculation

If — after the payment of the balance (in particular, after checks, reviews, audits or investigations; see Article 22) — the Agency rejects costs (see Article 42) or reduces the grant (see Article 43), it will calculate the '**revised final grant amount**' for the beneficiary concerned by the findings.

This amount is calculated by the Agency on the basis of the findings, as follows:

- in case of **rejection of costs**: by applying the reimbursement rate to the revised eligible costs approved by the Agency for the beneficiary concerned;

- in case of **reduction of the grant**: by calculating the concerned beneficiary's share in the grant amount reduced in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations (see Article 43.2).

In case of **rejection of costs and reduction of the grant**, the revised final grant amount for the beneficiary concerned will be the lower of the two amounts above.

ARTICLE 6 — ELIGIBLE AND INELIGIBLE COSTS

6.1 General conditions for costs to be eligible

Unit costs are eligible ('eligible costs') if:

(a) they are calculated as follows:

{amounts per unit set out in Annex 2

multiplied by

the number of actual units}.

(b) the number of actual units complies with the following:

- the units must be actually used or produced in the period set out in Article 3;

- the units must be necessary for implementing the action or produced by it, and

- the number of units must be identifiable and verifiable, in particular supported by records and documentation (see Article 18).

6.2 Specific conditions for costs to be eligible

Costs are eligible, if they comply with the general conditions (see above) and the specific conditions set out below for each of the following two budget categories:

A. Costs for recruited researchers (A.1 Living allowance, A.2 Mobility allowance and A.3 Family allowance) are eligible, if:

(a) the number of units declared:

(i) corresponds to the actual number of months spent by the recruited researchers on the research training activities and

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(ii) does not exceed 36 months (per researcher);

(b) the recruited researchers comply with the following conditions:

(i) be recruited by the beneficiary under an **employment contract** (or other direct contract with equivalent benefits, including social security coverage) or — if not otherwise possible under national law — under a fixed amount fellowship agreement with minimum social security coverage;

(ii) be employed for at least 3 months;

(iii) be employed full-time, unless the Agency has approved a part-time employment for personal or family reasons;

(iv) be working exclusively for the action;

(v) not have resided in the country of the recruiting beneficiary for more than 12 months in the 3 years immediately before the recruitment date (and not have carried out their main activity (work, studies, etc.) in that country) — unless as part of a procedure for obtaining refugee status under the Geneva Convention[1].

For beneficiaries that are international European interest organisations or international organisations: not have spent with the beneficiary more than 12 months in the 3 years immediately before the recruitment date.

(vi) be — at the date of recruitment — an '**early stage researcher**' (i.e. in the first four years of his/her research career and not have a doctoral degree).

(c) the costs have been fully incurred for the benefit of the recruited researchers.

This latter condition is met if:

{{{**total remuneration costs** (salaries, social security contributions, taxes and other costs included in the remuneration under the employment contract or other direct contract) or **total fixed-amount fellowship costs** for the researcher during the action

plus

total mobility costs (household, relocation and travel expenses and, if they must be paid under national law, taxes, duties and social security contributions) for the researcher during the action}

plus

total family costs for the researcher during the action}

divided by

the number of actual units}.

is equal to or higher than the following amount:

{{amount per unit cost set out in Annex 2 as living allowance

[1] 1951 Refugee Convention and the 1967 Protocol.

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plus

amount per unit cost set out in Annex 2 as mobility allowance}

plus

if it is due, amount per unit cost set out in Annex 2 as family allowance}.

The family allowance is due if the researcher has a family at the time of recruitment.

'Family' means persons linked to the researcher by marriage (or a relationship with equivalent status to a marriage recognised by the legislation of the country where this relationship was formalised) or dependent children who are actually being maintained by the researcher.

B. Institutional costs (B.1 Research, training and networking costs and B.2 Management and indirect costs) are eligible if the costs for the recruited researchers (living allowance, mobility allowance, family allowance; see above) are eligible.

6.3 Ineligible costs

'**Ineligible costs**' are:

(a) costs that do not comply with the conditions set out above (in Article 6.1), and in particular costs incurred during suspension of the action implementation (see Article 49);

(b) costs declared under another EU or Euratom grant (including grants awarded by a Member State and financed by the EU or Euratom budget and grants awarded by bodies other than the Agency for the purpose of implementing the EU or Euratom budget), in particular, indirect costs if the beneficiary is already receiving an operating grant financed by the EU or Euratom budget in the same period, unless it can demonstrate that the operating grant does not cover any costs of the action.

6.4 Consequences of declaration of ineligible costs

Declared costs that are ineligible will be rejected (see Article 42).

This may also lead to any of the other measures described in Chapter 6.

CHAPTER 4 RIGHTS AND OBLIGATIONS OF THE PARTIES

SECTION 1 RIGHTS AND OBLIGATIONS RELATED TO IMPLEMENTING THE ACTION

ARTICLE 7 — GENERAL OBLIGATION TO PROPERLY IMPLEMENT THE ACTION

7.1 General obligation to properly implement the action

The beneficiaries must implement the action as described in Annex 1 and in compliance with the provisions of the Agreement and all legal obligations under applicable EU, international and national law.

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7.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 8 — RESOURCES TO IMPLEMENT THE ACTION — THIRD PARTIES INVOLVED IN THE ACTION

The beneficiaries must have the appropriate resources to implement the action.

If it is necessary to implement the action, the beneficiaries may:

- call upon entities with a capital or legal link to the beneficiaries[2], to implement certain action tasks described in Annex 1 (i.e. hosting and training of researchers);
- call upon partner organisations to implement certain action tasks described in Annex 1 (i.e. hosting and training researchers during secondments).

In this case, the beneficiaries retain sole responsibility towards the Agency for implementing the action.

ARTICLE 9 — IMPLEMENTATION OF ACTION TASKS BY BENEFICIARIES NOT RECEIVING EU FUNDING

Not applicable

ARTICLE 10 — PURCHASE OF GOODS, WORKS OR SERVICES

Not applicable

ARTICLE 11 — USE OF IN-KIND CONTRIBUTIONS PROVIDED BY THIRD PARTIES AGAINST PAYMENT

Not applicable

ARTICLE 12 — USE OF IN-KIND CONTRIBUTIONS PROVIDED BY THIRD PARTIES FREE OF CHARGE

Not applicable

ARTICLE 13 — IMPLEMENTATION OF ACTION TASKS BY SUBCONTRACTORS

Not applicable

[2] '**Entities with a capital or legal link**' are entities that have a link with the beneficiary, in particular, a legal or capital link, which is neither limited to the action nor established for the sole purpose of its implementation.

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ARTICLE 14 — IMPLEMENTATION OF ACTION TASKS BY LINKED THIRD PARTIES

Not applicable

ARTICLE 15 — FINANCIAL SUPPORT TO THIRD PARTIES

Not applicable

ARTICLE 16 — PROVISION OF TRANS-NATIONAL OR VIRTUAL ACCESS TO RESEARCH INFRASTRUCTURE

Not applicable

SECTION 2 RIGHTS AND OBLIGATIONS RELATED TO THE GRANT ADMINISTRATION

ARTICLE 17 — GENERAL OBLIGATION TO INFORM

17.1 General obligation to provide information upon request

The beneficiaries must provide — during implementation of the action or afterwards and in accordance with Article 41.2 — any information requested in order to verify eligibility of the costs, proper implementation of the action and compliance with any other obligation under the Agreement.

17.2 Obligation to keep information up to date and to inform about events and circumstances likely to affect the Agreement

Each beneficiary must keep information stored in the Participant Portal Beneficiary Register (via the electronic exchange system; see Article 52) up to date, in particular, its name, address, legal representatives, legal form and organisation type.

Each beneficiary must immediately inform the coordinator — which must immediately inform the Agency and the other beneficiaries — of any of the following:

(a) **events** which are likely to affect significantly or delay the implementation of the action or the EU's financial interests, in particular:

(i) changes in its legal, financial, technical, organisational or ownership situation (or those of an entity with a capital or legal link);

(ii) changes in the name, address, legal form or organisation type of an entity with a capital or legal link;

(b) **circumstances** affecting:

(i) the decision to award the grant or

(ii) compliance with requirements under the Agreement.

17.3 Consequences of non-compliance

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If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 18 — KEEPING RECORDS — SUPPORTING DOCUMENTATION

18.1 Obligation to keep records and other supporting documentation

The beneficiaries must — for a period of five years after the payment of the balance — keep records and other supporting documentation in order to prove the proper implementation of the action and the costs they declare as eligible.

They must make them available upon request (see Article 17) or in the context of checks, reviews, audits or investigations (see Article 22).

If there are on-going checks, reviews, audits, investigations, litigation or other pursuits of claims under the Agreement (including the extension of findings; see Articles 22), the beneficiaries must keep the records and other supporting documentation until the end of these procedures.

The beneficiaries must keep the original documents. Digital and digitalised documents are considered originals if they are authorised by the applicable national law. The Agency may accept non-original documents if it considers that they offer a comparable level of assurance.

18.1.1 Records and other supporting documentation on the scientific and technical implementation

The beneficiaries must keep records and other supporting documentation on scientific and technical implementation of the action in line with the accepted standards in the respective field.

18.1.2 Records and other documentation to support the costs declared

The beneficiaries must keep adequate records and other supporting documentation to prove the number of units declared and that the costs for recruited researchers (living allowance, mobility allowance, family allowance) have been fully incurred for the benefit of the researchers.

18.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, costs insufficiently substantiated will be ineligible (see Article 6) and will be rejected (see Article 42), and the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 19 — SUBMISSION OF DELIVERABLES

19.1 Obligation to submit deliverables

The coordinator must:

- submit a '**progress report**' within 30 days after one year from the starting date of the action;

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- organise a '**mid-term meeting**' between the beneficiaries, entities with a capital or legal link, partner organisations and the Agency before the deadline for the submission of the report for RP 1 (reporting period 1);

- establish a **supervisory board** of the network;

- submit any **other deliverables** identified in Annex 1, in accordance with the timing and conditions set out in it.

The beneficiaries must:

- submit a '**researcher declaration**' within 20 days after the recruitment of each researcher.

19.2 Consequences of non-compliance

If a beneficiary or the coordinator breaches any of its obligations under this Article, the Agency may apply any of the measures provided for in Chapter 6.

ARTICLE 20 — REPORTING — PAYMENT REQUESTS

20.1 Obligation to submit reports

The coordinator must submit to the Agency (see Article 52) the technical and financial reports set out in this Article. These reports include the requests for payments and must be drawn up using the forms and templates provided in the electronic exchange system (see Article 52).

20.2 Reporting periods

The action is divided into the following '**reporting periods**':

- RP1: from month 1 to month 24
- RP2: from month 25 to month 48

20.3 Periodic reports — Requests for interim payments

The coordinator must submit a periodic report within 60 days following the end of each reporting period.

The **periodic report** must include the following:

(a) a '**periodic technical report**' containing:

(i) an **explanation of the work carried out** by the beneficiaries;

(ii) an **overview of the progress** towards the objectives of the action, including milestones and deliverables identified in Annex 1.

This report must include explanations justifying the differences between work expected to be carried out in accordance with Annex 1 and that actually carried out.

The report must detail the exploitation and dissemination of the results and — if required in Annex 1 — an updated '**plan for the exploitation and dissemination of the results**'.

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The report must indicate the communication activities;

(iii) a **summary** for publication by the Agency;

(iv) the answers to the '**questionnaire**', covering issues related to the action implementation and the economic and societal impact, notably in the context of the Horizon 2020 key performance indicators and the Horizon 2020 monitoring requirements;

(b) a '**periodic financial report**' containing:

(i) an '**individual financial statement**' (see Annex 4) from each beneficiary, for the reporting period concerned.

The individual financial statement must detail the eligible costs (see Article 6) for each budget category (see Annex 2).

The beneficiaries must declare all eligible costs even if they exceed the amounts indicated in the estimated budget (see Annex 2). Amounts which are not declared in the individual financial statement will not be taken into account by the Agency.

If an individual financial statement is not submitted for a reporting period, it may be included in the periodic financial report for the next reporting period.

Each beneficiary must **certify** that:

- the information provided is full, reliable and true;
- the costs declared are eligible (see Article 6);
- the costs can be substantiated by adequate records and supporting documentation (see Article 18) that will be produced upon request (see Article 17) or in the context of checks, reviews, audits and investigations (see Article 22)

(ii) not applicable;

(iii) not applicable;

(iv) a '**periodic summary financial statement**', created automatically by the electronic exchange system, consolidating the individual financial statements for the reporting period concerned and including — except for the last reporting period — the **request for interim payment**.

20.4 Final report — Request for payment of the balance

In addition to the periodic report for the last reporting period, the coordinator must submit the final report within 60 days following the end of the last reporting period.

The final report must include the following:

(a) a '**final technical report**' with a summary for publication containing:

(i) an overview of the results and their exploitation and dissemination;

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(ii) the conclusions on the action, and

(iii) the socio-economic impact of the action;

(b) a '**final financial report**' containing a '**final summary financial statement**', created automatically by the electronic exchange system, consolidating the individual financial statements for all reporting periods and including the **request for payment of the balance**

20.5 Information on cumulative expenditure incurred

Not applicable

20.6 Currency for financial statements

Financial statements must be drafted in euro.

20.7 Language of reports

All reports (technical and financial reports, including financial statements) must be submitted in the language of the Agreement.

20.8 Consequences of non-compliance

If the reports submitted do not comply with this Article, the Agency may suspend the payment deadline (see Article 47) and apply any of the other measures described in Chapter 6.

If the coordinator breaches its obligation to submit the reports and if it fails to comply with this obligation within 30 days following a written reminder, the Agency may terminate the Agreement or apply any of the other measures described in Chapter 6.

ARTICLE 21 — PAYMENTS AND PAYMENT ARRANGEMENTS

21.1 Payments to be made

The following payments will be made to the coordinator:

- one **pre-financing payment**;
- one or more **interim payments**, on the basis of the request(s) for interim payment (see Article 20), and
- one **payment of the balance**, on the basis of the request for payment of the balance (see Article 20).

21.2 Pre-financing payment — Amount — Amount retained for the Guarantee Fund

The aim of the pre-financing is to provide the beneficiaries with a float.

It remains the property of the EU until the payment of the balance.

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The amount of the pre-financing payment will be EUR **3 108 107.52** (three million one hundred and eight thousand one hundred and seven EURO and fifty two eurocents).

The Agency will — except if Article 48 applies — make the pre-financing payment to the coordinator within 30 days from the entry into force of the Agreement (see Article 58) or from 10 days before the starting date of the action (see Article 3).

An amount of EUR **194 256.72** (one hundred and ninety four thousand two hundred and fifty six EURO and seventy two eurocents), corresponding to 5% of the maximum grant amount (see Article 5.1), is retained by the Agency from the pre-financing payment and transferred into the '**Guarantee Fund**'.

21.3 Interim payments — Amount — Calculation

Interim payments reimburse the eligible costs incurred for the implementation of the action during the corresponding reporting periods.

The Agency will pay to the coordinator the amount due as interim payment within 90 days from receiving the periodic report (see Article 20.3), except if Articles 47 or 48 apply.

Payment is subject to the approval of the periodic report. Its approval does not imply recognition of the compliance, authenticity, completeness or correctness of its content.

The **amount due as interim payment** is calculated by the Agency in the following steps:

Step 1 – Application of the reimbursement rates

Step 2 – Limit to 90% of the maximum grant amount

21.3.1 Step 1 — Application of the reimbursement rates

The reimbursement rate(s) (see Article 5.2) are applied to the eligible costs (actual costs, unit costs and flat-rate costs; see Article 6) declared by the beneficiaries (see Article 20) and approved by the Agency (see above) for the concerned reporting period.

21.3.2 Step 2 — Limit to 90% of the maximum grant amount

The total amount of pre-financing and interim payments must not exceed 90% of the maximum grant amount set out in Article 5.1. The maximum amount for the interim payment will be calculated as follows:

{90% of the maximum grant amount (see Article 5.1)

minus

{pre-financing and previous interim payments}}.

21.4 Payment of the balance — Amount — Calculation — Release of the amount retained for the Guarantee Fund

The payment of the balance reimburses the remaining part of the eligible costs incurred by the beneficiaries for the implementation of the action.

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If the total amount of earlier payments is greater than the final grant amount (see Article 5.3), the payment of the balance takes the form of a recovery (see Article 44).

If the total amount of earlier payments is lower than the final grant amount, the Agency will pay the balance within 90 days from receiving the final report (see Article 20.4), except if Articles 47 or 48 apply.

Payment is subject to the approval of the final report. Its approval does not imply recognition of the compliance, authenticity, completeness or correctness of its content.

The amount due as the balance is calculated by the Agency by deducting the total amount of pre-financing and interim payments (if any) already made, from the final grant amount determined in accordance with Article 5.3:

{final grant amount (see Article 5.3)

minus

{pre-financing and interim payments (if any) made}}.

At the payment of the balance, the amount retained for the Guarantee Fund (see above) will be released and:

- if the balance is positive: the amount released will be paid in full to the coordinator together with the amount due as the balance;
- if the balance is negative (payment of the balance taking the form of recovery): it will be deducted from the amount released (see Article 44.1.2). If the resulting amount:
    - is positive, it will be paid to the coordinator
    - is negative, it will be recovered.

The amount to be paid may however be offset — without the beneficiaries' consent — against any other amount owed by a beneficiary to the Agency, the Commission or another executive agency (under the EU or Euratom budget), up to the maximum EU contribution indicated, for that beneficiary, in the estimated budget (see Annex 2).

21.5 Notification of amounts due

When making payments, the Agency will formally notify to the coordinator the amount due, specifying whether it concerns an interim payment or the payment of the balance.

For the payment of the balance, the notification will also specify the final grant amount.

In the case of reduction of the grant or recovery of undue amounts, the notification will be preceded by the contradictory procedure set out in Articles 43 and 44.

21.6 Currency for payments

The Agency will make all payments in euro.

21.7 Payments to the coordinator — Distribution to the beneficiaries

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Payments will be made to the coordinator.

Payments to the coordinator will discharge the Agency from its payment obligation.

The coordinator must distribute the payments between the beneficiaries without unjustified delay.

Pre-financing may however be distributed only:

(a) if the minimum number of beneficiaries set out in the call for proposals has acceded to the Agreement (see Article 56) and

(b) to beneficiaries that have acceded to the Agreement (see Article 56).

21.8 Bank account for payments

All payments will be made to the following bank account:

Name of bank: BANCO SANTANDER TOTTA, SA
Full name of the account holder: CENTRO DE NEUROCIENCIAS DE COIMBRA
IBAN code: PT50001800010020200611888

21.9 Costs of payment transfers

The cost of the payment transfers is borne as follows:

- the Agency bears the cost of transfers charged by its bank;
- the beneficiary bears the cost of transfers charged by its bank;
- the party causing a repetition of a transfer bears all costs of the repeated transfer.

21.10 Date of payment

Payments by the Agency are considered to have been carried out on the date when they are debited to its account.

21.11 Consequences of non-compliance

21.11.1 If the Agency does not pay within the payment deadlines (see above), the beneficiaries are entitled to **late-payment interest** at the rate applied by the European Central Bank (ECB) for its main refinancing operations in euros ('reference rate'), plus three and a half points. The reference rate is the rate in force on the first day of the month in which the payment deadline expires, as published in the C series of the *Official Journal of the European Union*.

If the late-payment interest is lower than or equal to EUR 200, it will be paid to the coordinator only upon request submitted within two months of receiving the late payment.

Late-payment interest is not due if all beneficiaries are EU Member States (including regional and local government authorities or other public bodies acting on behalf of a Member State for the purpose of this Agreement).

Suspension of the payment deadline or payments (see Articles 47 and 48) will not be considered as late payment.

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Late-payment interest covers the period running from the day following the due date for payment (see above), up to and including the date of payment.

Late-payment interest is not considered for the purposes of calculating the final grant amount.

21.11.2 If the coordinator breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or the participation of the coordinator may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 22 — CHECKS, REVIEWS, AUDITS AND INVESTIGATIONS — EXTENSION OF FINDINGS

22.1 Checks, reviews and audits by the Agency and the Commission

22.1.1 Right to carry out checks

The Agency or the Commission will — during the implementation of the action or afterwards — check the proper implementation of the action and compliance with the obligations under the Agreement, including assessing deliverables and reports.

For this purpose the Agency or the Commission may be assisted by external persons or bodies.

The Agency or the Commission may also request additional information in accordance with Article 17. The Agency or the Commission may request beneficiaries to provide such information to it directly.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

22.1.2 Right to carry out reviews

The Agency or the Commission may — during the implementation of the action or afterwards — carry out reviews on the proper implementation of the action (including assessment of deliverables and reports), compliance with the obligations under the Agreement and continued scientific or technological relevance of the action.

Reviews may be started up to two years after the payment of the balance. They will be formally notified to the coordinator or beneficiary concerned and will be considered to have started on the date of the formal notification.

The Agency or the Commission may carry out reviews directly (using its own staff) or indirectly (using external persons or bodies appointed to do so). It will inform the coordinator or beneficiary concerned of the identity of the external persons or bodies. They have the right to object to the appointment on grounds of commercial confidentiality.

The coordinator or beneficiary concerned must provide — within the deadline requested — any information and data in addition to deliverables and reports already submitted (including information on the use of resources). The Agency or the Commission may request beneficiaries to provide such information to it directly.

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The coordinator or beneficiary concerned may be requested to participate in meetings, including with external experts.

For **on-the-spot** reviews, the beneficiaries must allow access to their sites and premises, including to external persons or bodies, and must ensure that information requested is readily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the review findings, a '**review report**' will be drawn up.

The Agency or the Commission will formally notify the review report to the coordinator or beneficiary concerned, which has 30 days to formally notify observations ('**contradictory review procedure**').

Reviews (including review reports) are in the language of the Agreement.

22.1.3 Right to carry out audits

The Agency or the Commission may — during the implementation of the action or afterwards — carry out audits on the proper implementation of the action and compliance with the obligations under the Agreement.

Audits may be started up to two years after the payment of the balance. They will be formally notified to the coordinator or beneficiary concerned and will be considered to have started on the date of the formal notification.

The Agency or the Commission may carry out audits directly (using its own staff) or indirectly (using external persons or bodies appointed to do so). It will inform the coordinator or beneficiary concerned of the identity of the external persons or bodies. They have the right to object to the appointment on grounds of commercial confidentiality.

The coordinator or beneficiary concerned must provide — within the deadline requested — any information (including complete accounts, individual salary statements or other personal data) to verify compliance with the Agreement. The Agency or the Commission may request beneficiaries to provide such information to it directly.

For **on-the-spot** audits, the beneficiaries must allow access to their sites and premises, including to external persons or bodies, and must ensure that information requested is readily available.

Information provided must be accurate, precise and complete and in the format requested, including electronic format.

On the basis of the audit findings, a '**draft audit report**' will be drawn up.

The Agency or the Commission will formally notify the draft audit report to the coordinator or beneficiary concerned, which has 30 days to formally notify observations ('**contradictory audit procedure**'). This period may be extended by the Agency or the Commission in justified cases.

The '**final audit report**' will take into account observations by the coordinator or beneficiary concerned. The report will be formally notified to it.

Audits (including audit reports) are in the language of the Agreement.

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The Agency or the Commission may also access the beneficiaries' statutory records for the periodical assessment of unit costs or flat-rate amounts.

22.2 Investigations by the European Anti-Fraud Office (OLAF)

Under Regulations No 883/2013[3] and No 2185/96[4] (and in accordance with their provisions and procedures), the European Anti-Fraud Office (OLAF) may — at any moment during implementation of the action or afterwards — carry out investigations, including on-the-spot checks and inspections, to establish whether there has been fraud, corruption or any other illegal activity affecting the financial interests of the EU.

22.3 Checks and audits by the European Court of Auditors (ECA)

Under Article 287 of the Treaty on the Functioning of the European Union (TFEU) and Article 161 of the Financial Regulation No 966/2012[5], the European Court of Auditors (ECA) may — at any moment during implementation of the action or afterwards — carry out audits.

The ECA has the right of access for the purpose of checks and audits.

22.4 Checks, reviews, audits and investigations for international organisations

Not applicable

22.5 Consequences of findings in checks, reviews, audits and investigations — Extension of findings

22.5.1 Findings in this grant

Findings in checks, reviews, audits or investigations carried out in the context of this grant may lead to the rejection of ineligible costs (see Article 42), reduction of the grant (see Article 43), recovery of undue amounts (see Article 44) or to any of the other measures described in Chapter 6.

Rejection of costs or reduction of the grant after the payment of the balance will lead to a revised final grant amount (see Article 5.4).

Findings in checks, reviews, audits or investigations may lead to a request for amendment for the modification of Annex 1 (see Article 55).

Checks, reviews, audits or investigations that find systemic or recurrent errors, irregularities, fraud or breach of obligations may also lead to consequences in other EU or Euratom grants awarded under similar conditions ('**extension of findings from this grant to other grants**').

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[3] Regulation (EU, Euratom) No 883/2013 of the European Parliament and of the Council of 11 September 2013 concerning investigations conducted by the European Anti-Fraud Office (OLAF) and repealing Regulation (EC) No 1073/1999 of the European Parliament and of the Council and Council Regulation (Euratom) No 1074/1999 (OJ L 248, 18.09.2013, p. 1).

[4] Council Regulation (Euratom, EC) No 2185/1996 of 11 November 1996 concerning on-the-spot checks and inspections carried out by the Commission in order to protect the European Communities' financial interests against fraud and other irregularities (OJ L 292, 15.11.1996, p. 2).

[5] Regulation (EU, Euratom) No 966/2012 of the European Parliament and of the Council of 25 October 2012 on the financial rules applicable to the general budget of the Union and repealing Council Regulation (EC, Euratom) No 1605/2002 (OJ L 298, 26.10.2012, p. 1).

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Moreover, findings arising from an OLAF investigation may lead to criminal prosecution under national law.

22.5.2 Findings in other grants

The Agency or the Commission may extend findings from other grants to this grant ('**extension of findings from other grants to this grant**'), if:

(a) the beneficiary concerned is found, in other EU or Euratom grants awarded under similar conditions, to have committed systemic or recurrent errors, irregularities, fraud or breach of obligations that have a material impact on this grant and

(b) those findings are formally notified to the beneficiary concerned — together with the list of grants affected by the findings — no later than two years after the payment of the balance of this grant.

The extension of findings may lead to the rejection of costs (see Article 42), reduction of the grant (see Article 43), recovery of undue amounts (see Article 44), suspension of payments (see Article 48), suspension of the action implementation (see Article 49) or termination (see Article 50).

22.5.3 Procedure

The Agency or the Commission will formally notify the beneficiary concerned the systemic or recurrent errors and its intention to extend these audit findings, together with the list of grants affected.

22.5.3.1 If the findings concern **eligibility of costs**: the formal notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings;

(b) the request to submit **revised financial statements** for all grants affected;

(c) the **correction rate for extrapolation** established by the Agency or the Commission on the basis of the systemic or recurrent errors, to calculate the amounts to be rejected if the beneficiary concerned:

(i) considers that the submission of revised financial statements is not possible or practicable or

(ii) does not submit revised financial statements.

The beneficiary concerned has 90 days from receiving notification to submit observations, revised financial statements or to propose a duly substantiated **alternative correction method**. This period may be extended by the Agency or the Commission in justified cases.

The Agency or the Commission may then start a rejection procedure in accordance with Article 42, on the basis of:

- the revised financial statements, if approved;
- the proposed alternative correction method, if accepted

or

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- the initially notified correction rate for extrapolation, if it does not receive any observations or revised financial statements, does not accept the observations or the proposed alternative correction method or does not approve the revised financial statements.

22.5.3.2 If the findings concern **substantial errors**, **irregularities or fraud** or **serious breach of obligations**: the formal notification will include:

(a) an invitation to submit observations on the list of grants affected by the findings and

(b) the flat-rate the Agency or the Commission intends to apply according to the principle of proportionality.

The beneficiary concerned has 90 days from receiving notification to submit observations or to propose a duly substantiated alternative flat-rate.

The Agency or the Commission may then start a reduction procedure in accordance with Article 43, on the basis of:

- the proposed alternative flat-rate, if accepted

or

- the initially notified flat-rate, if it does not receive any observations or does not accept the observations or the proposed alternative flat-rate.

If the Agency or the Commission accepts the alternative flat-rate proposed by the beneficiary concerned, it will formally notify the application of the accepted alternative flat-rate.

22.6 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, any insufficiently substantiated costs will be ineligible (see Article 6) and will be rejected (see Article 42).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 23 — EVALUATION OF THE IMPACT OF THE ACTION

23.1 Right to evaluate the impact of the action

The Agency or the Commission may carry out interim and final evaluations of the impact of the action measured against the objective of the EU programme.

Evaluations may be started during implementation of the action and up to five years after the payment of the balance. The evaluation is considered to start on the date of the formal notification to the coordinator or beneficiaries.

The Agency or the Commission may make these evaluations directly (using its own staff) or indirectly (using external bodies or persons it has authorised to do so).

The coordinator or beneficiaries must provide any information relevant to evaluate the impact of the action, including information in electronic format.

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23.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the Agency may apply the measures described in Chapter 6.

SECTION 3 RIGHTS AND OBLIGATIONS RELATED TO BACKGROUND AND RESULTS

SUBSECTION 1 GENERAL

ARTICLE 23a — MANAGEMENT OF INTELLECTUAL PROPERTY

23a.1 Obligation to take measures to implement the Commission Recommendation on the management of intellectual property in knowledge transfer activities

Beneficiaries that are universities or other public research organisations must take measures to implement the principles set out in Points 1 and 2 of the Code of Practice annexed to the Commission Recommendation on the management of intellectual property in knowledge transfer activities[6].

This does not change the obligations set out in Subsections 2 and 3 of this Section.

The beneficiaries must ensure that the researchers, entities with a capital or legal link and partner organisations are aware of them.

23a.2 Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the Agency may apply any of the measures described in Chapter 6.

SUBSECTION 2 RIGHTS AND OBLIGATIONS RELATED TO BACKGROUND

ARTICLE 24 — AGREEMENT ON BACKGROUND

24.1 Agreement on background

The beneficiaries must identify and agree (in writing) on the background for the action ('**agreement on background**').

'**Background**' means any data, know-how or information — whatever its form or nature (tangible or intangible), including any rights such as intellectual property rights — that:

(a) is held by the beneficiaries before they acceded to the Agreement, and

(b) is needed to implement the action or exploit the results.

24.2 Consequences of non-compliance

[6] Commission Recommendation C (2008) 1329 of 10.4.2008 on the management of intellectual property in knowledge transfer activities and the Code of Practice for universities and other public research institutions attached to this recommendation.

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If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 25 — ACCESS RIGHTS TO BACKGROUND

25.1 Exercise of access rights, — Waiving of access rights — No sub-licensing

To exercise access rights, this must first be requested in writing ('**request for access**').

'**Access rights**' means rights to use results or background under the terms and conditions laid down in this Agreement.

Waivers of access rights are not valid unless in writing.

Unless agreed otherwise, access rights do not include the right to sub-license.

25.2 Access rights for other beneficiaries, for implementing their own tasks under the action

The beneficiaries must give each other access — on a royalty-free basis — to background needed to implement their own tasks under the action, unless the beneficiary that holds the background has — before acceding to the Agreement —:

(a) informed the other beneficiaries that access to its background is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel), or

(b) agreed with the other beneficiaries that access would not be on a royalty-free basis.

25.3 Access rights for other beneficiaries, for exploiting their own results

The beneficiaries must give each other access — under fair and reasonable conditions — to background needed for exploiting their own results, unless the beneficiary that holds the background has — before acceding to the Agreement — informed the other beneficiaries that access to its background is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel).

'**Fair and reasonable conditions**' means appropriate conditions, including possible financial terms or royalty-free conditions, taking into account the specific circumstances of the request for access, for example the actual or potential value of the results or background to which access is requested and/or the scope, duration or other characteristics of the exploitation envisaged.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

25.4 Access rights for affiliated entities

Unless otherwise agreed in the consortium agreement, access to background must also be given — under fair and reasonable conditions (see above; Article 25.3) and unless it is subject to legal restrictions or limits, including those imposed by the rights of third parties (including personnel) —

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to affiliated entities[7] established in an EU Member State or '**associated country**'[8], if this is needed to exploit the results generated by the beneficiaries to which they are affiliated.

Unless agreed otherwise (see above; Article 25.1), the affiliated entity concerned must make the request directly to the beneficiary that holds the background.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

25.5 Access rights for researchers

The beneficiaries must — on a royalty-free basis — give access to the recruited researchers to background necessary for their research training activities under the action.

25.6 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

SUBSECTION 3 RIGHTS AND OBLIGATIONS RELATED TO RESULTS

ARTICLE 26 — OWNERSHIP OF RESULTS

26.1 Ownership by the beneficiary that generates the results

Results are owned by the beneficiary that generates them.

'**Results**' means any (tangible or intangible) output of the action such as data, knowledge or information — whatever its form or nature, whether it can be protected or not — that is generated in the action, as well as any rights attached to it, including intellectual property rights.

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[7] For the definition, see Article 2.1(2) of Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" ('**Rules for Participation Regulation No 1290/2013**') (OJ L 347, 20.12.2013 p.81): '**affiliated entity**' means any legal entity that is:

- under the direct or indirect control of a participant, or
- under the same direct or indirect control as the participant, or
- directly or indirectly controlling a participant.

'Control' may take any of the following forms:

(a) the direct or indirect holding of more than 50% of the nominal value of the issued share capital in the legal entity concerned, or of a majority of the voting rights of the shareholders or associates of that entity;

(b) the direct or indirect holding, in fact or in law, of decision-making powers in the legal entity concerned.

However the following relationships between legal entities shall not in themselves be deemed to constitute controlling relationships:

(a) the same public investment corporation, institutional investor or venture-capital company has a direct or indirect holding of more than 50% of the nominal value of the issued share capital or a majority of voting rights of the shareholders or associates;

(b) the legal entities concerned are owned or supervised by the same public body.

[8] For the definition, see Article 2.1(3) Rules for Participation Regulation No 1290/2013: '**associated country**' means a non EU-country (third country) which is party to an international agreement with the Union, as identified in Article 7 of the H2020 Framework Programme Regulation No 1291/2013. Article 7 sets out the conditions for association of non-EU countries to Horizon 2020.

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26.2 Joint ownership by several beneficiaries

Two or more beneficiaries own results jointly if:

(a) they have jointly generated them and

(b) it is not possible to:

(i) establish the respective contribution of each beneficiary, or

(ii) separate them for the purpose of applying for, obtaining or maintaining their protection (see Article 27).

The joint owners must agree (in writing) on the allocation and terms of exercise of their joint ownership ('**joint ownership agreement**'), to ensure compliance with their obligations under this Agreement.

Unless otherwise agreed in the joint ownership agreement, each joint owner may grant non-exclusive licences to third parties to exploit jointly-owned results (without any right to sub-license), if the other joint owners are given:

(a) at least 45 days advance notice and

(b) fair and reasonable compensation.

Once the results have been generated, joint owners may agree (in writing) to apply another regime than joint ownership (such as, for instance, transfer to a single owner (see Article 30) with access rights for the others).

26.3 Rights of third parties (including personnel)

If third parties (including personnel) may claim rights to the results, the beneficiary concerned must ensure that it complies with its obligations under the Agreement.

If a third party generates results, the beneficiary concerned must obtain all necessary rights (transfer, licences or other) from the third party, in order to be able to respect its obligations as if those results were generated by the beneficiary itself.

If obtaining the rights is impossible, the beneficiary must refrain from using the third party to generate the results.

26.4 Agency ownership, to protect results

26.4.1 The Agency may — with the consent of the beneficiary concerned — assume ownership of results to protect them, if a beneficiary intends — up to four years after the period set out in Article 3 — to disseminate its results without protecting them, except in any of the following cases:

(a) the lack of protection is because protecting the results is not possible, reasonable or justified (given the circumstances);

(b) the lack of protection is because there is a lack of potential for commercial or industrial exploitation, or

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(c) the beneficiary intends to transfer the results to another beneficiary or third party established in an EU Member State or associated country, which will protect them.

Before the results are disseminated and unless any of the cases above under Points (a), (b) or (c) applies, the beneficiary must formally notify the Agency and at the same time inform it of any reasons for refusing consent. The beneficiary may refuse consent only if it can show that its legitimate interests would suffer significant harm.

If the Agency decides to assume ownership, it will formally notify the beneficiary concerned within 45 days of receiving notification.

No dissemination relating to these results may take place before the end of this period or, if the Agency takes a positive decision, until it has taken the necessary steps to protect the results.

26.4.2 The Agency may — with the consent of the beneficiary concerned — assume ownership of results to protect them, if a beneficiary intends — up to four years after the period set out in Article 3 — to stop protecting them or not to seek an extension of protection, except in any of the following cases:

(a) the protection is stopped because of a lack of potential for commercial or industrial exploitation;

(b) an extension would not be justified given the circumstances.

A beneficiary that intends to stop protecting results or not seek an extension must — unless any of the cases above under Points (a) or (b) applies — formally notify the Agency at least 60 days before the protection lapses or its extension is no longer possible and at the same time inform it of any reasons for refusing consent. The beneficiary may refuse consent only if it can show that its legitimate interests would suffer significant harm.

If the Agency decides to assume ownership, it will formally notify the beneficiary concerned within 45 days of receiving notification.

26.5 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to the any of the other measures described in Chapter 6.

ARTICLE 27 — PROTECTION OF RESULTS — VISIBILITY OF EU FUNDING

27.1 Obligation to protect the results

Each beneficiary must examine the possibility of protecting its results and must adequately protect them — for an appropriate period and with appropriate territorial coverage — if:

(a) the results can reasonably be expected to be commercially or industrially exploited and

(b) protecting them is possible, reasonable and justified (given the circumstances).

When deciding on protection, the beneficiary must consider its own legitimate interests and the legitimate interests (especially commercial) of the other beneficiaries.

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27.2 Agency ownership, to protect the results

If a beneficiary intends not to protect its results, to stop protecting them or not seek an extension of protection, the Agency may — under certain conditions (see Article 26.4) — assume ownership to ensure their (continued) protection.

27.3 Information on EU funding

Applications for protection of results (including patent applications) filed by or on behalf of a beneficiary must — unless the Agency requests or agrees otherwise or unless it is impossible — include the following:

> "The project leading to this application has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 813986".

27.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 28 — EXPLOITATION OF RESULTS

28.1 Obligation to exploit the results

Each beneficiary must — up to four years after the period set out in Article 3 — take measures aiming to ensure '**exploitation**' of its results (either directly or indirectly, in particular through transfer or licensing; see Article 30) by:

(a) using them in further research activities (outside the action);

(b) developing, creating or marketing a product or process;

(c) creating and providing a service, or

(d) using them in standardisation activities.

This does not change the security obligations in Article 37, which still apply.

28.2 Results that could contribute to European or international standards — Information on EU funding

If results are incorporated in a standard, the beneficiary concerned must — unless the Agency requests or agrees otherwise or unless it is impossible — ask the standardisation body to include the following statement in (information related to) the standard:

> "Results incorporated in this standard received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 813986".

28.3 Consequences of non-compliance

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If a beneficiary breaches any of its obligations under this Article, the grant may be reduced in accordance with Article 43.

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 29 — DISSEMINATION OF RESULTS — OPEN ACCESS — VISIBILITY OF EU FUNDING

29.1 Obligation to disseminate results

Unless it goes against their legitimate interests, each beneficiary must — as soon as possible — '**disseminate**' its results by disclosing them to the public by appropriate means (other than those resulting from protecting or exploiting the results), including in scientific publications (in any medium).

This does not change the obligation to protect results in Article 27, the confidentiality obligations in Article 36, the security obligations in Article 37 or the obligations to protect personal data in Article 39, all of which still apply.

A beneficiary that intends to disseminate its results must give advance notice to the other beneficiaries of — unless agreed otherwise — at least 45 days, together with sufficient information on the results it will disseminate.

Any other beneficiary may object within — unless agreed otherwise — 30 days of receiving notification, if it can show that its legitimate interests in relation to the results or background would be significantly harmed. In such cases, the dissemination may not take place unless appropriate steps are taken to safeguard these legitimate interests.

If a beneficiary intends not to protect its results, it may — under certain conditions (see Article 26.4.1) — need to formally notify the Agency before dissemination takes place.

29.2 Open access to scientific publications

Each beneficiary must ensure open access (free of charge online access for any user) to all peer-reviewed scientific publications relating to its results.

In particular, it must:

(a) as soon as possible and at the latest on publication, deposit a machine-readable electronic copy of the published version or final peer-reviewed manuscript accepted for publication in a repository for scientific publications;

Moreover, the beneficiary must aim to deposit at the same time the research data needed to validate the results presented in the deposited scientific publications.

(b) ensure open access to the deposited publication — via the repository — at the latest:

(i) on publication, if an electronic version is available for free via the publisher, or

(ii) within six months of publication (twelve months for publications in the social sciences and humanities) in any other case.

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(c) ensure open access — via the repository — to the bibliographic metadata that identify the deposited publication.

The bibliographic metadata must be in a standard format and must include all of the following:

- the terms “Marie Skłodowska-Curie Actions” ;
- the name of the action, acronym and grant number;
- the publication date, and length of embargo period if applicable, and
- a persistent identifier.

29.3 Open access to research data

Regarding the digital research data generated in the action (‘**data**’), the beneficiaries must:

(a) deposit in a research data repository and take measures to make it possible for third parties to access, mine, exploit, reproduce and disseminate — free of charge for any user — the following:

(i) the data, including associated metadata, needed to validate the results presented in scientific publications, as soon as possible;

(ii) other data, including associated metadata, as specified and within the deadlines laid down in the ‘data management plan’ (see Annex 1);

(b) provide information — via the repository — about tools and instruments at the disposal of the beneficiaries and necessary for validating the results (and — where possible — provide the tools and instruments themselves).

This does not change the obligation to protect results in Article 27, the confidentiality obligations in Article 36, the security obligations in Article 37 or the obligations to protect personal data in Article 39, all of which still apply.

As an exception, the beneficiaries do not have to ensure open access to specific parts of their research data if the achievement of the action's main objective (as described in Annex 1) would be jeopardised by making those specific parts of the research data openly accessible. In this case, the data management plan must contain the reasons for not giving access.

29.4 Information on EU funding — Obligation and right to use the EU emblem

Unless the Agency requests or agrees otherwise or unless it is impossible, any dissemination of results (in any form, including electronic) must:

(a) display the EU emblem and

(b) include the following text:

> “This project has received funding from the European Union’s Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 813986”.

When displayed together with another logo, the EU emblem must have appropriate prominence.

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For the purposes of their obligations under this Article, the beneficiaries may use the EU emblem without first obtaining approval from the Agency.

This does not however give them the right to exclusive use.

Moreover, they may not appropriate the EU emblem or any similar trademark or logo, either by registration or by any other means.

29.5 Disclaimer excluding Agency responsibility

Any dissemination of results must indicate that it reflects only the author's view and that the Agency is not responsible for any use that may be made of the information it contains.

29.6 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 30 — TRANSFER AND LICENSING OF RESULTS

30.1 Transfer of ownership

Each beneficiary may transfer ownership of its results.

It must however ensure that its obligations under Articles 26.2, 26.4, 27, 28, 29, 30 and 31 also apply to the new owner and that this owner has the obligation to pass them on in any subsequent transfer.

This does not change the security obligations in Article 37, which still apply.

Unless agreed otherwise (in writing) for specifically-identified third parties or unless impossible under applicable EU and national laws on mergers and acquisitions, a beneficiary that intends to transfer ownership of results must give at least 45 days advance notice (or less if agreed in writing) to the other beneficiaries that still have (or still may request) access rights to the results. This notification must include sufficient information on the new owner to enable any beneficiary concerned to assess the effects on its access rights.

Unless agreed otherwise (in writing) for specifically-identified third parties, any other beneficiary may object within 30 days of receiving notification (or less if agreed in writing), if it can show that the transfer would adversely affect its access rights. In this case, the transfer may not take place until agreement has been reached between the beneficiaries concerned.

30.2 Granting licenses

Each beneficiary may grant licences to its results (or otherwise give the right to exploit them), if:

(a) this does not impede the access rights under Article 31

(b) not applicable.

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In addition to Points (a) and (b), exclusive licences for results may be granted only if all the other beneficiaries concerned have waived their access rights (see Article 31.1).

This does not change the dissemination obligations in Article 29 or security obligations in Article 37, which still apply.

30.3 Agency right to object to transfers or licensing

Not applicable

30.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such a breach may also lead to any of the other measures described in Chapter 6.

ARTICLE 31 — ACCESS RIGHTS TO RESULTS

31.1 Exercise of access rights — Waiving of access rights — No sub-licensing

The conditions set out in Article 25.1 apply.

The obligations set out in this Article do not change the security obligations in Article 37, which still apply.

31.2 Access rights for other beneficiaries, for implementing their own tasks under the action

The beneficiaries must give each other access — on a royalty-free basis — to results needed for implementing their own tasks under the action.

31.3 Access rights for other beneficiaries, for exploiting their own results

The beneficiaries must give each other — under fair and reasonable conditions (see Article 25.3) — access to results needed for exploiting their own results.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

31.4 Access rights of affiliated entities

Unless agreed otherwise in the consortium agreement, access to results must also be given — under fair and reasonable conditions (Article 25.3) — to affiliated entities established in an EU Member State or associated country, if this is needed for those entities to exploit the results generated by the beneficiaries to which they are affiliated.

Unless agreed otherwise (see above; Article 31.1), the affiliated entity concerned must make any such request directly to the beneficiary that owns the results.

Requests for access may be made — unless agreed otherwise — up to one year after the period set out in Article 3.

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31.5 Access rights for the EU institutions, bodies, offices or agencies and EU Member States

The beneficiaries must give access to their results — on a royalty-free basis — to EU institutions, bodies, offices or agencies, for developing, implementing or monitoring EU policies or programmes.

Such access rights are limited to non-commercial and non-competitive use.

This does not change the right to use any material, document or information received from the beneficiaries for communication and publicising activities (see Article 38.2).

31.6 Access rights for researchers

The beneficiaries must — on a royalty-free basis — give access to the recruited researchers to results necessary for their research training activities under the action.

31.7 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

SECTION 4 OTHER RIGHTS AND OBLIGATIONS

ARTICLE 32 — RECRUITMENT AND WORKING CONDITIONS FOR RECRUITED RESEARCHERS

32.1 Obligations towards recruited researchers

The beneficiaries must respect the following recruitment and working conditions for the researchers recruited under the action:

(a) take all measures to implement the principles set out in the Commission Recommendation on the European Charter for Researchers and the Code of Conduct for the Recruitment of Researchers[9] and ensure that the researchers are aware of them;

(b) advertise and publish vacancies internationally, including on the web-sites requested by the Agency;

(c) recruit the researchers, following an open, transparent, impartial and equitable recruitment procedure, on the basis of:

(i) their scientific skills and the relevance of their research experience;

(ii) the impact of the proposed training on the researcher's career;

(iii) a fair gender representation (by promoting genuine equal access opportunities between men and women throughout the recruitment process);

[9] Commission Recommendation 2005/251/EC of 11 March 2005 on the European Charter for Researchers and on a Code of Conduct for the Recruitment of Researchers (OJ L 75, 22.3.2005, p.67).

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(d) ensure that no conflict of interest exists in or arises from the recruitment;

(e) ensure that the researchers enjoy at the place of the implementation at least the same standards and working conditions as those applicable to local researchers holding a similar position;

(f) ensure that the employment contract, other direct contract or fixed amount-fellowship agreement (see Article 6) specifies :

(i) the starting date and duration of the research training activities under the action;

(ii) the monthly support for the researcher under this Agreement (in euro and, if relevant, in the currency in which the remuneration is paid);

(iii) the obligation of the researcher to work exclusively for the action;

(iv) the obligation of the researcher not to receive for activities carried out in the frame of the action, other incomes than those received from the beneficiary (or other entity mentioned in Annex 1);

(v) the obligation of the researcher to inform the beneficiary as soon as possible of any events or circumstances likely to affect the Agreement (see Article 17);

(vi) the arrangements related to the intellectual property rights between the beneficiary and the researcher — during implementation of the action and afterwards;

(vii) the obligation of the researcher to maintain confidentiality (see Article 36);

(viii) the obligation of the researcher to ensure the visibility of EU funding in communications or publications and in applications for the protection of results (see Articles 27, 28, 29 and 38);

(g) assist the researchers in the administrative procedures related to their recruitment;

(h) inform the researchers about:

- the description, conditions, location and the timetable for the implementation of the research training activities under the action and the name of the supervisor;
- the rights and obligations of the beneficiary toward the researcher under this Agreement;
- the obligation of the researcher to complete and submit — at the end of the training — the evaluation questionnaire and — two years later — follow-up questionnaire provided by the Agency;

(i) ensure that the researchers do not receive, for activities carried out in the frame of the action, other incomes than those received from the beneficiaries (or other entity mentioned in Annex 1);

(j) ensure that the researchers do not have to bear any costs for the implementation of the action as described in Annex 1;

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(k) host the researchers at their premises (or at the premises of an entity with a capital or legal link);

(l) provide training and the necessary means for implementing the action (or ensure that such training and means are provided by entities with a capital or legal link);

(m) ensure that the researchers are adequately supervised;

(n) ensure that a career development plan is established and support its implementation;

(o) ensure an appropriate exposure to the non-academic sector;

(p) limit secondments to a maximum of 30% of the actual months spent implementing the research training activities under the action.

32.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 33 — GENDER EQUALITY

33.1 Obligation to aim for gender equality

The beneficiaries must take all measures to promote equal opportunities between men and women in the implementation of the action. They must aim, to the extent possible, for a gender balance at all levels of personnel assigned to the action, including at supervisory and managerial level.

33.2 Consequences of non-compliance

If a beneficiary breaches its obligations under this Article, the Agency may apply any of the measures described in Chapter 6.

ARTICLE 34 — ETHICS AND RESEARCH INTEGRITY

34.1 Obligation to comply with ethical and research integrity principles

The beneficiaries must carry out the action in compliance with:

(a) ethical principles (including the highest standards of research integrity)

and

(b) applicable international, EU and national law.

Funding will not be granted for activities carried out outside the EU if they are prohibited in all Member States or for activities which destroy human embryos (for example, for obtaining stem cells).

The beneficiaries must ensure that the activities under the action have an exclusive focus on civil applications.

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The beneficiaries must ensure that the activities under the action do not:

(a) aim at human cloning for reproductive purposes;

(b) intend to modify the genetic heritage of human beings which could make such changes heritable (with the exception of research relating to cancer treatment of the gonads, which may be financed), or

(c) intend to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including by means of somatic cell nuclear transfer.

In addition, the beneficiaries must respect the fundamental principle of research integrity — as set out, for instance, in the European Code of Conduct for Research Integrity[10].

This implies compliance with the following fundamental principles:

- **reliability** in ensuring the quality of research reflected in the design, the methodology, the analysis and the use of resources;

- **honesty** in developing, undertaking, reviewing, reporting and communicating research in a transparent, fair and unbiased way;

- **respect** for colleagues, research participants, society, ecosystems, cultural heritage and the environment;

- **accountability** for the research from idea to publication, for its management and organisation, for training, supervision and mentoring, and for its wider impacts

and means that beneficiaries must ensure that persons carrying out research tasks follow the good research practices and refrain from the research integrity violations described in this Code.

This does not change the other obligations under this Agreement or obligations under applicable international, EU or national law, all of which still apply.

34.2 Activities raising ethical issues

Activities raising ethical issues must comply with the '**ethics requirements**' set out as deliverables in Annex 1.

Before the beginning of an activity raising an ethical issue, each beneficiary must have obtained:

(a) any ethics committee opinion required under national law and

(b) any notification or authorisation for activities raising ethical issues required under national and/or European law

needed for implementing the action tasks in question.

The documents must be kept on file and be submitted upon request by the coordinator to the Agency (see Article 52). If they are not in English, they must be submitted together with an English summary,

[10] European Code of Conduct for Research Integrity of ALLEA (All European Academies) http://ec.europa.eu/research/participants/data/ref/h2020/other/hi/h2020-ethics_code-of-conduct_en.pdf

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which shows that the action tasks in question are covered and includes the conclusions of the committee or authority concerned (if available).

34.3 Activities involving human embryos or human embryonic stem cells

Activities involving research on human embryos or human embryonic stem cells may be carried out, in addition to Article 34.1, only if:

- they are set out in Annex 1 or
- the coordinator has obtained explicit approval (in writing) from the Agency (see Article 52).

34.4 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or participation of the beneficiary may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 35 — CONFLICT OF INTERESTS

35.1 Obligation to avoid a conflict of interests

The beneficiaries must take all measures to prevent any situation where the impartial and objective implementation of the action is compromised for reasons involving economic interest, political or national affinity, family or emotional ties or any other shared interest (‘**conflict of interests**’).

They must formally notify to the Agency without delay any situation constituting or likely to lead to a conflict of interests and immediately take all the necessary steps to rectify this situation.

The Agency may verify that the measures taken are appropriate and may require additional measures to be taken by a specified deadline.

35.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43) and the Agreement or participation of the beneficiary may be terminated (see Article 50).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 36 — CONFIDENTIALITY

36.1 General obligation to maintain confidentiality

During implementation of the action and for four years after the period set out in Article 3, the parties must keep confidential any data, documents or other material (in any form) that is identified as confidential at the time it is disclosed (‘**confidential information**’).

If a beneficiary requests, the Agency may agree to keep such information confidential for an additional period beyond the initial four years.

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If information has been identified as confidential only orally, it will be considered to be confidential only if this is confirmed in writing within 15 days of the oral disclosure.

Unless otherwise agreed between the parties, they may use confidential information only to implement the Agreement.

The beneficiaries may disclose confidential information to their personnel, entities with a capital or legal link or partner organisations only if they:

(a) need to know to implement the Agreement and

(b) are bound by an obligation of confidentiality.

This does not change the security obligations in Article 37, which still apply.

The Agency may disclose confidential information to its staff, other EU institutions and bodies. It may disclose confidential information to third parties, if:

(a) this is necessary to implement the Agreement or safeguard the EU's financial interests

and

(b) the recipients of the information are bound by an obligation of confidentiality.

Under the conditions set out in Article 4 of the Rules for Participation Regulation No 1290/2013[11], the Commission must moreover make available information on the results to other EU institutions, bodies, offices or agencies as well as Member States or associated countries.

The confidentiality obligations no longer apply if:

(a) the disclosing party agrees to release the other party;

(b) the information was already known by the recipient or is given to him without obligation of confidentiality by a third party that was not bound by any obligation of confidentiality;

(c) the recipient proves that the information was developed without the use of confidential information;

(d) the information becomes generally and publicly available, without breaching any confidentiality obligation, or

(e) the disclosure of the information is required by EU or national law.

36.2 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

[11] Regulation (EU) No 1290/2013 of the European Parliament and of the Council of 11 December 2013 laying down the rules for the participation and dissemination in "Horizon 2020 – the Framework Programme for Research and Innovation (2014-2020)" (OJ L 347, 20.12.2013 p.81).

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ARTICLE 37 — SECURITY-RELATED OBLIGATIONS

37.1 Results with a security recommendation

Not applicable

37.2 Classified information

Not applicable

37.3 ctivities involving dual-use goods or dangerous materials and substances

Not applicable

37.4 Consequences of non-compliance

Not applicable

ARTICLE 38 — PROMOTING THE ACTION — VISIBILITY OF EU FUNDING

38.1 Communication activities by beneficiaries

38.1.1 Obligation to promote the action and its results

The beneficiaries must promote the action and its results, by providing targeted information to multiple audiences (including the media and the public) in a strategic and effective manner.

This does not change the dissemination obligations in Article 29, the confidentiality obligations in Article 36 or the security obligations in Article 37, all of which still apply.

Before engaging in a communication activity expected to have a mainstream media coverage the beneficiaries must inform the Agency (see Article 52).

38.1.2 Information on EU funding — Obligation and right to use the EU emblem

Unless the Agency requests or agrees otherwise or unless it is impossible, any communication activity related to the action (including in electronic form, via social media, etc.) and any infrastructure, equipment and major results funded by the grant must:

(a) display the EU emblem and

(b) include the following text:

For communication activities:

"This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 813986".

For infrastructure, equipment and major results:

"This *[infrastructure][equipment][insert type of result]* is part of a project that has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 813986".

When displayed together with another logo, the EU emblem must have appropriate prominence.

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For the purposes of their obligations under this Article, the beneficiaries may use the EU emblem without first obtaining approval from the Agency.

This does not, however, give them the right to exclusive use.

Moreover, they may not appropriate the EU emblem or any similar trademark or logo, either by registration or by any other means.

38.1.3 Disclaimer excluding Agency and Commission responsibility

Any communication activity related to the action must indicate that it reflects only the author's view and that the Agency and the Commission are not responsible for any use that may be made of the information it contains.

38.2 Communication activities by the Agency and the Commission

38.2.1 Right to use beneficiaries' materials, documents or information

The Agency and the Commission may use, for its communication and publicising activities, information relating to the action, documents notably summaries for publication and public deliverables as well as any other material, such as pictures or audio-visual material received from any beneficiary (including in electronic form).

This does not change the confidentiality obligations in Article 36 and the security obligations in Article 37, all of which still apply.

If the Agency's or the Commission's use of these materials, documents or information would risk compromising legitimate interests, the beneficiary concerned may request the Agency or the Commission not to use it (see Article 52).

The right to use a beneficiary's materials, documents and information includes:

(a) **use for its own purposes** (in particular, making them available to persons working for the Agency, the Commission or any other EU institution, body, office or agency or body or institutions in EU Member States; and copying or reproducing them in whole or in part, in unlimited numbers);

(b) **distribution to the public** (in particular, publication as hard copies and in electronic or digital format, publication on the internet, as a downloadable or non-downloadable file, broadcasting by any channel, public display or presentation, communicating through press information services, or inclusion in widely accessible databases or indexes);

(c) **editing or redrafting** for communication and publicising activities (including shortening, summarising, inserting other elements (such as meta-data, legends, other graphic, visual, audio or text elements), extracting parts (e.g. audio or video files), dividing into parts, use in a compilation);

(d) translation;

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(e) giving **access in response to individual requests** under Regulation No 1049/2001[13], without the right to reproduce or exploit;

(f) **storage** in paper, electronic or other form;

(g) **archiving**, in line with applicable document-management rules, and

(h) the right to authorise **third parties** to act on its behalf or sub-license the modes of use set out in Points (b), (c), (d) and (f) to third parties if needed for the communication and publicising activities of the Agency or the Commission.

If the right of use is subject to rights of a third party (including personnel of the beneficiary), the beneficiary must ensure that it complies with its obligations under this Agreement (in particular, by obtaining the necessary approval from the third parties concerned).

Where applicable (and if provided by the beneficiaries), the Agency or the Commission will insert the following information:

> "© – [year] – [name of the copyright owner]. All rights reserved. Licensed to the Research Executive Agency (REA) and the European Union (EU) under conditions."

38.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under this Article, the grant may be reduced (see Article 43).

Such breaches may also lead to any of the other measures described in Chapter 6.

ARTICLE 39 — PROCESSING OF PERSONAL DATA

39.1 Processing of personal data by the Agency and the Commission

Any personal data under the Agreement will be processed by the Agency or the Commission under Regulation No 45/2001[14] and according to the 'notifications of the processing operations' to the Data Protection Officer (DPO) of the Agency or the Commission (publicly accessible in the DPO register).

Such data will be processed by the '**data controller**' of the Agency or the Commission for the purposes of implementing, managing and monitoring the Agreement or protecting the financial interests of the EU or Euratom (including checks, reviews, audits and investigations; see Article 22).

The persons whose personal data are processed have the right to access and correct their own personal data. For this purpose, they must send any queries about the processing of their personal data to the data controller, via the contact point indicated in the privacy statement(s) that are published on the Agency and the Commission websites.

[13] Regulation (EC) No 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, OJ L 145, 31.5.2001, p. 43.

[14] Regulation (EC) No 45/2001 of the European Parliament and of the Council of 18 December 2000 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data (OJ L 8, 12.01.2001, p. 1).

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They also have the right to have recourse at any time to the European Data Protection Supervisor (EDPS).

39.2 Processing of personal data by the beneficiaries

The beneficiaries must process personal data under the Agreement in compliance with applicable EU and national law on data protection (including authorisations or notification requirements).

The beneficiaries may grant their personnel access only to data that is strictly necessary for implementing, managing and monitoring the Agreement.

The beneficiaries must inform the personnel whose personal data are collected and processed by the Agency or the Commission. For this purpose, they must provide them with the privacy statement(s) (see above), before transmitting their data to the Agency or the Commission.

39.3 Consequences of non-compliance

If a beneficiary breaches any of its obligations under Article 39.2, the Agency may apply any of the measures described in Chapter 6.

ARTICLE 40 — ASSIGNMENTS OF CLAIMS FOR PAYMENT AGAINST THE AGENCY

The beneficiaries may not assign any of their claims for payment against the Agency to any third party, except if approved by the Agency on the basis of a reasoned, written request by the coordinator (on behalf of the beneficiary concerned).

If the Agency has not accepted the assignment or the terms of it are not observed, the assignment will have no effect on it.

In no circumstances will an assignment release the beneficiaries from their obligations towards the Agency.

CHAPTER 5 DIVISION OF BENEFICIARIES' ROLES AND RESPONSIBILITIES — RELATIONSHIP WITH COMPLEMENTARY BENEFICIARIES — RELATIONSHIP WITH PARTNERS OF A JOINT ACTION

ARTICLE 41 — DIVISION OF BENEFICIARIES' ROLES AND RESPONSIBILITIES — RELATIONSHIP WITH COMPLEMENTARY BENEFICIARIES — RELATIONSHIP WITH PARTNERS OF A JOINT ACTION

41.1 Roles and responsibility towards the Agency

The beneficiaries have full responsibility for implementing the action and complying with the Agreement.

The beneficiaries are jointly and severally liable for the **technical implementation** of the action as described in Annex 1. If a beneficiary fails to implement its part of the action, the other beneficiaries become responsible for implementing this part (without being entitled to any additional EU funding for doing so), unless the Agency expressly relieves them of this obligation.

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The **financial responsibility** of each beneficiary is governed by Article 44.

41.2 Internal division of roles and responsibilities

The internal roles and responsibilities of the beneficiaries are divided as follows:

(a) Each **beneficiary** must:

(i) keep information stored in the Participant Portal Beneficiary Register (via the electronic exchange system) up to date (see Article 17);

(ii) inform the coordinator immediately of any events or circumstances likely to affect significantly or delay the implementation of the action (see Article 17);

(iii) submit to the coordinator in good time:

- individual financial statements for itself and, if required, certificates on the financial statements (see Article 20);
- the data needed to draw up the technical reports (see Article 20);
- ethics committee opinions and notifications or authorisations for activities raising ethical issues (see Article 34);
- any other documents or information required by the Agency or the Commission under the Agreement, unless the Agreement requires the beneficiary to submit this information directly to the Agency or the Commission.

(b) The **coordinator** must:

(i) monitor that the action is implemented properly (see Article 7);

(ii) act as the intermediary for all communications between the beneficiaries and the Agency (in particular, providing the Agency with the information described in Article 17), unless the Agreement specifies otherwise;

(iii) request and review any documents or information required by the Agency and verify their completeness and correctness before passing them on to the Agency;

(iv) submit the deliverables and reports to the Agency (see Articles 19 and 20);

(v) ensure that all payments are made to the other beneficiaries without unjustified delay (see Article 21);

(vi) inform the Agency of the amounts paid to each beneficiary, when required under the Agreement (see Articles 44 and 50) or requested by the Agency.

The coordinator may not delegate or subcontract the above-mentioned tasks to any other beneficiary or third party (including entities with a capital or legal link and partner organisations).

41.3 Internal arrangements between beneficiaries — Consortium agreement

The beneficiaries must have internal arrangements regarding their operation and co-ordination to

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ensure that the action is implemented properly. These internal arrangements must be set out in a written '**consortium agreement**' between the beneficiaries, which may cover:

- internal organisation of the consortium;
- management of access to the electronic exchange system;
- distribution of EU funding;
- additional rules on rights and obligations related to background and results (including whether access rights remain or not, if a beneficiary is in breach of its obligations) (see Section 3 of Chapter 4);
- settlement of internal disputes;
- liability, indemnification and confidentiality arrangements between the beneficiaries.

The consortium agreement must not contain any provision contrary to the Agreement.

41.4 Relationship with complementary beneficiaries — Collaboration agreement

Not applicable

41.5 Relationship with partners of a joint action — Coordination agreement

Not applicable

CHAPTER 6 REJECTION OF COSTS — REDUCTION OF THE GRANT — RECOVERY — SANCTIONS — DAMAGES — SUSPENSION — TERMINATION — FORCE MAJEURE

SECTION 1 REJECTION OF COSTS — REDUCTION OF THE GRANT — RECOVERY — SANCTIONS

ARTICLE 42 — REJECTION OF INELIGIBLE COSTS

42.1 Conditions

The Agency will — after **termination of the participation of a beneficiary**, at the time of an **interim payment**, **at the payment of the balance** or **afterwards** — reject any costs which are ineligible (see Article 6), in particular following checks, reviews, audits or investigations (see Article 22).

The rejection may also be based on the **extension of findings from other grants to this grant** (see Article 22.5.2).

42.2 Ineligible costs to be rejected — Calculation — Procedure

Ineligible costs will be rejected in full.

If the rejection of costs does not lead to a recovery (see Article 44), the Agency will formally notify

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the coordinator or beneficiary concerned of the rejection of costs, the amounts and the reasons why (if applicable, together with the notification of amounts due; see Article 21.5). The coordinator or beneficiary concerned may — within 30 days of receiving notification — formally notify the Agency of its disagreement and the reasons why.

If the rejection of costs leads to a recovery, the Agency will follow the contradictory procedure with pre-information letter set out in Article 44.

42.3 Effects

If the Agency rejects costs **after termination of the participation of a beneficiary**, it will deduct them from the costs declared by the beneficiary in the termination report and include the rejection in the calculation after termination (see Article 50.2 and 50.3).

If the Agency rejects costs at the time of an **interim payment** or **the payment of the balance**, it will deduct them from the total eligible costs declared, for the action, in the periodic or final summary financial statement (see Articles 20.3 and 20.4). It will then calculate the interim payment or payment of the balance as set out in Articles 21.3 or 21.4.

If the Agency — **after an interim payment but before the payment of the balance** — rejects costs declared in a periodic summary financial statement, it will deduct them from the total eligible costs declared, for the action, in the next periodic summary financial statement or in the final summary financial statement. It will then calculate the interim payment or payment of the balance as set out in Articles 21.3 or 21.4.

If the Agency rejects costs **after the payment of the balance**, it will deduct the amount rejected from the total eligible costs declared, by the beneficiary, in the final summary financial statement. It will then calculate the revised final grant amount as set out in Article 5.4.

ARTICLE 43 — REDUCTION OF THE GRANT

43.1 Conditions

The Agency may — **after termination of the participation of a beneficiary**, **at the payment of the balance** or **afterwards** — reduce the grant, if :

(a) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed:

  (i) substantial errors, irregularities or fraud or

  (ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles) or

(b) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (**extension of findings from other grants to this grant**; see Article 22.5.2).

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43.2 Amount to be reduced — Calculation — Procedure

The amount of the reduction will be proportionate to the seriousness of the errors, irregularities or fraud or breach of obligations.

Before reduction of the grant, the Agency will formally notify a '**pre-information letter**' to the coordinator or beneficiary concerned:

- informing it of its intention to reduce the grant, the amount it intends to reduce and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If the Agency does not receive any observations or decides to pursue reduction despite the observations it has received, it will formally notify **confirmation** of the reduction (if applicable, together with the notification of amounts due; see Article 21).

43.3 Effects

If the Agency reduces the grant **after termination of the participation of a beneficiary**, it will calculate the reduced grant amount for that beneficiary and then determine the amount due to that beneficiary (see Article 50.2 and 50.3).

If the Agency reduces the grant **at the payment of the balance**, it will calculate the reduced grant amount for the action and then determine the amount due as payment of the balance (see Articles 5.3.4 and 21.4).

If the Agency reduces the grant **after the payment of the balance**, it will calculate the revised final grant amount for the beneficiary concerned (see Article 5.4). If the revised final grant amount for the beneficiary concerned is lower than its share of the final grant amount, the Agency will recover the difference (see Article 44).

ARTICLE 44 — RECOVERY OF UNDUE AMOUNTS

44.1 Amount to be recovered — Calculation — Procedure

The Agency will — after **termination of the participation of a beneficiary, at the payment of the balance** or **afterwards** — claim back any amount that was paid, but is not due under the Agreement.

Each beneficiary's financial responsibility in case of recovery is limited to its own debt, except for the amount retained for the Guarantee Fund (see Article 21.4).

44.1.1 Recovery after termination of a beneficiary's participation

If recovery takes place after termination of a beneficiary's participation (including the coordinator), the Agency will claim back the undue amount from the beneficiary concerned, by formally notifying it a debit note (see Article 50.2 and 50.3). This note will specify the amount to be recovered, the terms and the date for payment.

If payment is not made by the date specified in the debit note, the Agency or the Commission will **recover** the amount:

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(a) by '**offsetting**' it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the Agency, the Commission or another executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the Agency or the Commission may offset before the payment date specified in the debit note;

(b) not applicable;

(c) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial regulation No 966/2012.

If payment is not made by the date specified in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the payment date in the debit note, up to and including the date the Agency or the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC[15] applies.

44.1.2 Recovery at payment of the balance

If the payment of the balance takes the form of a recovery (see Article 21.4), the Agency will formally notify a '**pre-information letter**' to the coordinator:

- informing it of its intention to recover, the amount due as the balance and the reasons why;
- specifying that it intends to deduct the amount to be recovered from the amount retained for the Guarantee Fund;
- requesting the coordinator to submit a report on the distribution of payments to the beneficiaries within 30 days of receiving notification, and
- inviting the coordinator to submit observations within 30 days of receiving notification.

If no observations are submitted or the Agency decides to pursue recovery despite the observations it has received, it will **confirm recovery** (together with the notification of amounts due; see Article 21.5) and:

- pay the difference between the amount to be recovered and the amount retained for the Guarantee Fund, **if the difference is positive** or
- formally notify to the coordinator a **debit note** for the difference between the amount to be recovered and the amount retained for the Guarantee Fund, **if the difference is negative**. This note will also specify the terms and the date for payment.

[15] Directive 2007/64/EC of the European Parliament and of the Council of 13 November 2007 on payment services in the internal market amending Directives 97/7/EC, 2002/65/EC, 2005/60/EC and 2006/48/EC and repealing Directive 97/5/EC (OJ L 319, 05.12.2007, p. 1).

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If the coordinator does not repay the Agency by the date in the debit note and has not submitted the report on the distribution of payments: the Agency or the Commission will **recover** the amount set out in the debit note from the coordinator (see below).

If the coordinator does not repay the Agency by the date in the debit note, but has submitted the report on the distribution of payments: the Agency will:

(a) identify the beneficiaries for which the amount calculated as follows is negative:

{{{{beneficiary's costs declared in the final summary financial statement and approved by the Agency multiplied by the reimbursement rate set out in Article 5.2 for the beneficiary concerned}

divided by

the EU contribution for the action calculated according to Article 5.3.1}

multiplied by

the final grant amount (see Article 5.3)},

minus

{pre-financing and interim payments received by the beneficiary}}.

(b) formally notify to each beneficiary identified according to point (a) a **debit note** specifying the terms and date for payment. The amount of the debit note is calculated as follows:

{{amount calculated according to point (a) for the beneficiary concerned

divided by

the sum of the amounts calculated according to point (a) for all the beneficiaries identified according to point (a)}

multiplied by

the amount set out in the debit note formally notified to the coordinator}.

If payment is not made by the date specified in the debit note, the Agency or the Commission will **recover** the amount:

(a) by **offsetting** it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the Agency, the Commission or another executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the Agency or the Commission may offset before the payment date specified in the debit note;

(b) by **drawing on the Guarantee Fund**. The Agency or the Commission will formally notify the beneficiary concerned the debit note on behalf of the Guarantee Fund and recover the amount:

(i) not applicable;

(ii) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

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If payment is not made by the date in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the payment date in the debit note, up to and including the date the Agency or the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

44.1.3 Recovery of amounts after payment of the balance

If, for a beneficiary, the revised final grant amount (see Article 5.4) is lower than its share of the final grant amount, it must repay the difference to the Agency.

The beneficiary's share of the final grant amount is calculated as follows:

{{{beneficiary's costs declared in the final summary financial statement and approved by the Agency multiplied by the reimbursement rate set out in Article 5.2 for the beneficiary concerned}

divided by

the EU contribution for the action calculated according to Article 5.3.1}

multiplied by

the final grant amount (see Article 5.3)}.

If the coordinator has not distributed amounts received (see Article 21.7), the Agency will also recover these amounts.

The Agency will formally notify a **pre-information letter** to the beneficiary concerned:

- informing it of its intention to recover, the due amount and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If no observations are submitted or the Agency decides to pursue recovery despite the observations it has received, it will **confirm** the amount to be recovered and formally notify to the beneficiary concerned a **debit note**. This note will also specify the terms and the date for payment.

If payment is not made by the date specified in the debit note, the Agency or the Commission will **recover** the amount:

(a) by **offsetting** it — without the beneficiary's consent — against any amounts owed to the beneficiary concerned by the Agency, the Commission or another executive agency (from the EU or Euratom budget).

In exceptional circumstances, to safeguard the EU's financial interests, the Agency or the Commission may offset before the payment date specified in the debit note;

(b) by **drawing on the Guarantee Fund**. The Agency or the Commission will formally notify the beneficiary concerned the debit note on behalf of the Guarantee Fund and recover the amount:

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(i) not applicable;

(ii) by **taking legal action** (see Article 57) or by **adopting an enforceable decision** under Article 299 of the Treaty on the Functioning of the EU (TFEU) and Article 79(2) of the Financial Regulation No 966/2012.

If payment is not made by the date in the debit note, the amount to be recovered (see above) will be increased by **late-payment interest** at the rate set out in Article 21.11, from the day following the date for payment in the debit note, up to and including the date the Agency or the Commission receives full payment of the amount.

Partial payments will be first credited against expenses, charges and late-payment interest and then against the principal.

Bank charges incurred in the recovery process will be borne by the beneficiary, unless Directive 2007/64/EC applies.

ARTICLE 45 — ADMINISTRATIVE SANCTIONS

In addition to contractual measures, the Agency or the Commission may also adopt administrative sanctions under Articles 106 and 131(4) of the Financial Regulation No 966/2012 (i.e. exclusion from future procurement contracts, grants, prizes and expert contracts and/or financial penalties).

SECTION 2 LIABILITY FOR DAMAGES

ARTICLE 46 — LIABILITY FOR DAMAGES

46.1 Liability of the Agency

The Agency cannot be held liable for any damage caused to the beneficiaries or to third parties as a consequence of implementing the Agreement, including for gross negligence.

The Agency cannot be held liable for any damage caused by any of the beneficiaries or third parties involved in the action, as a consequence of implementing the Agreement.

46.2 Liability of the beneficiaries

Except in case of force majeure (see Article 51), the beneficiaries must compensate the Agency for any damage it sustains as a result of the implementation of the action or because the action was not implemented in full compliance with the Agreement.

SECTION 3 SUSPENSION AND TERMINATION

ARTICLE 47 — SUSPENSION OF PAYMENT DEADLINE

47.1 Conditions

The Agency may — at any moment — suspend the payment deadline (see Article 21.2 to 21.4) if a request for payment (see Article 20) cannot be approved because:

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(a) it does not comply with the provisions of the Agreement (see Article 20);

(b) the technical or financial reports have not been submitted or are not complete or additional information is needed, or

(c) there is doubt about the eligibility of the costs declared in the financial statements and additional checks, reviews, audits or investigations are necessary.

47.2 Procedure

The Agency will formally notify the coordinator of the suspension and the reasons why.

The suspension will **take effect** the day notification is sent by the Agency (see Article 52).

If the conditions for suspending the payment deadline are no longer met, the suspension will be **lifted** — and the remaining period will resume.

If the suspension exceeds two months, the coordinator may request the Agency if the suspension will continue.

If the payment deadline has been suspended due to the non-compliance of the technical or financial reports (see Article 20) and the revised report or statement is not submitted or was submitted but is also rejected, the Agency may also terminate the Agreement or the participation of the beneficiary (see Article 50.3.1(l)).

ARTICLE 48 — SUSPENSION OF PAYMENTS

48.1 Conditions

The Agency may — at any moment — suspend payments, in whole or in part and interim payments or the payment of the balance for one or more beneficiaries, if:

(a) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) has committed or is suspected of having committed:

  (i) substantial errors, irregularities or fraud or

  (ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles) or

(b) a beneficiary (or a natural person who has the power to represent or take decision on its behalf) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (**extension of findings from other grants to this grant**; see Article 22.5.2).

If payments are suspended for one or more beneficiaries, the Agency will make partial payment(s) for the part(s) not suspended. If suspension concerns the payment of the balance, — once suspension is lifted — the payment or the recovery of the amount(s) concerned will be considered the payment of the balance that closes the action.

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48.2 Procedure

Before suspending payments, the Agency will formally notify the coordinator or beneficiary concerned:

- informing it of its intention to suspend payments and the reasons why and
- inviting it to submit observations within 30 days of receiving notification.

If the Agency does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify **confirmation** of the suspension. Otherwise, it will formally notify that the suspension procedure is not continued.

The suspension will **take effect** the day the confirmation notification is sent by the Agency.

If the conditions for resuming payments are met, the suspension will be **lifted**. The Agency will formally notify the coordinator or beneficiary concerned.

During the suspension, the periodic report(s) for all reporting periods except the last one (see Article 20.3), must not contain any individual financial statements from the beneficiary concerned. The coordinator must include them in the next periodic report after the suspension is lifted or — if suspension is not lifted before the end of the action — in the last periodic report.

The beneficiaries may suspend implementation of the action (see Article 49.1) or terminate the Agreement or the participation of the beneficiary concerned (see Article 50.1 and 50.2).

ARTICLE 49 — SUSPENSION OF THE ACTION IMPLEMENTATION

49.1 Suspension of the action implementation, by the beneficiaries

49.1.1 Conditions

The beneficiaries may suspend implementation of the action or any part of it, if exceptional circumstances — in particular *force majeure* (see Article 51) — make implementation impossible or excessively difficult.

49.1.2 Procedure

The coordinator must immediately formally notify to the Agency the suspension (see Article 52), stating:

- the reasons why and
- the expected date of resumption.

The suspension will **take effect** the day this notification is received by the Agency.

Once circumstances allow for implementation to resume, the coordinator must immediately formally notify the Agency and request an **amendment** of the Agreement to set the date on which the action will be resumed, extend the duration of the action and make other changes necessary to adapt the action to the new situation (see Article 55) — unless the Agreement or the participation of a beneficiary has been terminated (see Article 50).

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The suspension will be **lifted** with effect from the resumption date set out in the amendment. This date may be before the date on which the amendment enters into force.

Costs incurred during suspension of the action implementation are not eligible (see Article 6).

49.2 Suspension of the action implementation, by the Agency

49.2.1 Conditions

The Agency may suspend implementation of the action or any part of it, if:

(a) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed or is suspected of having committed:

  (i) substantial errors, irregularities or fraud or

  (ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles);

(b) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (**extension of findings from other grants to this grant**; see Article 22.5.2), or

(c) the action is suspected of having lost its scientific or technological relevance.

49.2.2 Procedure

Before suspending implementation of the action, the Agency will formally notify the coordinator or beneficiary concerned:

- informing it of its intention to suspend the implementation and the reasons why and

- inviting it to submit observations within 30 days of receiving notification.

If the Agency does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify **confirmation** of the suspension. Otherwise, it will formally notify that the procedure is not continued.

The suspension will **take effect** five days after confirmation notification is received (or on a later date specified in the notification).

It will be **lifted** if the conditions for resuming implementation of the action are met.

The coordinator or beneficiary concerned will be formally notified of the lifting and the Agreement will be **amended** to set the date on which the action will be resumed, extend the duration of the action and make other changes necessary to adapt the action to the new situation (see Article 55) — unless the Agreement has already been terminated (see Article 50).

The suspension will be lifted with effect from the resumption date set out in the amendment. This date may be before the date on which the amendment enters into force.

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Costs incurred during suspension are not eligible (see Article 6).

The beneficiaries may not claim damages due to suspension by the Agency (see Article 46).

Suspension of the action implementation does not affect the Agency's right to terminate the Agreement or participation of a beneficiary (see Article 50), reduce the grant or recover amounts unduly paid (see Articles 43 and 44).

ARTICLE 50 — TERMINATION OF THE AGREEMENT OR OF THE PARTICIPATION OF ONE OR MORE BENEFICIARIES

50.1 Termination of the Agreement, by the beneficiaries

50.1.1 Conditions and procedure

The beneficiaries may terminate the Agreement.

The coordinator must formally notify termination to the Agency (see Article 52), stating:

- the reasons why and
- the date the termination will take effect. This date must be after the notification.

If no reasons are given or if the Agency considers the reasons do not justify termination, the Agreement will be considered to have been '**terminated improperly**'.

The termination will **take effect** on the day specified in the notification.

50.1.2 Effects

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a periodic report (for the open reporting period until termination; see Article 20.3) and

(ii) the final report (see Article 20.4).

If the Agency does not receive the reports within the deadline (see above), only costs which are included in an approved periodic report will be taken into account.

The Agency will **calculate** the final grant amount (see Article 5.3) and the balance (see Article 21.4) on the basis of the reports submitted. Only costs incurred until termination are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

Improper termination may lead to a reduction of the grant (see Article 43).

After termination, the beneficiaries' obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) continue to apply.

50.2 Termination of the participation of one or more beneficiaries, by the beneficiaries

50.2.1 Conditions and procedure

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The participation of one or more beneficiaries may be terminated by the coordinator, on request of the beneficiary concerned or on behalf of the other beneficiaries.

The coordinator must formally notify termination to the Agency (see Article 52) and inform the beneficiary concerned.

If the coordinator's participation is terminated without its agreement, the formal notification must be done by another beneficiary (acting on behalf of the other beneficiaries).

The notification must include:

- the reasons why;
- the opinion of the beneficiary concerned (or proof that this opinion has been requested in writing);
- the date the termination takes effect. This date must be after the notification, and
- a request for amendment (see Article 55), with a proposal for reallocation of the tasks and the estimated budget of the beneficiary concerned (see Annexes 1 and 2) and, if necessary, the addition of one or more new beneficiaries (see Article 56). If termination takes effect after the period set out in Article 3, no request for amendment must be included unless the beneficiary concerned is the coordinator. In this case, the request for amendment must propose a new coordinator.

If this information is not given or if the Agency considers that the reasons do not justify termination, the participation will be considered to have been **terminated improperly**.

The termination will **take effect** on the day specified in the notification.

50.2.2 Effects

The coordinator must — within 30 days from when termination takes effect — submit:

(i) a report on the distribution of payments to the beneficiary concerned and

(ii) if termination takes effect during the period set out in Article 3, a '**termination report**' from the beneficiary concerned, for the open reporting period until termination, containing an overview of the progress of the work, an overview of the use of resources, the individual financial statement and, if applicable, the certificate on the financial statement (see Articles 20.3 and 20.4).

The information in the termination report must also be included in the periodic report for the next reporting period (see Article 20.3).

If the request for amendment is rejected by the Agency, (because it calls into question the decision awarding the grant or breaches the principle of equal treatment of applicants), the Agreement may be terminated according to Article 50.3.1(c).

If the request for amendment is accepted by the Agency, the Agreement is **amended** to introduce the necessary changes (see Article 55).

The Agency will — on the basis of the periodic reports, the termination report and the report on

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the distribution of payments — **calculate** the amount which is due to the beneficiary and if the (pre-financing and interim) payments received by the beneficiary exceed this amount.

The **amount which is due** is calculated in the following steps:

Step 1 — Application of the reimbursement rate to the eligible costs

The grant amount for the beneficiary is calculated by applying the reimbursement rate(s) to the total eligible costs declared by the beneficiary in the termination report and approved by the Agency.

Only costs incurred by the beneficiary concerned until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

Step 2 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

In case of a reduction (see Article 43), the Agency will calculate the reduced grant amount for the beneficiary by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the grant amount for the beneficiary.

If the payments received **exceed the amounts due**:

- if termination takes effect during the period set out in Article 3 and the request for amendment is accepted, the beneficiary concerned must repay to the coordinator the amount unduly received. The Agency will formally notify the amount unduly received and request the beneficiary concerned to repay it to the coordinator within 30 days of receiving notification. If it does not repay the coordinator, the Agency will draw upon the Guarantee Fund to pay the coordinator and then notify a **debit note** on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- in all other cases, in particular if termination takes effect after the period set out in Article 3, the Agency will formally notify a **debit note** to the beneficiary concerned. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the Agency the amount due and the Agency will notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- if the beneficiary concerned is the former coordinator, it must repay the new coordinator according to the procedure above, unless:

    - termination takes effect after an interim payment and

    - the former coordinator has not distributed amounts received as pre-financing or interim payments (see Article 21.7).

  In this case, the Agency will formally notify a **debit note** to the former coordinator. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the Agency the amount due. The Agency will then pay the new coordinator and notify a debit note on behalf of the Guarantee Fund to the former coordinator (see Article 44).

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If the payments received **do not exceed the amounts due**: amounts owed to the beneficiary concerned will be included in the next interim or final payment.

If the Agency does not receive the termination report within the deadline (see above), only costs included in an approved periodic report will be taken into account.

If the Agency does not receive the report on the distribution of payments within the deadline (see above), it will consider that:

- the coordinator did not distribute any payment to the beneficiary concerned and that
- the beneficiary concerned must not repay any amount to the coordinator.

Improper termination may lead to a reduction of the grant (see Article 43) or termination of the Agreement (see Article 50).

After termination, the concerned beneficiary's obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) continue to apply.

50.3 Termination of the Agreement or the participation of one or more beneficiaries, by the Agency

50.3.1 Conditions

The Agency may terminate the Agreement or the participation of one or more beneficiaries, if:

(a) one or more beneficiaries do not accede to the Agreement (see Article 56);

(b) a change to their legal, financial, technical, organisational or ownership situation (or those of an entity with a capital or legal link) is likely to substantially affect or delay the implementation of the action or calls into question the decision to award the grant;

(c) following termination of participation for one or more beneficiaries (see above), the necessary changes to the Agreement would call into question the decision awarding the grant or breach the principle of equal treatment of applicants (see Article 55);

(d) implementation of the action is prevented by force majeure (see Article 51) or suspended by the coordinator (see Article 49.1) and either:

  (i) resumption is impossible, or

  (ii) the necessary changes to the Agreement would call into question the decision awarding the grant or breach the principle of equal treatment of applicants;

(e) a beneficiary is declared bankrupt, being wound up, having its affairs administered by the courts, has entered into an arrangement with creditors, has suspended business activities, or is subject to any other similar proceedings or procedures under national law;

(f) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has been found guilty of professional misconduct, proven by any means;

(g) a beneficiary does not comply with the applicable national law on taxes and social security;

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(h) the action has lost scientific or technological relevance;

(i) not applicable;

(j) not applicable;

(k) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed fraud, corruption, or is involved in a criminal organisation, money laundering or any other illegal activity;

(l) a beneficiary (or a natural person who has the power to represent or take decisions on its behalf) has committed:

(i) substantial errors, irregularities or fraud or

(ii) serious breach of obligations under the Agreement or during the award procedure (including improper implementation of the action, submission of false information, failure to provide required information, breach of ethical principles);

(m) a beneficiary (or the natural person who has the power to represent or take decisions on its behalf) has committed — in other EU or Euratom grants awarded to it under similar conditions — systemic or recurrent errors, irregularities, fraud or serious breach of obligations that have a material impact on this grant (**extension of findings from other grants to this grant**; see Article 22.5.2);

(n) despite a specific request by the Agency, a beneficiary does not request — through the coordinator — an amendment to the Agreement to end the participation of a partner organisation or an entity with a capital or legal link that is in one of the situations under points (e), (f), (g), (k), (l) or (m) and to reallocate its tasks.

50.3.2 Procedure

Before terminating the Agreement or participation of one or more beneficiaries, the Agency will formally notify the coordinator or beneficiary concerned:

- informing it of its intention to terminate and the reasons why and
- inviting it, within 30 days of receiving notification, to submit observations and — in case of Point (l.ii) above — to inform the Agency of the measures to ensure compliance with the obligations under the Agreement.

If the Agency does not receive observations or decides to pursue the procedure despite the observations it has received, it will formally notify to the coordinator or beneficiary concerned **confirmation** of the termination and the date it will take effect. Otherwise, it will formally notify that the procedure is not continued.

The termination will **take effect**:

- for terminations under Points (b), (c), (e), (g), (h), and (l.ii) above: on the day specified in the notification of the confirmation (see above);
- for terminations under Points (a), (d), (f), (k), (l.i) and (m) above: on the day after the notification of the confirmation is received.

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50.3.3 Effects

(a) for **termination of the Agreement**:

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a periodic report (for the last open reporting period until termination; see Article 20.3) and

(ii) a final report (see Article 20.4).

If the Agreement is terminated for breach of the obligation to submit reports (see Articles 20.8 and 50.3.1(l)), the coordinator may not submit any reports after termination.

If the Agency does not receive the reports within the deadline (see above), only costs which are included in an approved periodic report will be taken into account.

The Agency will **calculate** the final grant amount (see Article 5.3) and the balance (see Article 21.4) on the basis of the reports submitted. Only costs incurred until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

This does not affect the Agency's right to reduce the grant (see Article 43) or to impose administrative sanctions (Article 45).

The beneficiaries may not claim damages due to termination by the Agency (see Article 46).

After termination, the beneficiaries' obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) continue to apply.

(b) for **termination of the participation of one or more beneficiaries**:

The coordinator must — within 60 days from when termination takes effect — submit:

(i) a report on the distribution of payments to the beneficiary concerned;

(ii) a request for amendment (see Article 55), with a proposal for reallocation of the tasks and estimated budget of the beneficiary concerned (see Annexes 1 and 2) and, if necessary, the addition of one or more new beneficiaries (see Article 56). If termination is notified after the period set out in Article 3, no request for amendment must be submitted unless the beneficiary concerned is the coordinator. In this case the request for amendment must propose a new coordinator, and

(iii) if termination takes effect during the period set out in Article 3, a **termination report** from the beneficiary concerned, for the open reporting period until termination, containing an overview of the progress of the work, an overview of the use of resources, the individual financial statement and, if applicable, the certificate on the financial statement (see Article 20).

The information in the termination report must also be included in the periodic report for the next reporting period (see Article 20.3).

If the request for amendment is rejected by the Agency, (because it calls into question the decision

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awarding the grant or breaches the principle of equal treatment of applicants), the Agreement may be terminated according to Article 50.3.1(c).

If the request for amendment is accepted by the Agency, the Agreement is **amended** to introduce the necessary changes (see Article 55).

The Agency will — on the basis of the periodic reports, the termination report and the report on the distribution of payments — **calculate** the amount which is due to the beneficiary and if the (pre-financing and interim) payments received by the beneficiary exceed this amount.

The **amount which is due** is calculated in the following steps:

Step 1 — Application of the reimbursement rate to the eligible costs

The grant amount for the beneficiary is calculated by applying the reimbursement rate(s) to the total eligible costs declared by the beneficiary in the termination report and approved by the Agency.

Only costs incurred by the beneficiary concerned until termination takes effect are eligible (see Article 6). Costs relating to contracts due for execution only after termination are not eligible.

Step 2 — Reduction due to substantial errors, irregularities or fraud or serious breach of obligations

In case of a reduction (see Article 43), the Agency will calculate the reduced grant amount for the beneficiary by deducting the amount of the reduction (calculated in proportion to the seriousness of the errors, irregularities or fraud or breach of obligations, in accordance with Article 43.2) from the grant amount for the beneficiary.

If the payments received **exceed the amounts due**:

- if termination takes effect during the period set out in Article 3 and the request for amendment is accepted, the beneficiary concerned must repay to the coordinator the amount unduly received. The Agency will formally notify the amount unduly received and request the beneficiary concerned to repay it to the coordinator within 30 days of receiving notification. If it does not repay the coordinator, the Agency will draw upon the Guarantee Fund to pay the coordinator and then notify a **debit note** on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- in all other cases, in particular if termination takes effect after the period set out in Article 3, the Agency will formally notify a **debit note** to the beneficiary concerned. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the Agency the amount due and the Agency will notify a debit note on behalf of the Guarantee Fund to the beneficiary concerned (see Article 44);

- if the beneficiary concerned is the former coordinator, it must repay the new coordinator according to the procedure above, unless:

    - termination takes effect after an interim payment and

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- the former coordinator has not distributed amounts received as pre-financing or interim payments (see Article 21.7).

In this case, the Agency will formally notify a **debit note** to the former coordinator. If payment is not made by the date in the debit note, the Guarantee Fund will pay to the Agency the amount due. The Agency will then pay the new coordinator and notify a debit note on behalf of the Guarantee Fund to the former coordinator (see Article 44).

If the payments received **do not exceed the amounts due**: amounts owed to the beneficiary concerned will be included in the next interim or final payment.

If the Agency does not receive the termination report within the deadline (see above), only costs included in an approved periodic report will be taken into account.

If the Agency does not receive the report on the distribution of payments within the deadline (see above), it will consider that:

- the coordinator did not distribute any payment to the beneficiary concerned and that
- the beneficiary concerned must not repay any amount to the coordinator.

After termination, the concerned beneficiary's obligations (in particular Articles 20, 22, 23, Section 3 of Chapter 4, 36, 37, 38, 40, 42, 43 and 44) continue to apply.

SECTION 4 FORCE MAJEURE

ARTICLE 51 — FORCE MAJEURE

'Force majeure' means any situation or event that:

- prevents either party from fulfilling their obligations under the Agreement,
- was unforeseeable, exceptional situation and beyond the parties' control,
- was not due to error or negligence on their part (or on the part of third parties involved in the action), and
- proves to be inevitable in spite of exercising all due diligence.

The following cannot be invoked as force majeure:

- any default of a service, defect in equipment or material or delays in making them available, unless they stem directly from a relevant case of force majeure,
- labour disputes or strikes, or
- financial difficulties.

Any situation constituting force majeure must be formally notified to the other party without delay, stating the nature, likely duration and foreseeable effects.

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The parties must immediately take all the necessary steps to limit any damage due to force majeure and do their best to resume implementation of the action as soon as possible.

The party prevented by force majeure from fulfilling its obligations under the Agreement cannot be considered in breach of them.

CHAPTER 7 FINAL PROVISIONS

ARTICLE 52 — COMMUNICATION BETWEEN THE PARTIES

52.1 Form and means of communication

Communication under the Agreement (information, requests, submissions, 'formal notifications', etc.) must:

- be made in writing and
- bear the number of the Agreement.

All communication must be made through the Participant Portal **electronic** exchange system and using the forms and templates provided there.

If — after the payment of the balance — the Agency finds that a formal notification was not accessed, a second formal notification will be made by registered post with proof of delivery ('formal notification on **paper**'). Deadlines will be calculated from the moment of the second notification.

Communications in the electronic exchange system must be made by persons authorised according to the Participant Portal Terms & Conditions. For naming the authorised persons, each beneficiary must have designated — before the signature of this Agreement — a 'legal entity appointed representative (LEAR)'. The role and tasks of the LEAR are stipulated in his/her appointment letter (see Participant Portal Terms & Conditions).

If the electronic exchange system is temporarily unavailable, instructions will be given on the Agency and Commission websites.

52.2 Date of communication

Communications are considered to have been made when they are sent by the sending party (i.e. on the date and time they are sent through the electronic exchange system).

Formal notifications through the **electronic** exchange system are considered to have been made when they are received by the receiving party (i.e. on the date and time of acceptance by the receiving party, as indicated by the time stamp). A formal notification that has not been accepted within 10 days after sending is considered to have been accepted.

Formal notifications **on paper** sent by **registered post** with proof of delivery (only after the payment of the balance) are considered to have been made on either:

- the delivery date registered by the postal service or
- the deadline for collection at the post office.

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If the electronic exchange system is temporarily unavailable, the sending party cannot be considered in breach of its obligation to send a communication within a specified deadline.

52.3 Addresses for communication

The **electronic** exchange system must be accessed via the following URL:

https://ec.europa.eu/research/participants/portal/desktop/en/projects/

The Agency will formally notify the coordinator and beneficiaries in advance any changes to this URL.

Formal notifications on paper (only after the payment of the balance) addressed **to the Agency** must be sent to the official mailing address indicated on the Agency's website.

Formal notifications on paper (only after the payment of the balance) addressed **to the beneficiaries** must be sent to their legal address as specified in the Participant Portal Beneficiary Register.

ARTICLE 53 — INTERPRETATION OF THE AGREEMENT

53.1 Precedence of the Terms and Conditions over the Annexes

The provisions in the Terms and Conditions of the Agreement take precedence over its Annexes.

Annex 2 takes precedence over Annex 1.

53.2 Privileges and immunities

Not applicable

ARTICLE 54 — CALCULATION OF PERIODS, DATES AND DEADLINES

In accordance with Regulation No 1182/71[16], periods expressed in days, months or years are calculated from the moment the triggering event occurs.

The day during which that event occurs is not considered as falling within the period.

ARTICLE 55 — AMENDMENTS TO THE AGREEMENT

55.1 Conditions

The Agreement may be amended, unless the amendment entails changes to the Agreement which would call into question the decision awarding the grant or breach the principle of equal treatment of applicants.

Amendments may be requested by any of the parties.

55.2 Procedure

[16] Regulation (EEC, Euratom) No 1182/71 of the Council of 3 June 1971 determining the rules applicable to periods, dates and time-limits (OJ L 124, 8.6.1971, p. 1).

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The party requesting an amendment must submit a request for amendment signed in the electronic exchange system (see Article 52).

The coordinator submits and receives requests for amendment on behalf of the beneficiaries (see Annex 3).

If a change of coordinator is requested without its agreement, the submission must be done by another beneficiary (acting on behalf of the other beneficiaries).

The request for amendment must include:

- the reasons why;
- the appropriate supporting documents, and
- for a change of coordinator without its agreement: the opinion of the coordinator (or proof that this opinion has been requested in writing).

The Agency may request additional information.

If the party receiving the request agrees, it must sign the amendment in the electronic exchange system within 45 days of receiving notification (or any additional information the Agency has requested). If it does not agree, it must formally notify its disagreement within the same deadline. The deadline may be extended, if necessary for the assessment of the request. If no notification is received within the deadline, the request is considered to have been rejected

An amendment **enters into force** on the day of the signature of the receiving party.

An amendment **takes effect** on the date agreed by the parties or, in the absence of such an agreement, on the date on which the amendment enters into force.

ARTICLE 56 — ACCESSION TO THE AGREEMENT

56.1 Accession of the beneficiaries mentioned in the Preamble

The other beneficiaries must accede to the Agreement by signing the Accession Form (see Annex 3) in the electronic exchange system (see Article 52) within 30 days after its entry into force (see Article 58).

They will assume the rights and obligations under the Agreement with effect from the date of its entry into force (see Article 58).

If a beneficiary does not accede to the Agreement within the above deadline, the coordinator must — within 30 days — request an amendment to make any changes necessary to ensure proper implementation of the action. This does not affect the Agency's right to terminate the Agreement (see Article 50).

56.2 Addition of new beneficiaries

In justified cases, the beneficiaries may request the addition of a new beneficiary.

For this purpose, the coordinator must submit a request for amendment in accordance with Article 55.

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It must include an Accession Form (see Annex 3) signed by the new beneficiary in the electronic exchange system (see Article 52).

New beneficiaries must assume the rights and obligations under the Agreement with effect from the date of their accession specified in the Accession Form (see Annex 3).

ARTICLE 57 — APPLICABLE LAW AND SETTLEMENT OF DISPUTES

57.1 Applicable law

The Agreement is governed by the applicable EU law, supplemented if necessary by the law of Belgium.

57.2 Dispute settlement

If a dispute concerning the interpretation, application or validity of the Agreement cannot be settled amicably, the General Court — or, on appeal, the Court of Justice of the European Union — has sole jurisdiction. Such actions must be brought under Article 272 of the Treaty on the Functioning of the EU (TFEU).

As an exception, if such a dispute is between the Agency and ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE, the competent Belgian courts have sole jurisdiction.

If a dispute concerns administrative sanctions, offsetting or an enforceable decision under Article 299 TFEU (see Articles 44, 45 and 46), the beneficiaries must bring action before the General Court — or, on appeal, the Court of Justice of the European Union — under Article 263 TFEU. Actions against offsetting and enforceable decisions must be brought against the Commission (not against the Agency).

ARTICLE 58 — ENTRY INTO FORCE OF THE AGREEMENT

The Agreement will enter into force on the day of signature by the Agency or the coordinator, depending on which is later.

SIGNATURES

For the coordinator

Sílvia Marisa ESTEVES DE SOUSA with ECAS id nestevsi signed in the Participant Portal on 20/07/2018 at 12:09:48 (transaction id SigId-104520-zgPt7FXbSVn2LrHrXhzJavYoshUYzTKikDKIqpvuL0Us8QJzaxF0OXttG4fuh75WViaTUALYWJqGQTifDZ1hPE4-Jj71zxYb8yrHe5PcV7PX78-OgbuiYjZ5W2sq389gIZWaDVFyIXeKtzdcq02lOzd1dom). Timestamp by third party at Fri Jul 20 13:09:57 CEST 2018

For the Agency

Signed by Klaus-Guenther BARTHEL with ECAS id barthkl as an authorised representative on 20-08-2018 10:06:42 (transaction id SigId-69698-cuAb5brFUw3Nj6tvVUNIrWsJzXqA7UpoBnwuTT4uDzI9lrcPkK5KpqytJ2zcBrVlLPzVGyfxtouHkQdByPoG2iO-Jj71zxYb8yri1y2U3pzd5N-lOlu3P0LoDpeGSELDwGfAwE62PUhSwUYo8Br2umtfge) Mon Aug 20 10:06:49 CEST 2018

EUROPEAN RESEARCH EXECUTIVE AGENCY (REA)

REA.A – Marie Skłodowska-Curie Actions & Support to Experts
A.1 – MSCA Doctoral Networks

AMENDMENT Reference No AMD-813986-8

Grant Agreement number: 813986 — Synaptic Dysfunction in Neuropsychiatric Disorders (Syn2Psy)

The parties agree to amend the Grant Agreement as follows ('**Amendment**'):

1. Change of Annex 1 (description of the action)

Annex 1 is changed and replaced by the Annex 1 attached to this Amendment.

2. Change of the action's duration

The duration of the action in **Article 3** is changed to 54 months.

3. Change of the reporting periods

The reporting periods are changed.

This implies the **following changes** to the Grant Agreement:

- The reporting periods in **Article 20.2** are replaced by:

  - RP1: from month 1 to month 24
  - RP2: from month 25 to month 54

4 . Changes of Annex 2 (estimated budget)

Annex 2 is changed and replaced by the Annex 2 attached to this Amendment.

5. Change of the maximum grant amount (decrease)

The maximum grant amount set out in **Article 5.1** is changed to:

"**EUR 3 885 134.08** (three million eight hundred and eighty five thousand one hundred and thirty four EURO and eight eurocents)".

6. Change of the estimated eligible costs

The estimated eligible costs of the action set out in **Article 5.2** are changed to:

"**EUR 3 885 134.08** (three million eight hundred and eighty five thousand one hundred and thirty four EURO and eight eurocents)".

All other provisions of the Grant Agreement and its Annexes remain unchanged.

This Amendment **enters into force** on the day of the last signature.

This Amendment **takes effect** on the date on which the amendment enters into force, except where a different date has been agreed by the parties (for one or more changes).

Please inform the other members of the consortium of the Amendment.

SIGNATURES

For the coordinator

Sílvia Marisa ESTEVES DE SOUSA with ECAS id nestevsi signed in the Participant Portal on 01/08/2022 at 12:31:31 (transaction id SigId-96606-4Lmkr0mon92g9JToKZJS3B9yHPzLk8pC9F7wKsSBp1ljvgpt8yehQScmxdy7CNfzUF0YJM4r3rvaGCCTjDa0UL-yntOf97TTHq29yS3sozNII-2DNS0cTNTlo4kKMdkQ3YwdTHTd4ptzzczKInhCAL9q7pn36BCoopNSpIn9DqiAPYzskKzzemVhepoLpJTXh0s2OW). Timestamp by third party at
2022.08.01 13:31:51 CEST

For the Agency

Signed by Klaus HAUPT with ECAS id hauptkl as an authorised representative on 11-08-2022 18:02:57 (transaction id SigId-138786-o271MmkkCTRQl6h42vMVR3BL8M95K8oGW8Rb0ZTB7Cn6QHHy9MW3DIBaNvO5LunMzxskmoSXrDMaNkVhVNB6jq-rS0vSrmBGYC5A0GYws8iKq-OdQ6JhvEiuuruAGPKUENT0r81PbemMzvAgByAJlgTr1ZKyTjqjoEzgeYfcMhGkifrsUiEyqiAtPaL5mDMDnajg)
2022.08.11 18:03:01 CEST

Enclosures:

Annex 2
Annex 1



EUROPEAN RESEARCH EXECUTIVE AGENCY (REA)

REA.A – Marie Skłodowska-Curie Actions & Support to Experts
A.1 – MSCA Doctoral Networks

ANNEX 1 (part A)

European Training Networks

NUMBER — 813986 — Syn2Psy

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1.1. The project summary

Project Number [1]	813986	Project Acronym [2]	Syn2Psy

One form per project

General information	
Project title [3]	Synaptic Dysfunction in Neuropsychiatric Disorders
Starting date [4]	01/03/2019
Duration in months [5]	54
Call (part) identifier [6]	H2020-MSCA-ITN-2018
Topic	MSCA-ITN-2018 Innovative Training Networks
Fixed EC Keywords	Neural development and neuroplasticity, Psychiatric disorders and clinical psychology (e.g. schizophrenia, autism, Tourette's syndrome, obsessive compulsive disorder, depression, bipolar disorder, attention deficit hyperactivity disorder), Molecular and cellular neuroscience
Free keywords	Neuropsychiatric disorders, Synaptic dysfunction, Genetic animal models of disease, Rational therapies, Neuromodulators

Abstract [7]

The large public health burden and individual suffering associated with mental disorders speaks to the need to study their biological underpinning. Genetic research, animal models of disease and human neuroimaging studies have provided convergent evidence to common pathways implicated in their aetiology, namely pathways that regulate synapse development and plasticity, which result in abnormal structural and functional connectivity in the brain of neuropsychiatric patients. The time has come to integrate studies across different levels, leading to the identification of signatures of illness associated to specific risk pathways, which can drive the development of novel therapies.
The objective of Syn2Psy is to provide high-level Ph.D. training for 14 early stage researchers (ESRs) to answer three critical questions: 1) What are the synaptic defects at the basis of neuropsychiatric disorders? 2) Which are the neuronal circuits that are disrupted, and may be targets for therapies? 3) How and when can we modulate the course of disease? Syn2Psy combines strong scientific with complementary know-how from the non-academic sector, and network-wide actions on scientific and complementary soft skills, to train a new generation of high achieving ESRs and provide them with the transferable skills necessary for thriving careers in a flourishing area. Industrial partners Lundbeck, Eurotrials and ZEISS provide experience on drug, clinical trials and technology development, the Coimbra University Hospital will expose the students to clinical research, while the clinic for child development PIN and the Marionet theatre company offer training in societal awareness and outreach. The excellent basic scientific knowledge and diverse skills acquired by ESRs will enhance their employment prospects in both the academic and non-academic sectors, and their scientific contributions will inform novel therapeutic approaches for alleviating this leading cause of disability worldwide.

1.2. List of Beneficiaries

Project Number [1]	813986	Project Acronym [2]	Syn2Psy

List of Beneficiaries

No	Name	Short name	Country	Project entry date[8]	Project exit date
1	CENTRO DE NEUROCIENCIAS E BIOLOGIACELULAR ASSOCIACAO	CNC	Portugal		
2	CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE CNRS	CNRS	France		
3	ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE	EPFL	Switzerland		
4	IMPERIAL COLLEGE OF SCIENCE TECHNOLOGY AND MEDICINE	Imperial	United Kingdom		
5	THE UNIVERSITY OF EDINBURGH	UEDIN	United Kingdom		
6	H. LUNDBECK AS	H. LUNDBECK AS	Denmark		

1.3. Workplan Tables - Detailed implementation

1.3.1. WT1 List of work packages

WP Number[9]	WP Title	Lead beneficiary[10]	Start month[12]	End month[13]
WP1	New models of neuropsychiatric disorders	1 - CNC	6	54
WP2	Testing the Excitation/Inhibition imbalance hypothesis in neuropsychiatric disorders	2 - CNRS	6	54
WP3	Modulators of neuropsychiatric disorders	3 - EPFL	6	54
WP4	Training and Doctoral Programme plan	4 - Imperial	1	54
WP5	Dissemination & Communication and Exploitation (D&C)	2 - CNRS	1	54
WP6	Management	1 - CNC	1	54
WP7	Ethics requirements	1 - CNC	1	54

1.3.2. WT2 list of deliverables

Deliverable Number[14]	Deliverable Title	WP number[9]	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D1.1	Establishment of the role of stargazin in psychiatric disorders; development of targeted therapies	WP1	1 - CNC	Report	Public	54
D1.2	Identification of the role of specific mitochondrial genes for the development of psychopathologies	WP1	3 - EPFL	Report	Public	54
D1.3	Development and characterization of human-derived neurons and brain organoids as models of neurodevelopmental disorders	WP1	1 - CNC	Report	Public	54
D1.4	Oral/ Poster presentations in international scientific meetings (WP1)	WP1	1 - CNC	Report	Public	54
D1.5	PhD Theses (WP1)	WP1	1 - CNC	Report	Public	54
D2.2	Characterization of cortical excitation/ inhibition imbalance in vivo in models of synaptic dysfunction using mesoscopic methods	WP2	4 - Imperial	Report	Public	54
D2.3	Identification of defects in single NMDA receptor dynamics in psychosis	WP2	2 - CNRS	Report	Public	54
D2.4	Identification of presynaptic defects and alterations in glutamate receptor dynamics in Fragile X syndrome	WP2	1 - CNC	Report	Public	54
D2.5	Depiction of synapses and functional networks in a new paradigm to model Down syndrome (human iPSC-derived neurons from DS donors transplanted in the mouse brain)	WP2	4 - Imperial	Report	Public	54

Deliverable Number[14]	Deliverable Title	WP number[9]	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D2.6	Characterization of the synaptic and neural correlates of spatial memory deficits in a glycine receptor knock-out model of ASD	WP2	2 - CNRS	Report	Public	54
D2.7	Oral/ Poster presentations in international scientific meetings (WP2)	WP2	2 - CNRS	Report	Public	54
D2.8	PhD Theses (WP2)	WP2	2 - CNRS	Report	Public	54
D3.1	Definition of the therapeutic potential of the endocannabinoid system in an ASD model	WP3	2 - CNRS	Report	Public	54
D3.2	Identification of the role of the excitation/ inhibition (E/I) imbalance in the cortico-thalamic system in the development of neuropsychiatric disorders	WP3	6 - H. LUNDBECK AS	Report	Public	54
D3.3	Identification of aberrant synaptic mRNA translation as a point of convergence for multiple genetic causes of ASD/ID	WP3	5 - UEDIN	Report	Public	54
D3.4	Establishment of the impact of the corticotropic releasing hormone system on schizophrenia- and ASD-related endophenotype	WP3	3 - EPFL	Report	Public	54
D3.5	Identification of circuit deficits associated with ASD	WP3	5 - UEDIN	Report	Public	54
D3.6	Oral/ Poster presentations in international scientific meetings (WP3)	WP3	3 - EPFL	Report	Public	54
D3.7	PhD Theses (WP3)	WP3	3 - EPFL	Report	Public	54
D4.1	Final Conference	WP4	1 - CNC	Other	Public	54
D4.2	Report on network school 1 (NS1)	WP4	1 - CNC	Report	Public	8

Deliverable Number[14]	Deliverable Title	WP number[9]	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D4.3	Report on network school 2 (NS2)	WP4	2 - CNRS	Report	Public	38
D4.4	Report on network school 3 (NS3)	WP4	6 - H. LUNDBECK AS	Report	Public	29
D4.5	Report on network school 4 (NS4)	WP4	2 - CNRS	Report	Public	38
D4.6	Career development plan of ESRs	WP4	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	12
D4.7	Secondment reports	WP4	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	54
D4.8	Report on PhD courses	WP4	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D4.9	Supervisory board	WP4	1 - CNC	Other	Confidential, only for members of the consortium (including the Commission Services)	2
D5.1	Syn2Psy public website	WP5	1 - CNC	Websites, patents filing, etc.	Public	6
D5.2	Report on outreach & public engagement	WP5	1 - CNC	Report	Public	54
D5.3	Public media dissemination	WP5	1 - CNC	Report	Public	4
D5.4	Theatre	WP5	1 - CNC	Other	Public	54
D5.5	Report on the potential for results exploitation	WP5	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	54
D6.1	Report on the Kick-off meeting	WP6	1 - CNC	Report	Confidential, only for members of the consortium	8

Deliverable Number[14]	Deliverable Title	WP number[9]	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
					(including the Commission Services)	
D6.2	Syn2Psy internal website	WP6	1 - CNC	Websites, patents filing, etc.	Confidential, only for members of the consortium (including the Commission Services)	3
D6.3	Annual progress report 1	WP6	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	12
D6.4	Report for the intermediate Syn2Psy meeting	WP6	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	29
D6.5	Annual progress report 2	WP6	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D6.6	Annual progress report 3	WP6	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	36
D6.7	Final technical and financial project report	WP6	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	54
D6.8	Consortium agreement	WP6	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	2
D6.9	Data Management Plan	WP6	1 - CNC	ORDP: Open Research Data Pilot	Confidential, only for members of the consortium (including the	6

Deliverable Number[14]	Deliverable Title	WP number[9]	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
					Commission Services)	
D6.10	Potential input for Policy feedback	WP6	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	54
D7.1	H - Requirement No. 1	WP7	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.2	HCT - Requirement No. 2	WP7	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.3	POPD - Requirement No. 3	WP7	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.4	A - Requirement No. 4	WP7	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.5	EPQ - Requirement No. 5	WP7	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.6	GEN - Requirement No. 6	WP7	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12

1.3.3. WT3 Work package descriptions

Work package number [9]	WP1	Lead beneficiary [10]	1 - CNC
Work package title	New models of neuropsychiatric disorders		
Start month	6	End month	54

Objectives

•To characterize at the neurophysiological, morphological and behavioural levels new genetic models of ID, schizophrenia and ASD, available in the host laboratories, built based on human genetic data or on the implication of the candidate proteins in crucial pathophysiological pathways;
•To test human-derived neurons and brain organoids as a model for neurodevelopmental disorders;
•To identify shared pathways and neuronal circuits that are implicated in neuropsychiatric disorders.

Description of work and role of partners

WP1 - New models of neuropsychiatric disorders [Months: 6-54]
CNC
In Task 1.1 Cognitive disorders as defects in synaptic function: insight from human mutations in the CACNG2 gene encoding Stargazin (ESR1, supervisor Ana Luisa Carvalho, CNC), knock-in (KI) mouse models expressing ID- and schizophrenia-associated mutations in the CACNG2 gene encoding the synaptic protein Stargazin will be analysed. In vitro data show that these variants of Stargazin have impaired function in the traffic of AMPA-type glutamate receptors, and defects in mediating plasticity. Analyses of neuro-morphological, neuro-physiological and behaviour characteristics of the Stargazin KI animals will inform on the specific pathways that are impaired by the human mutations in CACNG2. The secondment at IINS-CNRS (with Daniel Choquet) will be fundamental to use state-of-the-art super-resolution methods for the nanoscopic characterization of AMPA receptors and Stargazin at the synapse and understand how Stargazin mutations affect synapse organization. Furthermore, the secondment at ICL (with Thomas Knöpfel) will lead to the mesoscopic monitoring in vivo of cortical E/I balance in these animals and thereby inform on alterations in cortical dynamics associated with Stargazin mutations. Testing a potential therapy (tianeptine) directed at boosting Stargazin function will determine whether a precision medicine approach can be effective to treat the effects of Stargazin disease-associated mutations.

In Task 1.2 Role of Mitofusins in neurodevelopmental trajectories of psychopathology (ESR2, supervised by Carmen Sandi and Simone Astori BMI-EPFL): contribution of mitofusin deficiency to the development of anxiety and depression and identification of the mechanisms caused by impaired mitochondrial dynamics involved in dysfunctional behaviours in specific nucleus accumbens neurons, through the use of mouse genetics and gene delivery. This project is based on findings that highlight reduced brain expression of the mitochondrial GTPase Mitofusins 1 (Mfn1) and 2 (Mfn2) in depression and stress-related psychopathologies. The study will be further developed through the secondments at IINS-CNRS, with Laurent Groc, to measure dynamics of synaptic NMDA receptors in the nucleus accumbens following Mfn2 loss of function in D1- or D2-mice; and at CIP-UEDIN, with Emily Osterweil, to investigate the impact of Mfn2 deficiency in accumbal neuronal subtypes on protein translation using TRAP.

Task 1.3. Production and testing of human-derived neurons and brain organoids: advanced model probing in neurodevelopmental disorders (ESR3, supervised by João Peça, CNC) deals with the creation of patient–derived neurons, and with probing the potential for organoid development from patients' dental stem cells to study how patient mutations affect cerebral formation. The study will address synaptic, morphological and electrophysiological properties in these neurons (also in collaboration with Emily Osterweil and Peter Kind at CIP-UEDIN), characterize interneurons in the preparation (with the collaboration of Lundbeck), and assay brain organoids as a biomedical platform for testing drugs.

Participation per Partner

Partner number and short name [10]
1 - CNC

Partner number and short name [10]
2 - CNRS
3 - EPFL
4 - Imperial
5 - UEDIN
6 - H. LUNDBECK AS

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D1.1	Establishment of the role of stargazin in psychiatric disorders; development of targeted therapies	1 - CNC	Report	Public	54
D1.2	Identification of the role of specific mitochondrial genes for the development of psychopathologies	3 - EPFL	Report	Public	54
D1.3	Development and characterization of human-derived neurons and brain organoids as models of neurodevelopmental disorders	1 - CNC	Report	Public	54
D1.4	Oral/ Poster presentations in international scientific meetings (WP1)	1 - CNC	Report	Public	54
D1.5	PhD Theses (WP1)	1 - CNC	Report	Public	54

Description of deliverables

1) Scientific publications: poster or oral presentations in major International Scientific Meetings;
2) Scientific publications: papers in scientific journals;
3) 3 PhD theses.

D1.1 : Establishment of the role of stargazin in psychiatric disorders; development of targeted therapies [54]

Presentation of scientific data in a peer-reviewed manuscript.

D1.2 : Identification of the role of specific mitochondrial genes for the development of psychopathologies [54]

Presentation of scientific data in peer-reviewed manuscript.

D1.3 : Development and characterization of human-derived neurons and brain organoids as models of neurodevelopmental disorders [54]

Presentation of scientific data in peer-reviewed manuscript.

D1.4 : Oral/ Poster presentations in international scientific meetings (WP1) [54]

Presentation of scientific data in: a) scientific meetings, as oral communications b) scientific meetings, as poster presentations.

D1.5 : PhD Theses (WP1) [54]
Three PhD Theses.

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS12	PhD theses completed (13)	1 - CNC	54	ESRs will have completed their theses at M54.

Work package number [9]	WP2	Lead beneficiary [10]	2 - CNRS
Work package title	Testing the Excitation/Inhibition imbalance hypothesis in neuropsychiatric disorders		
Start month	6	End month	54

Objectives

•Exploring the mechanisms underlying E/I imbalance in models of neuropsychiatric disease; •Dissecting nanostructural changes in synapse dynamics in models of neuropsychiatric disorders;
•Monitoring E/I balance at the population level using voltage-sensitive fluorescent proteins – analysing cortical dynamics;

Description of work and role of partners

WP2 - Testing the Excitation/Inhibition imbalance hypothesis in neuropsychiatric disorders [Months: 6-54]
CNRS
In Task 2.1 Linking autism related mutations in Shank3 over synaptic, network and behaviour defects (ESR4, supervised by Daniel Choquet, IINS-CNRS), the objective is to explore the mechanistic links between mutations in Shank3, an excitatory scaffold protein whose mutations account for many synaptic forms of ASD, resulting in alterations in synapse organization, neuronal circuits and behavioural phenotypes. Shank3 KO mice and patient-derived iPS cells with altered Shank3 expression will be used to detect at the nanoscale level alterations in the dynamic organization of excitatory synapses. A viral-mediated approach to silence Shank3 and express channel-rhodopsin will be utilized in ventral hippocampus, and neuronal projection to the mPFC will be analysed taking advantage of channel-rhodopsin expression in control and Shank3 negative axons. This approach will reveal the role of Shank3 in the hippocampus-mPFC connection.

Task 2.2 Monitoring E/I balance at the population level with voltage sensitive fluorescent proteins (ESR5, supervised by Thomas Knöpfel, ICL) will also focus on Shank3 KO mice, but in this case the objective is to determine how the cortical E/I balance is affected both at resting awake state and upon sensory processing of somatosensory/whisker or visual stimulation. The know-how developed in Thomas Knöpfel laboratory to use voltage sensitive fluorescent proteins (VSFP)15 will be instrumental for performing this analysis in a cell-type specific manner, upon expression of the chimeric VSFP Butterfly in identified cell classes. Mesoscopic optical voltage imaging will achieve large area population monitoring of E/I balance in the cortex, reveal differences in cortical dynamics between Shank3 KO mice and control mice, and allow testing the neuromodulatory effects of 5HT. Behavioural tasks relevant to ASD and Phelan-McDermid syndrome and amenable to in vivo optical imaging will be developed in collaboration with C. Betancur (IBPS-CNRS); ESR will also perform a secondment at CHUC to get exposure to clinical research and learn about the clinical evaluation of patients with autism and other neurodevelopmental disorders and the selection criteria for patients include in research cohorts.

Task 2.3 Physiopathological regulation of single NMDA receptor dynamics in psychosis (ESR6, supervised by Laurent Groc, IINS-CNRS) will address whether NMDA receptor dynamics is altered in models of psychosis, both pharmacological and developmental models, as well as genetic models (in collaboration with Ana Luisa Carvalho at CNC). State-of-the-art super-resolution approaches will be employed to provide the first high-density quantitative map of surface NMDA receptor subtypes in brain slices, and test how the map is changed in schizophrenia models. The ESR will do an internship at CHUC to get exposure to clinical research and learn about the clinical evaluation of psychosis patients and the selection criteria for patients in research cohorts.

Task 2.4 FMRP regulation of synapse dynamics (ESR7, supervised by Carlos Duarte, CNC) will investigate alterations in synaptic properties in fragile X syndrome, a neurodevelopmental disorder characterized by ID, features of ASD such as deficits in communication and social interaction, and in some cases seizures. This genetic condition is caused by mutations in the FMR1 gene, which encodes FMRP, an RNA-binding protein and a regulator of protein synthesis for subsets of neuronal transcripts. Given the role of local protein synthesis both in dendrites and axons, ESR7 will focus on interrogating synapse dynamics at the presynaptic and postsynaptic levels in Fmr1 KO mice. Presynaptic bouton formation and dynamics, presynaptic exocytotic release as well as postsynaptic AMPA and NMDA receptor dynamics will be analysed. The participation of Vincenzo De Paola (ICL) in the project will be crucial for the in vivo analysis of presynaptic bouton formation in Fmr1 KO mice, and the contribution of Niels Plath (Lundbeck) will be instrumental to characterize the morphological alterations in interneuron inhibitory synapses.

Task 2.5 Illuminating the mechanisms of synaptic and neural network dysfunction in a new in vivo model of Down's syndrome (ESR8 supervised by Vincenzo De Paola, ICL) will combine a recently developed in vivo model of DS, based on transplanted patient-derived neurons, with longitudinal multiphoton structural and functional in vivo imaging, rabies tracing, slice electrophysiology and molecular analyses to characterize the dynamics of synapses and neural networks in DS. Detailed analysis of synaptic molecular alterations will be done in collaboration with D. Choquet and L. Groc (IINS-CNRS), and ESR will be exposed to clinical research at CHUC.

In Task 2.6 Role of glycinergic signalling in ASD (ESR9 supervised by Catalina Betancur, IBPS-CNRS) the focus is on glycinergic signalling, based on recent evidence gathered by the group for abnormalities in this type of signalling in autism 16. Glycine receptors (GlyR) mediate inhibitory neurotransmission in the adult nervous system, but exert an excitatory action during development. Microdeletions and missense mutations have been found in autism in the gene encoding the GlyR α2 subunit, and KO mice for this subunit present memory and synaptic plasticity defects in the mPFC 16. Here, ESR8 will further investigate the cellular and behavioural correlates of PFC synaptic dysfunction in the absence of GlyR α2 subunit, and in collaboration with Thomas Knöpfel (ICL) image cortical dynamics and E/I balance in vivo in KO mice for GlyR α2. The collaboration with Peter Kind (CIP-U. Edinburgh) will compare cortical and hippocampal synaptic function in mutant mice. This project will provide important insight on how defects on inhibitory glycinergic signalling contribute to ASDs.

Participation per Partner

Partner number and short name [10]
1 - CNC
2 - CNRS
4 - Imperial
6 - H. LUNDBECK AS

List of deliverables

Deliverable Number[14]	**Deliverable Title**	**Lead beneficiary**	**Type**[15]	**Dissemination level**[16]	**Due Date (in months)**[17]
D2.2	Characterization of cortical excitation/ inhibition imbalance in vivo in models of synaptic dysfunction using mesoscopic methods	4 - Imperial	Report	Public	54
D2.3	Identification of defects in single NMDA receptor dynamics in psychosis	2 - CNRS	Report	Public	54
D2.4	Identification of presynaptic defects and alterations in glutamate receptor dynamics in Fragile X syndrome	1 - CNC	Report	Public	54
D2.5	Depiction of synapses and functional networks in a new paradigm to model Down syndrome	4 - Imperial	Report	Public	54

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
	(human iPSC-derived neurons from DS donors transplanted in the mouse brain)				
D2.6	Characterization of the synaptic and neural correlates of spatial memory deficits in a glycine receptor knock-out model of ASD	2 - CNRS	Report	Public	54
D2.7	Oral/ Poster presentations in international scientific meetings (WP2)	2 - CNRS	Report	Public	54
D2.8	PhD Theses (WP2)	2 - CNRS	Report	Public	54

Description of deliverables

1) Scientific publications: poster or oral presentations in major International Scientific Meetings;
2) Scientific publications: papers in scientific journals;
3) 5 PhD theses.

D2.2 : Characterization of cortical excitation/inhibition imbalance in vivo in models of synaptic dysfunction using mesoscopic methods [54]

Presentation of scientific data in peer-reviewed manuscript.

D2.3 : Identification of defects in single NMDA receptor dynamics in psychosis [54]

Presentation of scientific data in peer-reviewed manuscript.

D2.4 : Identification of presynaptic defects and alterations in glutamate receptor dynamics in Fragile X syndrome [54]

Presentation of scientific data in peer-reviewed manuscript.

D2.5 : Depiction of synapses and functional networks in a new paradigm to model Down syndrome (human iPSC-derived neurons from DS donors transplanted in the mouse brain) [54]

Presentation of scientific data in peer-reviewed manuscript.

D2.6 : Characterization of the synaptic and neural correlates of spatial memory deficits in a glycine receptor knock-out model of ASD [54]

Presentation of scientific data in peer-reviewed manuscript.

D2.7 : Oral/ Poster presentations in international scientific meetings (WP2) [54]

Presentation of scientific data in: a) scientific meetings, as oral communications, b) scientific meetings, as poster presentations.

D2.8 : PhD Theses (WP2) [54]

Five PhD Theses.

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS12	PhD theses completed (13)	1 - CNC	54	ESRs will have completed their theses at M54.

Work package number [9]	WP3	Lead beneficiary [10]	3 - EPFL
Work package title	Modulators of neuropsychiatric disorders		
Start month	6	End month	54

Objectives

•Testing the endocannabinoid system, fast spiking interneurons manipulation and proteastasis as modulatory targets in neuropsychiatric disorders;
•Assessing the interplay between prenatal stress and genetic risk in the development of disease;
•Evaluating the time window of opportunity for intervention in models of neuropsychiatric disorders;
•Testing gene therapy for Fragile X Syndrome.

Description of work and role of partners

WP3 - Modulators of neuropsychiatric disorders [Months: 6-54]
EPFL
In Task 3.1 The endocannabinoid system as a therapeutic target in Shank3-deficient mice, a model of autism spectrum disorder (ESR10, supervised by Catalina Betancur, IBPS-CNRS), it is proposed that modulation of the endocannabinoid system, a key modulator or neuronal excitability and synaptic plasticity, could have a beneficial effect in the Shank3 model of ASD. A new non-metabolisable molecule, an allosteric inhibitor of the CB1R, will be employed to test for phenotypic effects in Shank3+/- mice, at the behavioural, electrophysiological (in collaboration with João Peça, CNC, who generated one of the first Shank3 mouse models 17) and molecular levels. The findings on the neuromodulatory effects of the endocannabinoid system on this model could potentially be extended to other mouse models of ASD with synaptic abnormalities and displaying alterations in the E/I balance, and eventually to patients.

Task 3.2 Investigating the excitation/inhibition (E/I) imbalance hypothesis of neuropsychiatric disorders in the cortico-thalamic system with electrophysiological methods. ESR11 (supervised by Niels Plath and Kjartan Herrik, Lundbeck), will address the circuits and mechanisms that govern E/I balance in cortico-thalamic and thalamo-cortical networks, focusing in the interplay between the thalamic reticular nucleus, mediodorsal thalamus and medial prefrontal cortex, in the context of neuropsychiatric disorders, such as schizophrenia. This will be performed using a variety of electrophysiological methods, as well as pharmacological and chemogenetic tools. The study will be further developed through the secondments at BMI-EPFL, with Carmen Sandi and Simone Astori to learn of polysomnographic recordings and sleep scoring in freely moving rats before and after novel recognition tests; and at CIP-UEDIN, with Peter Kind, to generate a relevant transgenic model of thalamic reticular nucleus dysfunction.

In Task 3.3 Identifying convergent dysregulation of mRNA translation in multiple models of autism. ESR12 (supervised by Emily Osterweil, CIP-UEDIN) will assess how disruptions in local protein synthesis contribute to Autism Spectrum Disorder with associated Intellectual Disability, more specifically how mistranslating mRNAs in multiple circuits contribute to pathological phenotypes in mouse models of FX and SYNGAP1 haploinsufficiency syndrome, through TRAP-seq. Through the collaborations with CNC (with Ana Luísa Carvalho) and IINS-CNRS (Daniel Choquet and Laurent Groc), ESR12 will analyse ribosome trafficking and make use of Super-Resolution Microscopy to analyse spine dynamics in Fmr1 -/y versus Syngap +/- models.

Task 3.4 Establishment of the impact of the corticotropic releasing hormone system on schizophrenia- and ASD-related endophenotype (ESR13, supervised by Carmen Sandi and Simone Astori, BMI-EPFL): assessment of how the corticotropin-releasing hormone system affects the Thalamic Reticular Nucleus (TRN) excitability and thalamocortical sleep rhythms; and examination of the expression of schizophrenia and autism spectrum disorder-risk genes after chronic exposure to corticotropin-releasing hormone at early postnatal stages. This will be performed through the combination of ex-vivo cellular analyses and polysomnographic recordings. The study will be further developed through the secondments at IINS-CNRS with Laurent Groc, to measure the dynamics of synaptic receptors in the TRN of mice exposed to CRH/stress and at ICL, with Thomas Knöpfel, to monitor in vivo TRN activation with voltage/Ca2+ sensors during CRH/stress exposure.

Task 3.5 Circuit deficits associated with ASD/ID (ESR14, supervised by Peter Kind, CIP-UEDIN) will address the critical periods for the modulatory impact of regulators of the ERK pathway in Fmr1-/y and Syngap1+/- models of neurodevelopmental disorders. Behavioural, electrophysiological and morphologic phenotypes will be evaluated, and the critical time for intervention will be determined. The secondment at IINS-CNRS (Daniel Choquet/Laurent Groc)

will allow evaluating whether the molecular structure of the synapse (at the nanoscale level) is changed in these models, and whether and when the changes can be rescued. This task addresses a fundamental question in the field, related to the time of intervention in neurodevelopmental disorders.

Task 3.6 Testing gene therapy for Fragile X Syndrome (ESR15, supervised by Emily Osterweil, CIP-UEDIN) will address the genetic replacement of Fmr1 in two models (mouse and rat) of Fragile X Syndrome (FXS). After the injection of a viral gene therapy vector (AAV9-Fmr1) into specific regions of Fmr1 mouse and rat brains, characteristic phenotypes such as hippocampal protein synthesis, mGluR-LTD and audiogenic seizures will be accessed. This task addresses the long-standing question of whether re-introduction of Fmr1 can restore function in the adult nervous system and, if so, whether this replacement must occur early in development.

Participation per Partner

Partner number and short name [10]
1 - CNC
2 - CNRS
3 - EPFL
4 - Imperial
5 - UEDIN
6 - H. LUNDBECK AS

List of deliverables

Deliverable Number[14]	**Deliverable Title**	**Lead beneficiary**	**Type**[15]	**Dissemination level**[16]	**Due Date (in months)**[17]
D3.1	Definition of the therapeutic potential of the endocannabinoid system in an ASD model	2 - CNRS	Report	Public	54
D3.2	Identification of the role of the excitation/ inhibition (E/I) imbalance in the cortico-thalamic system in the development of neuropsychiatric disorders	6 - H. LUNDBECK AS	Report	Public	54
D3.3	Identification of aberrant synaptic mRNA translation as a point of convergence for multiple genetic causes of ASD/ ID	5 - UEDIN	Report	Public	54
D3.4	Establishment of the impact of the corticotropic releasing hormone system on	3 - EPFL	Report	Public	54

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
	schizophrenia- and ASD-related endophenotype				
D3.5	Identification of circuit deficits associated with ASD	5 - UEDIN	Report	Public	54
D3.6	Oral/ Poster presentations in international scientific meetings (WP3)	3 - EPFL	Report	Public	54
D3.7	PhD Theses (WP3)	3 - EPFL	Report	Public	54

Description of deliverables

1) Scientific publications: poster or oral presentations in major International Scientific Meetings;
2) Scientific publications: papers in scientific journals;
3) 5 PhD theses.

D3.1 : Definition of the therapeutic potential of the endocannabinoid system in an ASD model [54]

Presentation of scientific data in peer-reviewed manuscript.

D3.2 : Identification of the role of the excitation/inhibition (E/I) imbalance in the cortico-thalamic system in the development of neuropsychiatric disorders [54]

Presentation of scientific data in peer-reviewed manuscript.

D3.3 : Identification of aberrant synaptic mRNA translation as a point of convergence for multiple genetic causes of ASD/ID [54]

Presentation of scientific data in peer-reviewed manuscript.

D3.4 : Establishment of the impact of the corticotropic releasing hormone system on schizophrenia- and ASD-related endophenotype [54]

Presentation of scientific data in peer-reviewed manuscript.

D3.5 : Identification of circuit deficits associated with ASD [54]

Presentation of scientific data in peer-reviewed manuscript.

D3.6 : Oral/ Poster presentations in international scientific meetings (WP3) [54]

Presentation of scientific data in: a) scientific meetings, as oral communications, b) scientific meetings, as poster presentations.

D3.7 : PhD Theses (WP3) [54]

Five PhD Theses.

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
MS12	PhD theses completed (13)	1 - CNC	54	ESRs will have completed their theses at M54.

Work package number [9]	WP4	Lead beneficiary [10]	4 - Imperial
Work package title	Training and Doctoral Programme plan		
Start month	1	End month	54

Objectives

•To implement the Syn2Psy secondments and the network-wide training activities, network schools, common courses and workshops in the fields of synapse biology and neuropsychiatric disorders;
•To provide all ESRs with a complete set of capabilities for their future careers, focusing on research/communication/ impact skills, as well as on bridging the science-business and/or the science-society gaps.

Description of work and role of partners

WP4 - Training and Doctoral Programme plan [Months: 1-54]
Imperial
WP4 synchronizes all training activities (local and network wide), including doctoral studies, short courses, workshops, network schools and secondments, and integrates the training activities into the career plan for each ESR. The training/ doctoral studies committee will oversee all training plans with the help of the project manager that will prepare reports for each meeting and measures to disseminate training opportunities. ICL will be responsible for this WP, which will also involve all other partners. The network training activities and personal career development plan are described in the following tasks.

Task 4.1 Local training/Doctoral courses and workshops. Syn2Psy fellows will have the opportunity to enrol in courses offered by the host laboratory PhD program, as well as to network with other fellows and researchers at their host and seconded institutions. The training/doctoral studies committee has a formal accountability role for overseeing the progress of training/doctoral courses and informs the supervisory board, the main responsible for guaranteeing the high-quality provided by the Syn2Psy network, as well as for detecting and solving any difficulty identified through the working plan. Curriculum and credit plan will also be decided in the kick-off meeting, and confirmed by the Management Board (MB). Final information will be available in the website of the project.

Task 4.2 Network schools and final conference. Syn2Psy will organise 4 wide-ranging Network Schools (please also see section 1.2) for the ESRs, which will also be open to a limited number of external researchers. Syn2Psy will organise advanced training aiming at transferable skills that ESRs will need in their future careers, such as science writing, outreach and dissemination initiatives, communication and public engagement efforts and impact. The plan intends to train ESRs to be skilled in creative, independent problem solving under time and resource constraints typical of a scientific and technical working environment in continuous contact with the academic and non-academic sectors.

Task 4.3 Secondments. All ESRs will undertake secondments in other beneficiary and/or partner organisation for a duration of up to 30% of the recruitment period (36 months) to expand their international, intersectoral and interdisciplinary research and training, and to assist them in building networks of working relationships to aid them in their future careers.

Task 4.4 Personal Career Development Plan. Each ESR will develop together with the supervisors her/his own scientific and training plan, with the end-goal of finding a job of her/his preference after the Syn2Psy contract.

Participation per Partner

Partner number and short name [10]
1 - CNC
2 - CNRS
3 - EPFL
4 - Imperial
5 - UEDIN

Partner number and short name [10]
6 - H. LUNDBECK AS

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D4.1	Final Conference	1 - CNC	Other	Public	54
D4.2	Report on network school 1 (NS1)	1 - CNC	Report	Public	8
D4.3	Report on network school 2 (NS2)	2 - CNRS	Report	Public	38
D4.4	Report on network school 3 (NS3)	6 - H. LUNDBECK AS	Report	Public	29
D4.5	Report on network school 4 (NS4)	2 - CNRS	Report	Public	38
D4.6	Career development plan of ESRs	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	12
D4.7	Secondment reports	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	54
D4.8	Report on PhD courses	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	18
D4.9	Supervisory board	1 - CNC	Other	Confidential, only for members of the consortium (including the Commission Services)	2

Description of deliverables

1) Organization and report on network schools performed;
2) Report on PhD courses;
3) Organization and report on the secondments performed;
4) Personal Career Development Plan;
5) Final conference;
6) PhD theses.

D4.1 : Final Conference [54]

Final project conference.

D4.2 : Report on network school 1 (NS1) [8]

Report will be produced after the network school 1, indicating the activities and summaries of the different lectures/ laboratory activities.

D4.3 : Report on network school 2 (NS2) [38]

Report will be produced after the network school 2, indicating the activities and summaries of the different lectures/ laboratory activities.

D4.4 : Report on network school 3 (NS3) [29]

Report will be produced after the network school 3, indicating the activities and summaries of the different lectures/ laboratory activities.

D4.5 : Report on network school 4 (NS4) [38]

Report will be produced after the network school 4, indicating the activities and summaries of the different lectures/ laboratory activities.

D4.6 : Career development plan of ESRs [12]

A document will be prepared containing the development plan for all ESRs, including the activities undertaken to help prepare the fellows for the post-programme life.

D4.7 : Secondment reports [54]

At month 42, one report will be produced containing a summary of all the ESR secondment activities, including brief description of obtained results and the current status of their progress towards a PhD degree.

D4.8 : Report on PhD courses [18]

Report on PhD courses taken by the ESRs in their host PhD programs.

D4.9 : Supervisory board [2]

The SB is composed of the PC (who will chair it), the PM, the representatives of the three Committees, and one ESR (chosen by the peers via the ESRs board). The SB has complete responsibility for guaranteeing that high quality research and training is provided by the network, and for detecting and solving any difficulties with the supervision and work progress of ESRs.The SB will communicate with all ESRs aiming at providing feedback on the supervision arrangements, the training activities and the secondments.

Schedule of relevant Milestones

Milestone number[18]	**Milestone title**	**Lead beneficiary**	**Due Date (in months)**	**Means of verification**
MS7	Syn2Psy intermediate meeting	1 - CNC	27	Written report of intermediate meeting will be produced.
MS9	Personal career development plan	1 - CNC	24	Written report concerning the ESRs personal career development plan will be produced.
MS12	PhD theses completed (13)	1 - CNC	54	ESRs will have completed their theses at M54.
MS13	Syn2Psy final meeting	1 - CNC	54	Syn2Psy final report.

Work package number [9]	WP5	Lead beneficiary [10]	2 - CNRS
Work package title	Dissemination & Communication and Exploitation (D&C)		
Start month	1	End month	54

Objectives

•To promote the project visibility by creating its own identity and dissemination strategy targeting different audiences and the general public;
•To design effective outreach initiatives for non-scientific audiences;
•To promote dialogue and knowledge exchange between relevant players (e.g., pharmaceutical industry, medical/patient community) to establish two-way communication actions;
•To implement the communication and public engagement strategy of the project;
•To disseminate the objectives, approaches and results of Syn2Psy in media;
•To ensure that outputs of the project succeed in the research community, open access science, and industry context.

Description of work and role of partners

WP5 - Dissemination & Communication and Exploitation (D&C) [Months: 1-54]
CNRS
As exposed in sections 2.3 and 2.4, Syn2Psy covers an ample DC&S strategy targeting different audiences: academy, pharmaceutical industry, clinical practice, patient associations and the general public. It will also have a key role in fostering information exchange and production of science contents to target audiences and general public. The creation of proper science contents to multiple audiences, beginning from young publics, is a major topic in this project. WP5, led by CNC, will involve actively all ESRs and Syn2Psy network, under the observation of the D&C committee. WP5 will have the help of a project manager, and the experience of PIN, as well as the science communication office at CNC for implementing and measuring the effectiveness of the activities.

Task 5.1 Public website [mo1-6] will be designed and implemented during the first months of the project, with content added as the work progresses (it will have persistent URLs; the primary language will be English, at least one presentation per year can be given in the national languages of the consortium). The website will provide information on the Syn2Psy network (including details of partners, objectives, work areas, etc.) and the work in progress (results, presentations, publications, technical notes, social media, public deliverables, etc.). The website content will be handled by the project manager with the support of the WP leaders and the D&C committee. The content will be updated at regular, periodic intervals; all ESRs will contribute on the production of contents. The Syn2Psy website will be one of the main channels for general public information dissemination generated within the project.

Task 5.2 Presentations, publications and reports [mo6-48]
During the project's lifetime, Syn2Psy network will discuss and present research results and other outcomes at major neuroscience events, such as the Society for Neuroscience and FENS meeting. Syn2Psy network will publish ESRs research in main neuroscience scientific journals such as Neuron, Nature Neuroscience, PNAS, eLife, and others. All ESRs and senior researchers and partners will contribute to the dissemination of the Syn2Psy outcomes at seminars and conferences (national and international). The supervisors and co-supervisors of ESRs are responsible for adopting main decisions regarding the presentations and publication content. The manager of the project is responsible for reporting the work progress and helping the supervisory board and the coordinator to select the public deliverables in the project website.

Task 5.3 Workshops and seminars [mo12-42]
Open seminars during the network schools will contribute to disseminate the outcomes of the project beyond the consortium.

Task 5.4 Two-way communication [mo6-42] along with increasing awareness by engagement with: i) relevant societal actors (e.g., hospitals, patient associations), ii) various audiences at in European and global campaigns to increase public awareness of the progress and benefits of brain research (e.g. Brain Awareness Week), but also other public health initiatives, and iii) multiple publics at local/national/European-wide public events dedicated to popular science and fun learning (e.g. European Researchers' Night, schools visits, conferences, meetings and group discussions.

Task 5.5 Communication articles shaped for younger audiences and targeting patient families

Articles on neuropsychiatric disorders will be produced by ESRs in collaboration with PIN. These articles will be translated to Portuguese in collaboration with the CNC Science Communication Office and with the participation of CNC investigators working in the field. These articles will be published at the PIN and Syn2Psy websites, as well as in the websites of other patient organisations (e.g. Phelan-McDermid syndrome Foundation).

Task 5.6 Script of a play on the activities of Syn2Psy
ESRs will write the script and perform a play, in the Syn2Psy final meeting, under the guidance of Marionet.

Participation per Partner

Partner number and short name [10]
1 - CNC
2 - CNRS
3 - EPFL
4 - Imperial
5 - UEDIN
6 - H. LUNDBECK AS

List of deliverables

Deliverable Number[14]	**Deliverable Title**	**Lead beneficiary**	**Type**[15]	**Dissemination level**[16]	**Due Date (in months)**[17]
D5.1	Syn2Psy public website	1 - CNC	Websites, patents filing, etc.	Public	6
D5.2	Report on outreach & public engagement	1 - CNC	Report	Public	54
D5.3	Public media dissemination	1 - CNC	Report	Public	4
D5.4	Theatre	1 - CNC	Other	Public	54
D5.5	Report on the potential for results exploitation	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	54

Description of deliverables

1) Syn2Psy website;
2) Scientific presentations (poster or oral) in major international scientific meetings;
3) Scientific publications in journals;
4) Report on the potential for results exploitation;
5) Progress on D&C and report;
6) Articles for the younger audiences and the patient associations;
7) Theatre.

D5.1 : Syn2Psy public website [6]

A public website will be prepared, open to the general public and demonstrating the general activities of the consortium, plus scientific data originating from the programme, biographies from the involved reserachers, important links, etc.

D5.2 : Report on outreach & public engagement [54]

A final outreach report, containing a description of all outreach initiatives, with feedback from the public, appropriate metrics, photos (and adicional videos) will be prepared by month 48.

D5.3 : Public media dissemination [4]

We expect that several deliverables will be produced based on press reports focusing on particular aspects of the Syn2Psy research programme. We expect that media outlets will pick up the press releases and perform media articles, including interviews with involved scientists and ESRs.

D5.4 : Theatre [54]

Theatre play written and interpreted by the ESRs in collaboration with the Marionet theatre company.

D5.5 : Report on the potential for results exploitation [54]

The report will detail the potetial of all results for exploitation.

Schedule of relevant Milestones

Milestone number[18]	**Milestone title**	**Lead beneficiary**	**Due Date (in months)**	**Means of verification**
MS2	Syn2Psy internal website	1 - CNC	3	Website available for the consortium members with updates on documentation, progress on ESR projects and important information for the different partners. Access will be limited.
MS6	Public website	1 - CNC	12	Operational public website by M12.
MS10	Public media dissemination	1 - CNC	54	Press releases, reports will be produced during the duration of the project.
MS11	Provisional patents established	1 - CNC	54	Provisional patent certification.
MS13	Syn2Psy final meeting	1 - CNC	54	Syn2Psy final report.

Work package number [9]	WP6	**Lead beneficiary** [10]	1 - CNC
Work package title	Management		
Start month	1	**End month**	54

Objectives

•Ensure an efficient operational, administrative and financial management of the project so as to meet the proposed objectives with well-established European Commission (EC) rules;
•Provide ESRs with comprehensive experience in delivering a full project lifecycle and working alongside the host institutions management officers and Syn2Psy project manager;
•Establish the internal communication channels between partners and set up the local and network-wide events, including secondments, with maximal, optimized interaction between ESRs and all partners;
•Progress monitoring and evaluation, quality control, corrective actions, formal and financial communication with / reporting to the EC.

Description of work and role of partners

WP6 - Management [Months: 1-54]
CNC
Task 6.1 Overall project management and reporting [mo1-48]
All partners are experienced in participating in EC Framework Programmes, having a proactive role to meet the ETN's objectives and timely produce the deliverables and information. An appropriate governance and management structure will be implemented to ensure a seamless and efficient management of the project implementation, and internal rules clearly established so that each partner is aware of its role and responsibilities (please see section 3.2). A project manager, based at CNC, will handle administrative, financial and legal management. The project manager will provide direct assistance to the project coordinator, oversee the ESRs recruitment process, the logistical preparation of the network training courses, and the production of technical and financial reports.

Task 6.2 Project meetings and internal communication [mo1-48]
The primary source of internal communication will be email and the blackboard hosted on the website. All partners agree on the relevance of regular internal communication. Communication within the network will mainly occur by using dedicated mailing lists, which will be created at all levels: consortium, WPs, administration, and training. Literature, lectures, results and sharing data will all be managed through the Syn2Psy website and mailing list. The internal area of the web will also be used to assist ESR research progress and evaluation. Face-to-face project meetings (starting with the kick-off meeting) include network schools, courses and conferences. The kick-off meeting will take place in Coimbra, in month 6, and will allow the consortium to elect the three committees: training/doctoral studies committee, D&C committee, research coordination committee, and the supervisory board that will integrate all supervisors and co-supervisors (academic and non-academic).

Task 6.3 Recruitment of researchers [mo1-6]
Fourteen ESRs will be enrolled on fixed term contracts at month 6. The recruitment procedure will start after signing of the Grant Agreement, following the good practice procedures in the European Code of Conduct for the Recruitment of Researchers (please also see section 3.2). ESRs vacancies will be advertised in an efficient, transparent, supportive and internationally comparable manner using EU portals like EURAXESS or ERACAREERS, Syn2Psy website, Marie Skłodowska-Curie website and host institutions websites. The information of the open call will also be sent electronically to international scientific journals in the field of synaptic biology and neuropsychiatric disorders, high-visibility scientific journals, and an extensive list of universities and research organisations. The coordinator and the project manager will oversee the recruitment to ensure transparency, good practice, and good balance of skills, nationalities and gender. The supervisors and co-supervisors (assisted by the project manager) will be strongly involved in the recruitment and selection process. In the first three to four months from the beginning of the contact, ESRs must design, with their main supervisors and co-supervisors, the PCDP and submit it to the management board. The ESRs should also appoint their representatives in the supervisory board. The supervisory board is responsible for approving career development plans within two months (month 12 of the project), the same holds for updates thereafter.

Task 6.4 Project monitoring and quality control [mo1-48] is devoted to guarantee that the project is kept on track and on schedule. A quality control process in terms of revision of the project outputs will be implemented, within which all deliverables will be primarily revised by the coordinator, helped by the project manager.

Participation per Partner

Partner number and short name [10]
1 - CNC
2 - CNRS
3 - EPFL
4 - Imperial
5 - UEDIN
6 - H. LUNDBECK AS

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D6.1	Report on the Kick-off meeting	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	8
D6.2	Syn2Psy internal website	1 - CNC	Websites, patents filing, etc.	Confidential, only for members of the consortium (including the Commission Services)	3
D6.3	Annual progress report 1	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	12
D6.4	Report for the intermediate Syn2Psy meeting	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	29
D6.5	Annual progress report 2	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	24
D6.6	Annual progress report 3	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	36

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D6.7	Final technical and financial project report	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	54
D6.8	Consortium agreement	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	2
D6.9	Data Management Plan	1 - CNC	ORDP: Open Research Data Pilot	Confidential, only for members of the consortium (including the Commission Services)	6
D6.10	Potential input for Policy feedback	1 - CNC	Report	Confidential, only for members of the consortium (including the Commission Services)	54

Description of deliverables

1) Organization and report of the kick-off meeting;
2) Recruitment ESRs report;
3) Syn2Psy internal website;
4) Annual progress report;
5) Organization and report on the secondments performed;
6) Final technical and financial project report.

D6.1 : Report on the Kick-off meeting [8]

A report will be prepared folllowing the Consortium Kick-off meeting (month 6), including consortium agreements and definition of extra rules for the programme, as well as definition of SB, MB, ESR Board and EAB.

D6.2 : Syn2Psy internal website [3]

Website available for the consortium members with updates on documentation, progress on ESR projects and important information for the different partners. Access will be limited.

D6.3 : Annual progress report 1 [12]

Progress report for M1-M12.

D6.4 : Report for the intermediate Syn2Psy meeting [29]

Report for the intermediate consortium meeting.

D6.5 : Annual progress report 2 [24]

Progress report from M13-M24.

D6.6 : Annual progress report 3 [36]

Progress Report from M25-M36.

D6.7 : Final technical and financial project report [54]

The final report must include the following: (a) a ‘final technical report’ with a summary for publication containing: (i) an overview of the results and their exploitation and dissemination; (ii) the conclusions on the action, and (iii) the socio-economic impact of the action; (b) a ‘final financial report’.

D6.8 : Consortium agreement [2]

The consortium agreement will describe internal arrangements regarding coordination to ensure that the action is implemented properly. It will cover: 1) internal organization of the consortium; 2) management of access to the electronic exchange system; 3) distribution of EU funding; 4) additional rules on rights and obligations related to background and results - IPR.

D6.9 : Data Management Plan [6]

The strategy set in the data management plan will follow the Open Access to Research Data in Horizon 2020. At the kick-off meeting, the Supervisory Board will define a strategy to prevent, monitor and counteract scientific misconduct, guided by the ERC Scientific Misconduct Strategy.

D6.10 : Potential input for Policy feedback [54]

This report will address the following aspects: 1) Contribution to doctoral/ESR training at EU level and to strengthening EU innovation capacity; 2) Contribution to structuring doctoral/early-stage research training at the European level; 3) Meaningful contribution of the non-academic sector to the doctoral/research training; 4) Strengthening European innovation capacity.

Schedule of relevant Milestones

Milestone number[18]	**Milestone title**	**Lead beneficiary**	**Due Date (in months)**	**Means of verification**
MS1	Kick-off meeting	1 - CNC	6	Consortium Kick-off meeting will include: 1) all members of the consortium will provide a list of specialized courses currently occurring in the partner’s institutions. The supervisors and co-supervisors, together with the respective ESR(s), will identify useful courses; 2) We will discuss the initial research training activities, such as PhD doctoral programmes, network schools, conferences, the D&C strategy, and the overall training and management plan. 3) A Data Management Plan for making Syn2Psy data accessible, interoperable and reusable will be devised. 4) The logistics associated to the ESR recruitment plan and the Syn2Psy commitment responsibilities concerning the network-wide training events and conferences will be discussed. 5) PIN will be associated with Syn2Psy since the kick-off meeting, and provide guidance on how

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification
				to dialogue with clinicians, the general public and with patients and patients' families 6) Marionet will participate in the kick-off meeting of Syn2Psy, with the objective of guiding the ESRs in writing the script for a play on Syn2Psy and its contributions 6) Definition of extra rules for the programme, as well as definition of SB, MB, ExtB.
MS2	Syn2Psy internal website	1 - CNC	3	Website available for the consortium members with updates on documentation, progress on ESR projects and important information for the different partners. Access will be limited.
MS3	Accomplished ESR recruitment	1 - CNC	12	All ESRs will be recruited by M12. Report indicating all the selected ESR candidates and the criteria for choice will be produced.
MS4	Designing research/outreach plan	1 - CNC	9	Full research plan for ESRs, including predicted secondments.
MS5	Annual progress report 1	1 - CNC	12	Written report.
MS7	Syn2Psy intermediate meeting	1 - CNC	27	Written report of intermediate meeting will be produced.
MS8	Project check	1 - CNC	27	Written report will be produced.
MS9	Personal career development plan	1 - CNC	24	Written report concerning the ESRs personal career development plan will be produced.
MS13	Syn2Psy final meeting	1 - CNC	54	Syn2Psy final report.

Work package number [9]	WP7	Lead beneficiary [10]	1 - CNC
Work package title	Ethics requirements		
Start month	1	End month	54

Objectives

The objective is to ensure compliance with the 'ethics requirements' set out in this work package.

Description of work and role of partners

WP7 - Ethics requirements [Months: 1-54]
CNC
This work package sets out the 'ethics requirements' that the project must comply with.

List of deliverables

Deliverable Number[14]	Deliverable Title	Lead beneficiary	Type[15]	Dissemination level[16]	Due Date (in months)[17]
D7.1	H - Requirement No. 1	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.2	HCT - Requirement No. 2	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.3	POPD - Requirement No. 3	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.4	A - Requirement No. 4	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.5	EPQ - Requirement No. 5	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12
D7.6	GEN - Requirement No. 6	1 - CNC	Ethics	Confidential, only for members of the consortium (including the Commission Services)	12

Description of deliverables

The 'ethics requirements' that the project must comply with are included as deliverables in this work package.

D7.1 : H - Requirement No. 1 [12]

1. Details on the procedures and criteria that will be used to identify/recruit research participants must be submitted as a deliverable to the REA before the commencement of the relevant work. 2. Detailed information on the informed consent procedures that will be implemented for the participation of humans must be submitted as a deliverable to the REA before the commencement of the relevant work. 3. English translations/summaries of the ethics approvals for the research with humans must be submitted as a deliverable to the REA before the commencement of the relevant work. 4. English translations of the informed consent forms and information sheet must be submitted as a deliverable to the REA before the commencement of the relevant work. 5. The applicant must clarify how consent/assent will be ensured in case of children and/or adults unable to give informed consent before the commencement of the relevant work. 6. Details on incidental findings policy must be provided to the REA before the commencement of the relevant work.

D7.2 : HCT - Requirement No. 2 [12]

1. For human cells/tissues obtained within another project, details on cells/tissues type and authorisation by primary owner of data must be submitted as a deliverable to the REA prior to the commencement of the relevant work. 2. For human cells/tissues obtained om a biobank, details on cells/tissues type as well as details on the biobank and access to it must be obtained and kept on file before the relevant work commences, and submitted upon request to the REA. 3. For human cells/tissues available commercially, details on cells/tissues type and provider must be obtained and kept on file before the relevant work commences and submitted upon request to the REA.

D7.3 : POPD - Requirement No. 3 [12]

1. The applicant must check if special derogations pertaining to the rights of data subjects or the processing of genetic, biometric and/or health data have been established under the national legislation of the country where the research takes place and submit a declaration of compliance with respective national legal framework(s) as a deliverable to the REA before the relevant work commences. 2. A description of the technical and organisational measures that will be implemented to safeguard the rights and freedoms of the data subjects/research participants must be submitted to the REA before the relevant work commences. 3. For further processing of previously collected personal data, an explicit confirmation that the applicant has lawful basis for the data processing and that the appropriate technical and organisational measures are in place to safeguard the rights of the data subjects must be submitted before the relevant work commences.

D7.4 : A - Requirement No. 4 [12]

1. The applicant must obtain the relevant authorisations (for breeders, suppliers, users, and facilities) for animal experiments. These must be kept on file and submitted to the REA upon request. 2. Copy of project specific authorisation (covering also the work with genetically-modified animals) with English translation summary must be submitted as a deliverable to the REA before the commencement of the relevant work. 3. If applicable, copies of training certificates/personal licenses of the staff involved in animal experiments must be kept on file and submitted upon request.

D7.5 : EPQ - Requirement No. 5 [12]

1. The applicant must confirm that facilities authorizations have been obtained (e.g. security classification of laboratory, GMO authorization), and are kept on file. 2. The applicant must ensure that appropriate health and safety procedures conforming to relevant local/national guidelines/legislation are followed for staff involved in this project before the work commences.

D7.6 : GEN - Requirement No. 6 [12]

An independent External Ethics Advisor must be appointed to monitor ethics issues associated with the project, especially the research involving children and persons unable to give informed consent. Ethics Reports must be submitted to the REA together with the Periodic Reports.

Schedule of relevant Milestones

Milestone number[18]	Milestone title	Lead beneficiary	Due Date (in months)	Means of verification

1.3.4. WT4 List of milestones

Milestone number[18]	Milestone title	WP number[9]	Lead beneficiary	Due Date (in months)[17]	Means of verification
MS1	Kick-off meeting	WP6	1 - CNC	6	Consortium Kick-off meeting will include: 1) all members of the consortium will provide a list of specialized courses currently occurring in the partner's institutions. The supervisors and co-supervisors, together with the respective ESR(s), will identify useful courses; 2) We will discuss the initial research training activities, such as PhD doctoral programmes, network schools, conferences, the D&C strategy, and the overall training and management plan. 3) A Data Management Plan for making Syn2Psy data accessible, interoperable and reusable will be devised. 4) The logistics associated to the ESR recruitment plan and the Syn2Psy commitment responsibilities concerning the network-wide training events and conferences will be discussed. 5) PIN will be associated with Syn2Psy since the kick-off meeting, and provide guidance on how to dialogue with clinicians, the general public and with patients and patients' families 6) Marionet will participate in the kick-off meeting of Syn2Psy, with the objective of guiding the ESRs in writing the script for a play on Syn2Psy and its contributions 6) Definition of extra rules for the programme, as well as definition of SB, MB, ExtB.
MS2	Syn2Psy internal website	WP5, WP6	1 - CNC	3	Website available for the consortium members with updates on documentation, progress on ESR projects and important information for the different partners. Access will be limited.

Milestone number[18]	Milestone title	WP number[9]	Lead beneficiary	Due Date (in months)[17]	Means of verification
MS3	Accomplished ESR recruitment	WP6	1 - CNC	12	All ESRs will be recruited by M12. Report indicating all the selected ESR candidates and the criteria for choice will be produced.
MS4	Designing research/ outreach plan	WP6	1 - CNC	9	Full research plan for ESRs, including predicted secondments.
MS5	Annual progress report 1	WP6	1 - CNC	12	Written report.
MS6	Public website	WP5	1 - CNC	12	Operational public website by M12.
MS7	Syn2Psy intermediate meeting	WP4, WP6	1 - CNC	27	Written report of intermediate meeting will be produced.
MS8	Project check	WP6	1 - CNC	27	Written report will be produced.
MS9	Personal career development plan	WP4, WP6	1 - CNC	24	Written report concerning the ESRs personal career development plan will be produced.
MS10	Public media dissemination	WP5	1 - CNC	54	Press releases, reports will be produced during the duration of the project.
MS11	Provisional patents established	WP5	1 - CNC	54	Provisional patent certification.
MS12	PhD theses completed (13)	WP1, WP2, WP3, WP4	1 - CNC	54	ESRs will have completed their theses at M54.
MS13	Syn2Psy final meeting	WP4, WP5, WP6	1 - CNC	54	Syn2Psy final report.

1.3.5. WT5 Critical Implementation risks and mitigation actions

Risk number	Description of risk	WP Number	Proposed risk-mitigation measures
1	Risk associated to Recruitment (not all ESRs recruited in the first year). Likelihood: medium; Impact: high.	WP6	We anticipate that 6 months provide sufficient time for recruitment. If any delay occurs, we will focus on additional supervision and resources on the specific project. As a last alternative, shorter sub-projects can be defined.
2	No acceptance of ESR on Doctoral Programme from host institution. Likelihood: very low; Impact: high.	WP6	Our experience is that ESRs recruited through similar EU based network programmes are accepted in local doctoral programmes. If any ESR is not admitted, we plan training within the network partners to assure completion of ECTS credits for the PhD graduation.
3	Supplementary funding demand for more demanding projects. Likelihood: medium; Impact: high.	WP1, WP2, WP3, WP4	Network management will advise on applying to supplementary funding sources (WP6).
4	ESR fails in his/her tasks and there is no proper progress in the project. Likelihood: medium; Impact: high.	WP1, WP2, WP3, WP4	Regular meetings will attempt the adjustment(s) in the ESR projects. If any difficulty occurs, there will be a contingency plan at research/training. Failure of mediation may cease the ESR contract. The SB/MB will decide whether the ESR should be replaced.
5	(Co)Supervisors do not agree on ESR research project direction. Likelihood: low; Impact: high.	WP1, WP2, WP3, WP4	SB/MB will mediate agreement between supervisors. If mediation fails, exchange of institutions supervising the researcher may occur.
6	Predicted secondments are not enough. Likelihood: medium; Impact: low.	WP1, WP2, WP3, WP4	Supervisor and co-supervisor(s) can select institutions outside the network for any necessary extra training to provide the work required (this will be mediated by the MB).
7	Some deliverables or milestones not achieved in due time. Likelihood: low; Impact: high.	WP1, WP2, WP3, WP4, WP5, WP6	Syn2Psy deliverable and milestones are planned in a realistic way. The project manager hired by the network is responsible for monitoring the progress of the project and report it to supervisory board and project coordinator. The three Committees and the external advisory board will regularly review the research/training progress and suggest alternatives if needed.
8	IP protection issues associated to PhD theses and publications. Likelihood: medium; Impact: high.	WP6	The measures include: a) Embargo period to PhD publication in open access databases; b) Limited protected information in the PhD thesis; and c) Non-disclosure agreements signed by attendees. In terms of presentations in meetings or research publications, the supervisors will confer IP before each information submission.

1.3.6. WT6 Summary of project effort contribution

	WP1	WP2	WP3	WP4	WP5	WP6	WP7
1 - CNC	✓	✓	✓	✓	✓	✓	✓
2 - CNRS	✓	✓	✓	✓	✓	✓	
3 - EPFL	✓		✓	✓	✓	✓	
4 - Imperial	✓	✓	✓	✓	✓	✓	
5 - UEDIN	✓		✓	✓	✓	✓	
6 - H. LUNDBECK AS	✓	✓	✓	✓	✓	✓	

1.3.7. WT7 Tentative schedule of project reviews

No project reviews indicated

1. Project number

The project number has been assigned by the Commission as the unique identifier for your project. It cannot be changed. The project number **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

2. Project acronym

Use the project acronym as given in the submitted proposal. It can generally not be changed. The same acronym **should appear on each page of the grant agreement preparation documents (part A and part B)** to prevent errors during its handling.

3. Project title

Use the title (preferably no longer than 200 characters) as indicated in the submitted proposal. Minor corrections are possible if agreed during the preparation of the grant agreement.

4. Starting date

Unless a specific (fixed) starting date is duly justified and agreed upon during the preparation of the Grant Agreement, the project will start on the first day of the month following the entry into force of the Grant Agreement (NB : entry into force = signature by the Agency). Please note that if a fixed starting date is used, you will be required to provide a written justification.

5. Duration

Insert the duration of the project in full months.

6. Call (part) identifier

The Call (part) identifier is the reference number given in the call or part of the call you were addressing, as indicated in the publication of the call in the Official Journal of the European Union. You have to use the identifier given by the Commission in the letter inviting to prepare the grant agreement.

7. Abstract

8. Project Entry Month

The month at which the participant joined the consortium, month 1 marking the start date of the project, and all other start dates being relative to this start date.

9. Work Package number

Work package number: WP1, WP2, WP3, ..., WPn

10. Lead beneficiary

This must be one of the beneficiaries in the grant (not a third party) - Number of the beneficiary leading the work in this work package

11. Person-months per work package

The total number of person-months allocated to each work package.

12. Start month

Relative start date for the work in the specific work packages, month 1 marking the start date of the project, and all other start dates being relative to this start date.

13. End month

Relative end date, month 1 marking the start date of the project, and all end dates being relative to this start date.

14. Deliverable number

Deliverable numbers: D1 - Dn

15. Type

Please indicate the type of the deliverable using one of the following codes:

R	Document, report
DEM	Demonstrator, pilot, prototype
DEC	Websites, patent fillings, videos, etc.
OTHER	
ETHICS	Ethics requirement
ORDP	Open Research Data Pilot
DATA	data sets, microdata, etc.

16. Dissemination level

Please indicate the dissemination level using one of the following codes:

PU	Public
CO	Confidential, only for members of the consortium (including the Commission Services)
EU-RES	Classified Information: RESTREINT UE (Commission Decision 2005/444/EC)
EU-CON	Classified Information: CONFIDENTIEL UE (Commission Decision 2005/444/EC)
EU-SEC	Classified Information: SECRET UE (Commission Decision 2005/444/EC)

17. Delivery date for Deliverable

Month in which the deliverables will be available, month 1 marking the start date of the project, and all delivery dates being relative to this start date.

18. Milestone number

Milestone number:MS1, MS2, ..., MSn

19. Review number

Review number: RV1, RV2, ..., RVn

20. Installation Number

Number progressively the installations of a same infrastructure. An installation is a part of an infrastructure that could be used independently from the rest.

21. Installation country

Code of the country where the installation is located or IO if the access provider (the beneficiary or linked third party) is an international organization, an ERIC or a similar legal entity.

22. Type of access

TA-uc	if trans-national access with access costs declared on the basis of unit cost,
TA-ac	if trans-national access with access costs declared as actual costs, and
TA-cb	if trans-national access with access costs declared as a combination of actual costs and costs on the basis of unit cost,
VA-uc	if virtual access with access costs declared on the basis of unit cost,
VA-ac	if virtual access with access costs declared as actual costs, and
VA-cb	if virtual access with access costs declared as a combination of actual costs and costs on the basis of unit cost.

23. Access costs

Cost of the access provided under the project. For virtual access fill only the second column. For trans-national access fill one of the two columns or both according to the way access costs are declared. Trans-national access costs on the basis of unit cost will result from the unit cost by the quantity of access to be provided.



Marie Skłodowska-Curie Actions (MSCA)
Innovative Training Networks (ITN)
H2020-MSCA-ITN-2018

Syn2Psy - 813986

Annex 1 to the Grant Agreement
(Description of the Action)
Part B

HISTORY OF CHANGES

Page-section	Nature of change
Part A	
5/38-1.3.1	End month of all work packages was modified to month 54
6/38-1.3.2	Deliverables 1.1 to 1.5 due date was modified to month 54
6/38-1.3.2	Deliverable 2.1 was removed
6-7/38-1.3.2	Deliverables 2.2 to 2.8 due date was modified to month 54
7-8/38-1.3.2	Deliverables 3.1 to 3.7, 4.1, 4.7, 5.2, 5.4 and 5.5 due date was modified to month 54
8/38-1.3.2	Deliverables 4.3 and 4.5 due date was modified to month 38
9-10/38-1.3.2	Deliverables 6.7 and 6.10 due date was modified to month 54
11/38-WP1	End month of WP1 was modified to 54
12/38-WP1	Deliverables 1.1 to 1.5 due date was modified to month 54
13/38-WP1	Under "Schedule of relevant Milestones" the number of PhD theses completed on M12 was modified to 13 and the due date to month 54
14/38-WP2	End month of WP2 was modified to 54
14/38-WP2	On task 2.1 the two last sentences were eliminated since this project will end at month 43 and these collaborations will not be developed.
15/38-WP2	Deliverable 2.1 was removed
16/38-WP2	Deliverables 2.2 to 2.8 due date was modified to month 54
16/38-WP2	Under "Description of deliverables", "3) 6 PhD theses" was modified to "3) 5 PhD theses"
17/38-WP2	Under "Description of deliverables", D2.8 was modified from "Six PhD Theses" to "Five PhD Theses"
17/38-WP2	Under "Schedule of relevant Milestones" the number of PhD theses completed on M12 was modified to 13 and the due date to month 54
18/38-WP3	End month of WP3 was modified to 54
18/38-WP3	Under "Objectives" the following objective was added "•Testing gene therapy for Fragile X Syndrome."
19/38-WP3	Task 3.6 was added to include the task of the new project, under the supervision of Prof. Emily Osterweil at UEDIN.
19-20/38-WP3	Deliverables 3.1 to 3.7 due date was modified to month 54
20/38-WP3	Under "Schedule of relevant Milestones" the number of PhD theses completed on M12 was modified to 13 and the due date to month 54
21/38-WP4	End month of WP4 was modified to 54
22/38-WP4	Deliverables 4.1, 4.7 due date was modified to month 54 and deliverables 4.3 and 4.5 to month 38
23/38-WP4	Under "Schedule of relevant Milestones" the number of PhD theses completed on M12 was modified to 13 and the due date to month 54; The Syn2Psy final meeting due date was modified to month 54
24/38-WP5	End month of WP5 was modified to 54
25/38-WP5	Deliverables 5.2, 5.4 and 5.5 due date was modified to month 54
26/38-WP5	Under "Schedule of relevant Milestones" M10, M11 and M13 due date was modified to month 54
27/38-WP6	End month of WP6 was modified to 54
28-29/38-WP6	Deliverables 6.7 and 6.10 due date was modified to month 54
31/38-WP6	Under "Schedule of relevant Milestones" M10, M11 and M13 due date was modified to month 54
32/38-WP7	End month of WP7 was modified to 54
35/38-1.3.4	Milestones" M10, M11, M12 and M13 due date was modified to month 54; the number of PhD theses completed on M12 was modified to 13
Part B	
10-Table 1.1	End month of all WPs was modified to 54 and ESR15 was added to the list of ESRs
11-Table 1.2a	ESR4 secondary supervisor was modified to UEDIN, removing CNC and the duration was modified to 27.6; ESR15 project at UEDIN, starting at month 44 and with a duration of 7.6

	months was included in the table. The duration of ESR4/ESR15 was included in the text below, indicating that these projects do not have a 36 months duration.
14-Table 1.2c	Final meeting month was modified to month 54
18-Syn2Psy chart	ESR4 Secondment 1 was modified from CNC to UEDIN and ESR15 was added to the table
25-Table 3.1d	ESR4 project's duration was modified to 27.6 and the secondment at CNC was replaced by the secondment at UEDIN: Testing gene therapy for Fragile X Sindrome
33-Table 3.1d	ESR15 Individual research project was included with a description of the project objectives and tasks, under the supervision of Prof. Emily Osterweil at UEDIN, starting at month 44, with a duration of 7.6 months and with no enrolment in PhD
37-Gantt chart	The Gant chart was modified to reflect the extension of all projects and WPs to 54 months, as well as deliverables and milestones due date modified to month 54

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2. Impact
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2.2 Contribution to structuring doctoral / early-stage research training at the European level and to strengthening European innovation capacity, including the potential for:
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- Commitment of beneficiaries and partner organisations to the programme

4. GANTT Chart
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5.3 Ethics approval

LIST OF PARTICIPANTS

Consortium Member	Legal Entity Short Name	Academic	Non-academic	Awards PhD	Country	Depart. Division Lab.	Scientist-in-Charge	Role of Partner
Beneficiaries								
Centro de Neurociências e Biologia Celular	CNC	✓		✓	Portugal	CNC	Ana Luísa Carvalho	
Interdisciplinary Institute for Neuroscience - Centre National de la Recherche Scientifique	CNRS	✓		✓	France	IINS-CNRS	Daniel Choquet	
Ecole Polytechnique Federale de Lausanne - Brain and Mind Institute	EPFL	✓		✓	Switzerland	BMI-EPFL	Carmen Sandi	
Center for Integrative Physiology – University of Edinburgh	UEDIN	✓		✓	Scotland	CIP-UEDIN	Peter Kind, Emily Osterweil	
Imperial College London	ICL	✓		✓	United Kingdom	ICL	Vincenzo De Paola, Thomas Knöpfel	
Institut de Biologie Paris-Seine - Centre National de la Recherche Scientifique	CNRS	✓		✓	France	IBPS-CNRS	Catalina Betancur	
Lundbeck	Lundbeck		✓		Denmark	Lundbeck	Niels Plath	
Partner Organisations								
Carl Zeiss Microscopy GmbH	ZEISS		✓		Germany		Monika Marx	Training
Eurotrials – scientific consultants (part of CTI - Clinical Trial and Consulting Services, USA)	Eurotrials				Portugal		Ana Patacão	Secondments Training
Coimbra University Hospital	CHUC		✓		Portugal	Neurodev. Unit, Paediatric Hospital	Guiomar Oliveira	Secondments Training
Portuguese Institution for Children Development	PIN		✓		Portugal		Nuno Lobo Antunes	Training
Marionet	Marionet		✓		Portugal		Mário Montenegro	Training

DATA FOR NON-ACADEMIC BENEFICIARIES

Name	Location of research premises	Type of R&D activities	No. of full-time employees	No. of employees in R&D	Web site	Annual turnover (€)	Enterprise status	SME status
Lundbeck	Valby/ Denmark	*In vitro* and *in vivo* approaches to psychiatric and neurological disorders	App. 5000	App 1200	www.lundbeck.com/global	1.96 billion Euro (2015)	Yes	No

DECLARATIONS

Name (Institution / Individual)	Nature of inter-relationship
None	No inter-relationships to be disclosed.

1. Excellence

1.1 Quality, innovative aspects and credibility of the research programme

- **Introduction, objectives and overview of the research programme.** Neuropsychiatric disorders represent one of the greatest medical and societal challenges of the twenty first century, being the leading cause of years lived with disability worldwide [1]. Major health policy decisions have historically been guided by disease-associated mortality, but mental disorders, associated with low mortality but high morbidity, account for a large proportion of the world's disease burden, aggravated by the fact that few effective treatments for core symptoms are available. Advances in effective prevention and treatment of neuropsychiatric disorders are urgent, but have been hampered by high clinical heterogeneity between affected individuals, and the limited understanding of disease aetiology and pathogenesis. However, recent collaborative efforts have led to an expansion in the discovery of susceptibility genes associated with mental disorders [2], and have revealed coherent biological pathways implicated in their pathogenesis, namely pathways that regulate synapse development and plasticity [3,4,5]. Causal genetic variants of genes encoding synaptic proteins, with varying effect sizes ranging from rare variants of moderate to large effect to common variants with small effect, have been associated with neuropsychiatric disorders, prompting the next step: to unravel the biological impact of these variants, and their contribution to disease phenotype at the molecular, cellular, circuits and behavioural levels. This approach is bound to inform **better therapeutic strategies**, configures a **new mindset for the research community devoted to the investigation of neuropsychiatric disorders**, and urges the **creation of innovative advanced training programmes** to adequately prepare the next generation of researchers in the field.

The ETN *Synaptic Dysfunction in Neuropsychiatric Disorders* (**Syn2Psy**) addresses this challenge by **providing PhD-level training for 14 early stage researchers (ESRs) to integrate molecules, synapses, neurons, circuits and behaviour, to understand and treat neuropsychiatric disorders**. Syn2Psy scientific aims are to: 1) Identify synaptic mechanisms that are dysfunctional in neuropsychiatric disorders; 2) Generate and characterize human cell-derived and animal models of disease that will inform on neuronal pathways that are disrupted and may be targets for therapies; 3) Test rational therapies, and understand how life stress impacts on disease pathways. **Syn2Psy leverages on a multidisciplinary research team**, from **6 top-level Research Institutions and Universities**, **involving scientists with a comprehensive know-how in the field of neuroscience**, ranging from molecular and cellular studies to neurophysiology, neuronal circuits, neural dynamics and behaviour, **complemented by leading 6 non-academic organisations,** the industrial partners **Lundbeck, ZEISS** and **Eurotrials**, the **Coimbra University Hospital (CHUC)**, the **Portuguese Institution for Child Development (PIN)** and the **theatre company Marionet**. The combination of interdisciplinary and intersectoral expertise is particularly suited for addressing synapse pathology in neuropsychiatric disorders, and creating competitive training to answer a critical societal challenge.

- **Research methodology and approach.** Neuropsychiatric disorders, traditionally diagnosed on the basis of clusters of symptoms, are now considered syndromes of neural and behavioural systems. There is the need to establish new research that can improve our understanding of the biological underpinning of the abnormal neural processes associated with these disorders. Biological research will help define subgroups of patients based on imaging, neurophysiological or genomic characteristics, rather than an absolute reliance on clinical symptoms (Fig. 1), and will also transform treatment by focusing on specific neural pathology. This new approach of a stratified medicine for mental disorders will move the field forward [7], provided that biological characterization of neural pathology associated with disease is advanced. This is precisely the contribution that Syn2Psy aims to make. Recent studies show that many neuropsychiatric disorders are characterized by synaptic pathology, including altered synapse morphology and density, and aberrant synapse signalling and synaptic plasticity [3,4,8-12] (Fig. 2).

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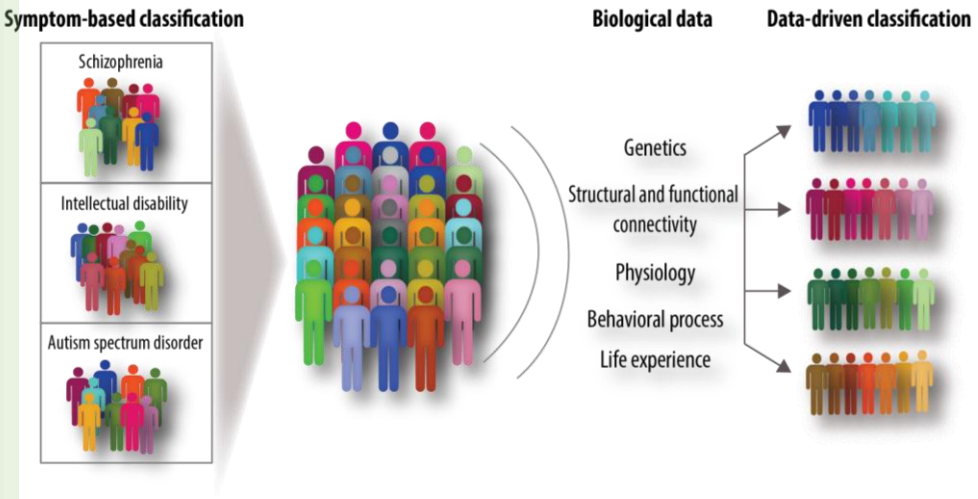


Fig. 1. Towards stratified medicine for neuropsychiatric disorders. The uncovering of the etiological mechanisms underlying mental disorders, and the identification of the abnormal biological processes implicated, allow evolving from diagnosing heterogeneous traditional symptom-based categories to a stratification of patients based in more homogenous clusters of biological defects. This shift in how neuropsychiatric disorders are approached will result in an increase in diagnostic precision and in more targeted treatments. (Figure adapted from [6]).

Neuroimaging studies have provided ample evidence of structural and functional connectivity alterations in the brain of neuropsychiatric patients, supporting the notion that these disorders arise from abnormal connectivity between neuronal systems [13]. The convergence of the genetic and phenotypic evidence to common pathways paves the way to meaningful functional studies aimed at understanding disease mechanisms in cellular and animal model systems. The time is now ripe to integrate studies across different levels that can lead to the identification of signatures of illness for specific risk pathways, provide a means for psychiatric patient stratification, optimizing current therapies, and development of novel approaches.

The clinical manifestations of neuropsychiatric disorders, which range from altered social interaction, impaired executive function, abnormal perceptual processes and diminished intellectual ability, are likely to derive from alterations in synapse function and in neural wiring. The present challenge is to **combine the identification of defects in synaptic proteins associated to disease with understanding the synaptic and circuit mechanisms responsible for their pathophysiology**. Integrating human sequencing data with a detailed characterization of the impact that newly discovered mutations in genes encoding synaptic proteins pose to neuronal development, plasticity and structural and functional brain connectivity is a promising strategy to build informed specific hypotheses for the development of novel therapies for these devastating disorders.

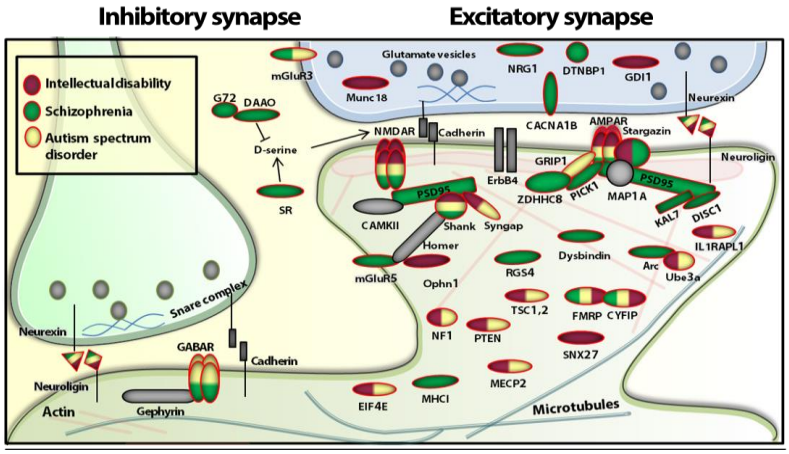


Fig. 2. Synaptic proteins implicated in neuropsychiatric disorders. The panel shows an excitatory synapse on a spine, and an inhibitory synapse along the dendritic shaft, and presents an overview of human genes implicated in intellectual disability (ID), autism spectrum disorders (ASD) and schizophrenia (SCZ) with associated protein localization at synapses. Proteins are color-coded based on their genetic association with ID (*red*), ASD (*yellow*), or SCZ (green). (Figure adapted from [3]).

The Syn2Psy program aims to develop 14 PhD research projects to link disease-associated mutations over synaptic, network and behaviour defects. Syn2Psy will intersect basic research with technological development and transfer and social outreach, under a common and focused strategy. We will address the following scientific questions:

Q1: How do genetic alterations in genes encoding synaptic proteins result in synaptic, cellular, neurophysiological, circuits and behavioural phenotypes? Do different risk factors result in common phenotypes?

Q2: What are the mechanisms underlying excitation/inhibition imbalance in different animal models of neuropsychiatric disorders, and can they be harnessed as therapeutic targets?

Q3: Can nanoscopic and mesoscopic analyses be integrated to understand how synaptic defects result in alterations in neural dynamics?

Q4: Can the course of neuropsychiatric disorders be altered by strategies that modulate mechanisms of disease? When are these strategies effective?

These questions define the topics around which Syn2Psy builds 14 individual projects for ESR/PhD level studentships, each leading to a PhD thesis (see Table 1.1). Each project will address one or more of these topics, and builds on solid previous and ongoing research in the partner academic and non-academic laboratories on synapse biology and neuropsychiatric disorders. The proposed projects are an opportunity to follow new innovative lines of collaborative research, and also to explore new angles in ongoing projects and previous collaborative efforts between partners.

The main goal of Work Package 1 (WP1), coordinated by CNC, is to characterize new models of neuropsychiatric disorders. Two of these models have already been generated in the host laboratories, and were built based on human genetic data, or on the implication of the candidate proteins in crucial pathways that regulate synapse formation, function and regulation. A third model will be generated using human-derived neurons and brain organoids. These models will be characterized to identify neurophysiological, morphological and behavioural alterations, to dissect neuronal circuits that are affected, and to monitor excitation/inhibition balance *in vivo*. The information gathered through the multidisciplinary studies in WP1, which benefit from the interaction between different partners in the Syn2Psy consortium, will allow characterizing the landscape of synaptic, neuronal, circuits and behaviour alterations associated with different genetic defects linked to intellectual disability (ID), schizophrenia (SCZ) and autism spectrum disorder (ASD). It is expected that characterization of different disease models will highlight shared pathways and neuronal circuits that are implicated, and that this mechanistic insight will begin to point to new approaches to translate genetic information to the development of new medicines (see ESR1-3 projects).

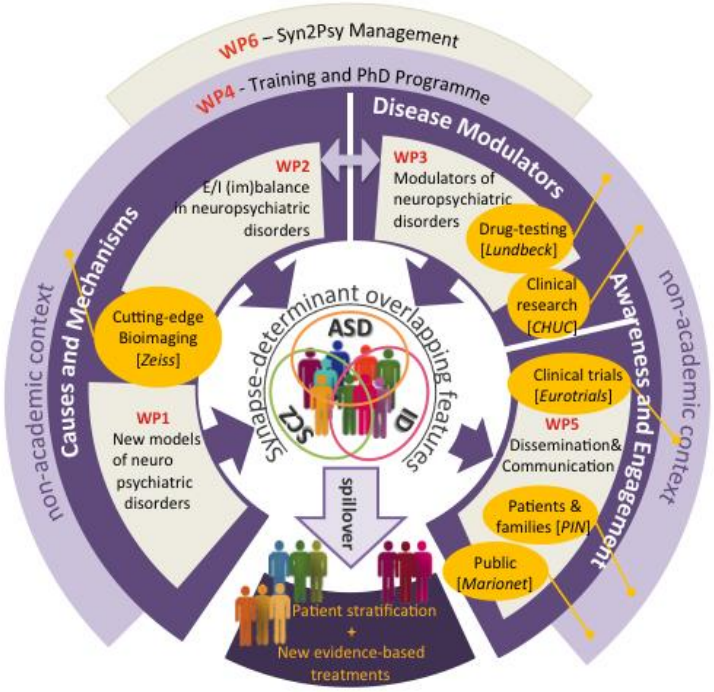


Fig. 3. Syn2Psy rationale and Work Package (WP) interrelation and complementarity. Ovals in yellow highlight the major roles of the non-academic partners.

In WP2, coordinated by IINS-CNRS, we aim to test the excitation/inhibition (E/I) imbalance hypothesis in neuropsychiatric disorders using different models of disease. There is ample evidence in the literature that a tight E/I balance at the level of synaptic inputs and neural circuits is required for normal brain function and that it is critical during development. In agreement with this idea, disrupted E/I balance has been found in ASD, schizophrenia and other brain disorders[14]. E/I balance is regulated by many factors, both at the synaptic level (such as the development of excitatory/inhibitory synapses, synaptic plasticity, pathways downstream of synaptic transmission, neuronal excitability) and at the circuit level (e.g. the interplay between inhibitory interneurons and target pyramidal cells). In some animal models of neuropsychiatric disorders, candidate mechanisms involved in causing E/I imbalances have been characterized, and correction of the E/I imbalance normalizes behaviour, e.g. autistic-like phenotypes in animal models of ASD [14]. These are important indications that E/I imbalances may represent an important therapeutic target if their mechanisms are understood. In WP2 the aim is to address this question at different levels in several mouse models of disease and in a novel model using iPSC-derived neurons from human patients transplanted in the adult mouse brain. Overall, WP2 (see ERS4-9 projects for detailed description) will use approaches ranging from nanoscopic to mesoscopic analyses, together with functional electrophysiological and behavioural evaluation, to pinpoint specific defects in models of neuropsychiatric disorders that result in altered E/I balance, an outcome shared by many of these disorders. This mechanistic insight is the only way to rationally progress towards the identification of druggable targets.

13. Fornito, A., Zalesky, A., Pantelis, C. & Bullmore, E.T. Schizophrenia, neuroimaging and connectomics. *NeuroImage* **62**, 2296-2314 (2012).

14. Lee, E., Lee, J. & Kim, E. Excitation/Inhibition Imbalance in Animal Models of Autism Spectrum Disorders. *Biol. Psychiatry* 81, 838-847 (2017).

Whereas WP1 and WP2 concern understanding neuropsychiatric disorders, **WP3, led by BMI-EPFL, deals with testing strategies to modify the course of disease**. Modulators that halt or slow down disease progress are of obvious interest, but identifying modulators that aggravate disease phenotype can be revealing, especially in understanding how the environment and individual's experience impact on these diseases, and in the design of actionable policies aimed at disease prevention. The projects in WP3 (ESR10-15 projects) address various modulatory strategies (positive and negative) with the potential to impact disease progress. Importantly, in each case the basis for a modulatory effect will be explored, with the objective of pinpointing crucial disease pathways that are amenable to modulation. These projects will explore excitatory/inhibitory imbalance, altered mRNA translation, corticotropin effects, and circuits' deficits at the basis of neuropsychiatric disorders. Additionally, the timing for intervention will be addressed.

The ESRs will be exposed to complementary training in non-academic environment, through secondments at Lundbeck, Eurotrials or at the Coimbra University Hospital. These internships provide the opportunity for students to be exposed to clinical research, drug development and clinical trials, in an industrial or clinical setting.

WP4, led by ICL, synchronizes all training activities offered by the network. **WP5, led by IBPS-INRS,** focuses on the Dissemination & Communication (D&C) strategy, plainly committed with science and knowledge in a participative society. Finally, **WP5, led by IBPS-CNRS,** will evaluate the ESRs transferable skills linked to outreach, and **WP6, coordinated by CNC, refers to the supervision of the Syn2Psy research training programme, as well as the ETN macro-managing with all partners and European Commission**.

Table 1.1 Work Package (WP) List.

WP	WP Title	LB No.	Start mo	End mo	Activity Type	LB Short Name	ESRs
1	New models of neuropsychiatric disorders	1	1	54	R	CNC	ESR1-3
2	Testing the excitation/inhibition imbalance hypothesis in neuropsychiatric disorders	2	1	54	R	IINS-CNRS	ESR4-9
3	Modulators of neuropsychiatric disorders	4	1	54	R	BMI-EPFL	ESR10-15
4	Training and Doctoral Programme plan	1	1	54	T	ICL	All
5	Dissemination and Communication (D&C)	1	1	54	T, O	IBPS-CNRS	All
6	Management	1	1	54	M	CNC	All

LB= Lead Beneficiary No.; Activity type: R (Research), O (Outreach), T (Training), and M (Management)

- **Originality and innovative aspects of the research programme**. Syn2Psy aims at creating cutting edge knowledge in neuropsychiatric disorders while providing advanced training for early stage researchers. Key aspects of originality and innovation in Syn2Psy centre on three pillars: a) **Point-to-point study of human disorders** [studies that range from genes to behaviour, including using human models of disease with translational impact]; b) **Excellence and furthering of European Networks** [bringing together leaders in the field]; c) **Societal Impact** [both immediate, through promoting knowledge in a participative society, and far reaching impact through practical applications]. To our knowledge, Syn2Psy will be the first program dedicated to forming a new generation of researchers with the **combined and integrated know-how** necessary to tackle a group of neuropsychiatric disorders with major impact on society.

More specifically, Syn2Psy innovative approach centres on topics that cover: i) generation of novel models of disease, including human derived neurons and brain organoids; ii) testing the promising focal point of E/I imbalance in neuropsychiatric disorders; and iii) exploration of disease modulatory elements (both positive and negative). The programme brings together experts using specialized techniques and applies their combined potential to **tackle neuropsychiatric disorder research in a truly interdisciplinary, multimodal and intersectoral framework**. By combining human geneticists with laboratories developing new animal models all the way to companies and groups testing new hypotheses and compounds, Syn2Psy can have true impact in the development of novel agents towards improving the quality of life of neuropsychiatric disease patients.

The specific projects to be developed under Syn2Psy are at the forefront of scientific knowledge and employ the most advanced techniques currently used in neurobiology research. This includes both the generation of novel animal models created to mimic specific human mutations (ESR1,2); the innovative use of human-derived neurons and brain organoids (ESR3,8) and IPSCs derived from patients (ESR4,8) as models of neurodevelopmental disorders. Other projects rely on recently developed techniques in super-resolution imaging (ERS4,6; also secondments for ESR1,3,8,11,12) and in novel synaptic and mesoscopic imaging (ERS5,8; also secondments for ESR1,3,7,10,12). In addition, optogenetic tools and in vivo recording of neuronal activity in awake behaving animals are featured (ESR4). Projects are designed and supervised by lead investigators that have accrued significant contributions towards understanding the function of the mammalian brain.

Since the focus of Syn2Psy is clearly disease oriented, with potential for discoveries with impact for human health, we are determined to provide a framework within **Syn2Psy that is geared towards meaningful public engagement and education**. The flow of this information across a pipeline of channels is a key aspect in the Syn2Psy training network and one key strategy is the partnership with PIN - "Progresso Infantil" and Marionet. PIN is a private patient care institution dedicated to improving the quality of life for patients and their families. PIN´s experience in raising awareness and privileged channels for public outreach will leverage Syn2Psy ability to reach and educate the community. Finally, the Marionet's experience in working with scientists will bring Syn2Psy to the general public in a unique manner. The script, constructed by all ESRs, senior researchers and Marionet will be published for further performances. ESRs selected within this programme will be endowed with the knowledge, both theoretical and applied, to tackle the complex question about the way the brain functions in both health and disease.

1.2 Quality and innovative aspects of the training programme

- **Overview and content structure of the training** Training will consist of: **1) Local training** (Table 1.2a; please see also section 3), with the individual research projects and specialized courses associated to the doctoral programmes in the host institutions (Table 1.2b); **2) Network-wide training** (Table 1.2c), namely 4 Network Schools, workshops and a final conference, that will educate the ESRs on ground-breaking advances in the understanding and treatment of neuropsychiatric disorders and in transferable skills; **3) Secondment periods** (Table 1.2a), each ESR will perform mentored work at 3 organisations of our network, in the majority of cases (10/14 ESRs) including a non-academic experience; **4) Personal Career Development Plan** (PCDP), which is mandatory and will be designed with ESRs supervisors to include research, training, **D&C experience**, **project management practice**, and career planning (described in detail below).

Table 1.2a Recruitment deliverables per beneficiary.

ESR No.	Recruiting Participant* + (secondary supervisor)	Research Project	Planned Start Month	Duration (months)
ESR1	CNC (ICL + Eurotrials)	1.1	6	36
ESR2	BMI-EPFL (IINS-CNRS + CIP-UEDIN)	1.2	6	36
ESR3	CNC (CIP-UEDIN + Lundbeck + CHUC)	1.3	6	36
ESR4	IINS-CNRS (UEDIN+ Eurotrials)	2.1	6	27 .6
ESR5	ICL (IBPS-CNRS + CHUC)	2.2	6	36
ESR6	IINS-CNRS (CNC + Lundbeck)	2.3	6	36
ESR7	CNC (ICL + Lundbeck)	2.4	6	36

ESR No.	Recruiting Participant* + (secondary supervisor)	Research Project	Planned Start Month	Duration (months)
ESR8	ICL (IINS-CNRS + CHUC + Lundbeck)	2.5	6	36
ESR9	IBPS-CNRS (ICL + CIP-UEDIN)	2.6	6	36
ESR10	IBPS-CNRS (CNC + Eurotrials)	3.1	6	36
ESR11	Lundbeck (BMI-EPFL+CIP-UEDIN)	3.2	6	36
ESR12	CIP-UEDIN (CNC + IINS-CNRS)	3.3	6	36
ESR13	BMI-EPFL (IINS-CNRS + ICL)	3.4	6	36
ESR14	CIP-UEDIN (IINS-CNRS + Eurotrials)	3.5	6	36
ESR15	CIP-UEDIN	3.6	44	7.6

*Institution providing the PhD degree

Local training: Individual research projects & PhD courses in the research institutions. Each ESR will be allocated to the supervisor from the host organisation responsible for the chosen project, who will be the primary responsible for the fruitful accomplishment of the project. The supervisor will integrate a joint supervisory committee for the individual ESR as detailed in section 1.3.2. Local supervising will take place through bi-weekly training meetings at the host institution to safeguard the tutoring of specific procedures and techniques. In addition to one-to-one supervision, ESRs will participate in research seminars associated to the research on-going in the host institution. Table 1.2a summarizes the recruitment deliverables per ESR, and the training programme the ESR will be allocated to. All ESR projects (with the exception of ESR4/ESR15) will have a 36 month duration, commencing on month 6 of the ETN, and will be associated to the doctoral programme of their host institution (Table 1.2b). The ESRs will strive to obtain a PhD title during their Syn2Psy research and training, hosted by top-level Research Institutions and Universities (Table 1.2b). The ESR hosted at Lundbeck (outside academia) will enrol in the Neuroscience PhD School of the University of Copenhagen, which acts as the PhD-awarding institution in this case. The PhD programmes provide courses, seminars, journal clubs, thematic conferences and other academic training and transferable skills. We plan to take full advantage of the complete training associated to graduate and post-graduate studies in all partner's institutions. In the kick-off meeting (mo1), all members of the consortium will provide a list of specialized courses currently occurring in the partner's institutions. The supervisors and co-supervisors, together with the respective ESR(s), will identify useful courses, in view of the needs for the successful accomplishment of the research project, and a wide-ranging training in transferable skills. In particular, a course on training for animal experiments will be taken by all students (e.g. FELASA course-category B).

Table 1.2b PhD programmes in the Syn2Psy research institutions.

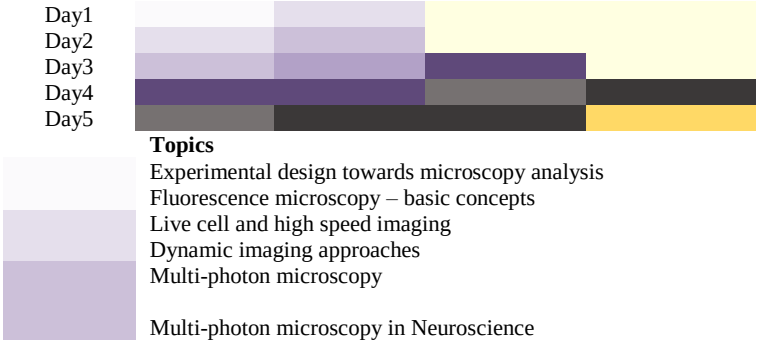
CNC	In-house international PhD programme in **Experimental Biology and Biomedicine** (BEB). The BEB focuses on 1) Neuroscience and Brain Diseases, 2) Metabolism and Aging, and 3) Advanced Therapies. The PhD is awarded via the Institute for Interdisciplinary Research (IIIUC) at the University of Coimbra, CNC's major trustee.
IINS-CNRS	The **École Doctorale des Sciences de la Vie et de la Santé** (*The Life and Health Science Doctorate School*) accredited by the Bordeaux University, gathers 34 laboratories and is the only life science doctorate school in Bordeaux. It gathers teams in the fields of Biochemistry, Bioimaging, Bioinformatics, Cellular Biology and Physiopathology, Plant Biology, Genetics, Chemical Biology, Microbiology-Immunology, Neuroscience, Nutrition, and Enology.
BMI-EPFL	The **EPFL PhD program in Neuroscience** (EDNE) provides its students with training from the genetic to the behavioural level, in close collaboration with the Neuroscience programs of the Universities of Geneva and Lausanne.
CIP-UEDIN	**Edinburgh Neuroscience** includes several in-house PhD programmes including Integrative Physiology, Neuroregeneration, Cognitive & Neural Systems, SPRINT-MND/MS (Scottish Government funded) and Translation Neuroscience (Wellcome Trust funded) and contribute to PhD programmes in Tissue repair (Wellcome Trust funded) and Precision Medicine (MRC funded). Edinburgh Neuroscience comprises over 500 fundamental and clinical researchers plus 200 PhD students.
ICL	1) **MRC-funded PhD program** with the MRC London Institute of Medical Sciences (LMS, formerly CSC), a part of the Institute of Clinical Sciences. 2) **Centre for Doctoral Training** (CDT) in Neurotechnology for Life and Health and 3) **Translational Medicine Training (TMT) Fellowship Programme**. This 3-year course provides teaching and training in neurotechnology, neurophysiology and brain sciences. 4) Clinical Medicine Research for PhD at the Department of Medicine.
IBPS-CNRS	The **École Doctorale Cerveau-Cognition-Comportement** (*The Brain-Cognition-Behaviour Doctoral School*, ED3C), co-accredited by Sorbonne Université (SU), Université Paris-Descartes, École Normale Supérieure (ENS) and École des Hautes Études en Sciences Sociales (EHESS), gathers teams working in the fields of neurosciences and cognitive sciences from SU, Paris-Descartes, Paris-Diderot, Paris-Sud, ENS, EHESS, Collège de France, Institut Pasteur, CEA (Alternative Energies and Atomic Energy Commission) and Institut Curie.
Lundbeck	PhD degrees are awarded though partnership with the **Graduate Program in Neuroscience** from the Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.

Training by means of secondments. The Syn2Psy secondments assure international, intersectoral training to all individual ESRs projects, and reinforce the synergy of the consortium. Nine non-academic secondments (at Lundbeck, Eurotrials and CHUC) will take place, to expose the students to clinical and industrial environments. Although the duration of the secondments is already planned (please see Table 3.1d and Gantt chart), there may be minor adjustments. The secondments plans will be evaluated in the intermediate meeting (IM, Mo18, Lausanne, Switzerland).

Network-wide training activities: Network Schools. Four Network Schools (NS) will be organized, on: NS1) Basic concepts on imaging tools and data analysis; NS2) Genetic approaches for the study of neuropsychiatric disorders; NS3) Drug discovery and development: from idea to product; and NS4) Advanced methods for imaging the brain: from nanoscopic to mesoscopic perspectives (see network school syllabus below). They are designed to provide theoretical background as well as practical skills in the selected topics, through hands-on training. Basic transversal skills will also be provided. The topics were chosen to train the students in areas crucial for research in neuropsychiatric disorders, and to take full advantage of the partners' know-how. NSs are jointly organized by beneficiaries and partner organisations, and will be offered to Syn2Psy ESRs but also to a small number of external researchers. State-of the art lectures in the NSs will be by scientists in Syn2Psy and invited renowned researchers in the field. Lundbeck organizes the NS3 on Drug development and ZEISS will be deeply involved in both NS1 and NS4.

Network school I: Basic concepts on imaging tools and data analysis, Month 6, Coimbra, Portugal

	Speakers	
1	Luísa Cortes, CNC, PT (**Organizer**)	LC
2	Monika Marx, ZEISS, DE (**Organizer**)	MM
3	Ana Luisa Carvalho, CNC, PT	ALC
4	Ramiro Almeida, CNC, PT	RA
5	Margarida Caldeira, CNC, PT	MC
6	Soren Prag, ZEISS, DE	SP
7	José Rino, IMM, PT	JR
8	Gabriel Martins, IGC, PT	GM
9	Jorge Valero, Achucarro, ES	JV
10	Claúdia Florindo, CBMR-UAlg, PT	CF



3D imaging
Intracellular calcium imaging
Spine dynamics visualization
Axon dynamics studies
Basic concepts on image analysis; ethics on image processing
Introduction to macro design for image analysis
Microscopy hands-on sessions
Image analysis hands-on sessions
Statistics and data analysis

Network school II: Genetic approaches for the study of neuropsychiatric disorders, Month 32-35, Paris, France

	Speakers	
1	Catalina Betancur, IBPS-CNRS, FR (**Organizer**)	CB
2	Joseph D. Buxbaum, Icahn School of Medicine at Mount Sinai, USA	JDB
3	Michael C. O'Donovan, Cardiff University, UK	MCO
4	George Kirov, Cardiff University, UK	GK
5	Joris Veltman, Radboud University, NL	JV
6	Daniel Geschwind, UCLA, USA	DG
7	Gerome Breen, King's College, UK	GB
8	Sarah Blackford, Society for Experimental Biology, UK	SB

Day1
Day2
Day3
Day4
Day5

Topics

Complex genetics – basic concepts (CB)
Genetic association studies (MCO)
Copy number variation studies (GK)
Whole exome and whole genome sequencing (JV)
RNA sequencing and specialty sequencing (DG)
Epigenetics/epigenomics (DG)
Network and pathway analysis of omics data (GB)
Functional dissection (JDB)
Genetics of autism spectrum disorder (JDB, CB)
Genetics of schizophrenia (MCO)
Workshop – Case studies and critical thinking in neuropsychiatric genetics (CB)
Genetics of intellectual disability (JV)
SHANK genes and Phelan-McDermid syndrome (CB, JDB)
Hands-on experience with modern computational methods for rare and common variation (JDB, CB and others)
Workshop – Professional skills for doctoral students: Career planning (SB)

Network school III: Drug discovery and development: from idea to product, Month 27, Copenhagen, Denmark

	Speakers	
1	Niels Plath, Lundbeck, Germany (**Organizer**)	NP
2	Jesper Frank Bastlund, Lundbeck, DK	JFB
3	Michael Didricksen, Lundbeck, DK	MD
4	Francois Gastambide, Lundbeck, FR	FG

Day1
Day2

Topics

Target overview
What is a target?
How is a target validated?
The drug discovery value chain
Translational biomarkers
In vivo models –and limitations in CNS research
Clinical development

Network school IV: Advanced methods for imaging the brain: from nanoscopic to mesoscopic perspectives, Month 32-35, Bordeaux, France

	Speakers	
1	Daniel Choquet, IINS-CNRS, FR (**Organizer**)	DC
2	Thomas Knöpfel, ICL, UK	TK
3	Jean-Baptiste Sibarita, IINS, Bordeaux, FR	JBS
4	Eric Hosy, IINS, Bordeaux, FR	EH
5	Christel Poujol, BIC, Bordeaux, FR	CP
6	Valentin Naegerl, IINS, Bordeaux, FR	VN
7	Markus Sauer, Würzburg, DE	MS
8	Markus Heileman, Munich, DE	MH
9	Monika Marx, ZEISS, DE	MM

Day1
Day2
Day3
Day4
Day5

Topics

Introduction to fluorescence microscopy
General description of super-resolution techniques
Advantages and limitations of the different SR techniques
In vivo optical imaging approaches
Light sheet microscopy
Photo-physics of fluorescent probes for super-resolution
Genetically encoded indicators of neuronal activities
Preparation of samples
Microscopy hands-on sessions
Image analysis hands-on sessions

Network schools, local PhD program-based courses and workshops offer the following transferable skills to all ESRs: **1) Experimental design, statistics and data analyses**; **2) Scientific writing**, to develop critical thinking

skills, to develop argumentation skills, and to learn procedures concerning Open Science platforms (on-line publications, bibliometrics for papers and researchers); **3) Effective dissemination** regarding the design of multifaceted tools oriented to different target audiences (academic and non-academic) and the general public; **4) Effective communication** which comprises chairing and participating in meetings; speaking in public and to the media; **5) Language courses** (the official language is English, courses to learn local languages are offered to facilitate student integration in the host institutions); **6) Networking**, in particular recognizing the importance of knowing peers and of creating a network of trusted collaborators; **7) Career development**, understanding the different career alternatives, and having a lucid perspective about pros and cons of different options; **8) Project management** such as report writing, job application, ethical issues and (inter)national legislation; **9) Acquiring private and public funding**, learn about research proposal writing and evaluation and national funding agencies functioning; **10) New Product Development (NPD)**, strategic thinking, learning about various stages and sub-processes of NPD which integrates R&D, marketing and financing, market survey strategies; **11) Ethics**, being aware that scientific falsification and plagiarism, misuse of funds and double funding are intolerable (the supervisory board will elaborate a text that will be given to all ESRs after the recruitment); and **12) Education for animal experiments**, learning animal experimental design, procedures, regulation and ethics.

Network-wide training: Other training activities. There will be three project meetings, the **kick-off meeting** (K, mo6), an **intermediate meeting** (IM, mo18) and a **final conference** (C, mo42), which will make the final outcome of the network (please see Table 1.2c). In the kick-off meeting, we will discuss the initial research training activities, such as PhD doctoral programmes, network schools, conferences, the D&C strategy, and the overall training and management plan. A Data Management Plan for making Syn2Psy data accessible, interoperable and reusable will be devised. At the kick-off meeting the logistics associated to the ESR recruitment plan and the Syn2Psy commitment responsibilities concerning the network-wide training events and conferences will be discussed (Table 1.2 b). The final conference will have one day committed to oral presentations by all ESRs, reflecting their individual research projects and transferable skills. This final conference will be a scientific meeting on *Synaptic Dysfunction in Neuropsychiatric Disorders*, the theme of Syn2Psy. All Syn2Psy researchers will make an oral presentation, and invited reputed scientists in the field will present their work. The final conference will be followed by a 3 days **science communication workshop**, in which ESRs will work with PIN and science communication officers from the partner institutions, to produce contents to patient associations and the general public. PIN will participate in the dissemination of these documents among the Portuguese public, and the documents will be available through Syn2Psy website also.

Table 1.2c Main network-wide training events, conferences and contribution of beneficiaries.

Nº	Code	Main Training Events & Conferences	ECTS	Lead Institution	Project Month	Venue
1	K	Kick-off meeting: Welcome to Syn2Psy ETN. Introduction to the research training programme	n.a.	CNC	6	Coimbra, PT
2	NS1	Basic concepts on imaging tools and data analysis	6	CNC+ZEISS	6	Coimbra, PT
3	NS2	Genetic approaches for the study of neuropsychiatric disorders	6	IBPS-CNRS	32-35	Paris, FR
4	IM	Intermediate meeting	n.a.	BMI-EPFL + all partners	27	Copenhagen, DK
5	NS3	Drug discovery and development: from idea to product	3	Lundbeck	27	Copenhagen, DK
6	NS4	Advanced methods for imaging the brain: from nanoscopic to mesoscopic perspectives	6	IINS-CNRS + ICL + ZEISS	32-35	Bordeaux, FR
7	FM/W1	Final meeting / Science communication workshop	1.5	CNC+ all partners	54	Coimbra, PT

Personal Career Development Plan (PCDP). Researchers will be recruited in month 6 of the programme. Three months after the enrolment, each ESR should have a PCDP designed with the supervisors, organized in research, training, transferable skills/outreach experience, project management, and career planning (Table 1.2d). The PCDP will be subject to approval by the supervisory board each year of the project.

Table 1.2d ESR Personal Career Development Plan.

Doctoral training	Counts with a list of courses (local and network-wide) to be taken by the ESRs during their programme, including the ECTS credit requirements, and a list of monographs and number of publications to be completed. Courses will also cover training in transferable skills, as detailed in section 1.2.1.4.
Research	Comprises the description of the individual research project, including the research methodology and approach, the secondments programme, and the publication plan (with provisional articles expected). The research will be accompanied by the supervisors and regularly updated (every six months) depending on the work progress. A personalised analysis of the research and training requirements and goals of the planned project for the ESR will be taken into account.

Project	Defines the overall ESR project, including the "hands-on" research training and secondment plans, with a description of the work and a justification of how activities fit the training objectives. Part of the project plan will include a list of complementary missions in which the ESRs will be enrolled as part of Syn2Psy D&C strategy. These will be agreed between ESR and supervisors, and subjected to approval by the supervisory board, upon the condition that they will not compromise the dedication of the ESR to his/her project.
Outreach/ Management experience	Combines multiple initiatives that promote the ESR capacity to communicate with different target audiences and general public. The partners PIN and Marionet provide training and the opportunity for diversified activities in this context, with a significant contribution to raise social awareness to research on neurological disorders. The engagement of the ESR in collective and participatory research as well as the organization of target seminars (local/national/international), network-wide training events, and conferences, is expected to contribute significantly to Syn2Psy D&C strategy and overall management.
Career development after ETN	Covers a list of experiences that ESR will need to undertake with the purpose of finding a job promptly after the end of the contract. The plan should explain how the doctoral training, the "hands-on" research training and secondment experience, and the transferable skills contribute to his/ her career development. The PCDP advances a scheme for supervisors and ESRs to reflect and discuss periodically on the trajectory of the researcher, with the end-goal of finding a job of her/his preference after the ETN contract.

The PCDP will be planned and monitored as to ensure that ESRs accumulate adequate competences and progressively become more independent in their activities. A one-day workshop (NS2) will be dedicated to the discussion of PCDP and future careers available to all researchers, how to create value in their research and on how to perfect their CV and interview skills, with the guidance of experienced members/partners of Syn2Psy network.

- **Role of non-academic sector in the training programme.** The non-academic sector has a crucial contribution to Syn2Psy, with the participation of **Lundbeck, Eurotrials, ZEISS, CHUC, PIN and the Marionet theatre company**. All ESRs will be exposed to the private sector, either through direct enrolment (with Lundbeck), via secondments (Lundbeck, Eurotrials and CHUC) or network-wide training (ZEISS, PIN, Marionet), and will be guided to identify promising technological applications. This will ensure that Syn2Psy is a balanced network providing a proper exposure of young researchers to academia, clinical practice and the pharma-industry. **Lundbeck** is a global pharmaceutical company engaged in the research and development, production, marketing and sales of drugs for the treatment of disorders of the CNS, including mental disorders. Lundbeck will host ESR11, who will develop his/her scientific research within the company R&D division, in a collaborative project with two academic labs (CNC and ICL). In addition Lundbeck will receive two ESRs for secondments, providing the opportunity for these students to develop research in a pharmaceutical company environment, perceive the ethics and IP-related aspects associated with working in the private sector, as well as envision how industrial and academic partners can work together towards finding new pharmaceuticals. Importantly, Lundbeck will organize NS3 in Copenhagen, on the drug development process. The ESRs will visit Lundbeck departments that provide legal assistance in IPR, and learn about their rationale and procedures. **ZEISS** is an internationally leading technology enterprise of the optical and optoelectronic industry. ZEISS develops and distributes microscopes and medical technology, and constantly advances the world of optics. ZEISS will actively contribute to Syn2Psy by co-organizing network schools (NSs 1 and 4, in Coimbra and Bordeaux, respectively) and by providing last-generation microscopes for in situ specialized training during the network schools, as well as technical support and training personnel. These events will provide training in microscopy with the highest standards, in methods at the forefront of the field, as well as provide an opportunity for the interaction between ZEISS and academic research groups in the consortium. **CHUC** is one of the biggest Portuguese hospitals, offers comprehensive care across all the leading medical and surgical specialities, comprises 19 accredited reference centres and belongs to the collaborative network M8 Alliance of Academic Health Centres, known for their educational and research excellence. At the Autism Unit in the Paediatric Hospital at CHUC, ESRs will be exposed to clinical research performed by neurodevelopmental paediatricians who participate in genetic studies for ASD. Students will learn about the phenotype of various developmental disorders, while becoming familiar with the selection criteria and thorough clinical data compilation for patients' inclusion in large patient cohorts for genetic studies. **Eurotrials** is a scientific consultant company (part of CTI -Clinical Trial and Consulting Services, USA) with strong expertise in Europe and Latin America. Eurotrials services cover all the steps of clinical translational research projects, and provide drug and clinical trials development, in accordance with global and specific regional requirements. Eurotrials will contribute to Syn2Psy by hosting students in short-term secondments on medical writing, clinical trials as well as regulatory affairs.

Non-academic and academic partners will guide ESRs in the production of tools that contextualize the topics of Syn2Psy to a broader audience. One such audience are patients and patients' families, who will be reached by Syn2Psy through **PIN**-Progresso Infantil, a private medical clinic devoted to the treatment of children with neurodevelopmental disorders. PIN will be associated with Syn2Psy since the kick-off meeting, and provide

guidance on how to dialogue with clinicians, the general public and with patients and patients' families. PIN will be present also in the intermediate and final meetings, and organize a 1 day workshop for exchange between their team and ESRs. Finally, the partner **Marionet**, a theatre company based in Coimbra and with a tradition of collaborative work with CNC, will participate in the kick-off, intermediate and final meetings of Syn2Psy, with the objective of guiding the ESRs in writing the script for a play on Syn2Psy and its contributions. The script will be developed throughout Syn2Psy, and Marionet will direct ESRs in the production of the play, which will be performed at the end of the Final Meeting.

1.3. Quality of the supervision

The supervision approach and quality standards will follow the guidelines of the **European Charter and Code for Researchers**, as all the beneficiary academic institutions have already endorsed the Charter & Code principles, a few being HRS4R acknowledged institutions [ICL, UE(CIP), INSERM, and the University of Copenhagen (Lundbeck)]. Each individual project will have a detailed PhD plan and a Career Development Plan (PCDP), tailored to the project specificities and the profile and expectations of the ESR; these plans will be devised following the procedures outlined above and in section 3. The trainees will be part of an extended international research laboratory where a set of monitoring committees for both the projects and the fellows will be implemented (details in sections 3.2.1 and 3.2.2).

- **Qualifications and supervision experience of supervisors**. All supervisors and co-supervisors have been identified (sections 3.1.1 and 3.1.3) and their expertise detailed in section 5, the leading investigators being pioneers in their field(s). Academic supervisors have experience in teaching and training students from the undergraduate to the PhD level, as well as in (co-)supervising post-doctoral fellows, and have been actively involved in at least one advanced training international network (e.g., the MSCA-ETN Syndegene) where interdisciplinarity and international plus intersectoral mobility is fostered. Several past alumni now pursue fruitful research-driven careers in both the academic and non-academic sectors.

Many senior supervisors hold professorship and scientific managerial positions in their institutions, thus being able to implement an effective, high quality supervision. All supervisors are recognized experts in their research fields, with a track-record of high-impact scientific publications within the Syn2Psy field of research (vide section 5), regular participation in journal peer-reviewing and international conferences, and coordination/participation of national and international research projects (e.g., the P7-HEALTH-2013-INNOVATION project MATRICS). At Lundbeck, supervision is assured by a PhD-level senior researcher holding a full professor honorary title (vide section5). Within the non-academic partners co-supervision counts with PhD- and/or high-level professionals in their respective sectors.

- **Quality of the joint supervision arrangements**. Co-supervision is implemented for all projects and the partners are clearly identified in Table 1.2a. Several partners have already successfully co-supervised doctorates in the past and are thus familiar with the requirements of the respective institutions. As a rule, each ESR will have a main academic PhD supervisor (at the host institution) and one academic co-supervisor (at the academic institution welcoming the ESR's main secondment), both responsible for the ESR supervision and for the elaboration of his/her PhD and Career Development plans. This dual-supervision fits with the requirements for the title of European Doctorate and promotes research interception between the network's partners. A third **non-academic** training co-supervisor, will join the two academic (co)supervisors in a supervisory committee of the individual ESR (see also section 3) The two main supervisors will have a monthly videoconference with the ESR to ensure appropriate monitoring and the effective individual research project progress; the supervisory committee will maintain regular Skype meetings with the ESR, following progress, and will guide the fellow in all matters regarding the fellowship, including administrative, e.g., PhD enrolment, aspects related to courses and credits, submission of requested documentation, final PhD defence. The ESR at Lundbeck will have an analogous supervising scheme, compatible with the agreement between Lundbeck and the University of Copenhagen already implemented in other H2020-ITNs.

1.4. Quality of the proposed interaction between the participating organisations

- **Contribution of all participants to the research and training programme**. All participants (beneficiaries and partners) actively contribute to the research and training programme by providing either supervisory skills, secondment capacity, network schools, access to cutting edge applications/methodologies and processes, and training in complementary and soft/transferable skills. Major expertise contribution(s) of each participant to Syn2Psy are summarized together with other cross-linked aspects (interplay between partners, expertise and individual projects) in the chart below. Their contributions are further described and itemised in section 1.2 above, not forgetting the matching enterprise-based research perspective (Lundbeck, ZEISS, CHUC,

Eurotrials) and the social perspective of science communication to end-users/general public (PIN, Marionet) delivered by the non-academic participants.

- **Synergies between participants**. The partners of Syn2Psy were thoughtfully considered for their excellence in the relevant fields of expertise and envisaged synergies among them necessary to put together a common and consistent training-through-research advanced programme, while embodying the idea that biomedical research makes its greatest impact when top-research, international collaboration, a market-oriented perspective and social awareness are brought together. No single partner could tackle all these aspects alone or prepare the next generation of researchers for such an integrated mind-set. Hence, Syn2Psy combines the complementary expertise of the academic partners in key topics/methodologies directed to the exploration of the causes and mechanisms of the diseases, paving the way for a more rational neuromodulatory drug development (the realm of Lundbeck), clinical trials (as those conducted by Eurotrials) and clinical translation of discovery (as performed at CHUC). Partners cooperate in project design and share methodology. A fruitful dialogue with the potential end-users (physicians, patients and families, PIN) and other target audiences (Marionet) will be established. As for ZEISS, it plays an important role in the training process, as cutting-edge biomedical research extensively depends on state-of-the-art bioimaging technology.

This integrated approach will strengthen existing collaborations (e.g. between the CNC and IINS, the IINS and IBPS, the CNC and EPFL; see also section 1.3.1.) and prompt long-term partnerships, new and already ongoing: the microscopy core facility at CNC, for instance, is a ZEISS labs@location Partner since 2015. The involved enterprises may well become the future employers of some of the freshly PhD-graduated researchers, strengthening the links and continue to develop new collaborative research and training projects with the other Syn2Psy partners.

Syn2Psy Chart: Contribution of all participants to the research and training programme.

Beneficiaries	1. CNC		x	x		x	x	x	x			x		Ana Luisa Carvalho, Carlos Duarte, João Peça, Ramiro Almeida, Paulo Pinheiro, Luisa Cortes		
	2. IINS-CNRS		x	x	x			x	x			x		Daniel Choquet, Laurent Groc, Yann Humeau		
	3. IBPS-CNRS	x	x	x					x			x		Catalina Betancur		
	4. BMI-EPFL		x	x		x		x	x			x		Carmen Sandi		
	5. ICL		x	x	x	x	x	x	x	x		x		Vincenzo De Paola, Thomas Knöpfel		
	6. CIP-UEDIN		x	x		x		x	x			x		Emily Osterweil, Peter Kind		
	7. Lundbeck		x	x					x					Niels Plath		
Partners	8. ZEISS				x									Monika Marx		
	9. CHUC	x									x	x	X	Guiomar Oliveira, Frederico Duque		
	10. PIN											x	x	Nuno Lobo Antunes		
	11. Eurotrials										x	x		Ana Patacão		
	12. Marionet											x		Mário Montenegro		
Work package (Lead Partner)	**Individual fellow project**	**Expertise**	Human genetics	Neuronal cell biology	Neurophysiology	Super-resolution microscopy	Mouse genetics	*In vivo* brain imaging/recordings	Optogenetics	Animal behaviour	Neural Dynamics	Clinical translation	Outreach and public awareness	Experience with patient dialogue and engagement	**Host Institution (Supervisor)**	**Partner 1 / Secondment 1**	**Partner 2 / Secondment 2**
		Title															
WP1 (CNC)	ESR1	Cognitive disorders as defects in synaptic function: insight from human mutations in the *CACNG2* gene encoding Stargazin		x	x	x	x			x	x		x	x	CNC	ICL	Eurotrials
	ESR2	Role of mitofusins in neurodevelopmental trajectories of psychopathology			x								x	x	BMI-EPFL	IINS-CNRS	CIP-UEDIN
	ESR3	Production and testing of human-derived neurons and brain organoids: advanced model probing in neurodevelopmental disorders	x	x	x						x		x	x	CNC	CIP-UEDIN	Lundbeck + CHUC

WP2 (IINS-CNRS)	ESR4	Linking autism related mutations in Shank3 over synaptic, network and behaviour defects	x	x	x	x			x	x			x	x	IINS-CNRS	UEDIN	Eurotrials
	ESR5	Mesoscopic monitoring and analysis of cortical excitation/ inhibition balance in an animal model of synaptic dysfunction			x		x	x	x	x	x		x	x	ICL	IBPS-CNRS	CHUC
	ESR6	Physiopathological regulation of single NMDA receptor dynamics in psychosis		x		x							x	x	IINS-CNRS	CNC	Lundbeck
	ESR7	FMRP regulation of synapse dynamics												x	CNC	ICL	Lundbeck
	ESR8	Illuminating the mechanisms of synaptic and neural network dysfunction in a new *in vivo* model of Down's syndrome		x	x	x	x	x	x	x	x		x	x	ICL	IINS-CRNS	Lundbeck +CHUC
	ESR9	Role of glycinergic signalling in autism spectrum disorder	x	x	x					x	x		x	x	IBPS-CNRS	ICL	CIP-UEDIN
WP3 (BMI-EPFL)	ESR 10	The endocannabinoid system as a therapeutic target in *Shank3*-deficient mice, a model of autism spectrum disorder		x	x					x			x	x	IBPS-CNRS	CNC	Eurotrials
	ESR 11	Investigating the excitation/inhibition (E/I) imbalance hypothesis of neuropsychiatric disorders in the cortico-thalamic system with electrophysiological methods		x						x	x		x	x	Lundbeck	BMI-EPFL	CIP-UEDIN
	ESR 12	Identifying convergent dysregulation of mRNA translation in multiple models of autism		x	x	x				x			x	x	CIP-UEDIN	CNC	IINS-CNRS
	ESR 13	Effect of corticotropin-releasing hormone on a thalamic hub for neurodevelopmental disorders			x	x		x		x	x		x	x	BMI-EPFL	IINS-CNRS	ICL
	ESR 14	Circuit deficits associated with ASD/ID		x	x		x			x			x	x	CIP-UEDIN	IINS-CNRS	Eurotrials
	ESR 15	Testing gene therapy for Fragile X Syndrome	x	x	x		x			x		x	x	x	CIP-UEDIN	-	-

- **Exposure of researchers to different (research) environments, and the complementarity thereof**

The Syn2Psy network counts with the participation of large universities (ICL, CIP-UE), two research institutes (IINS and IBPS) affiliated with large universities and a governmental research agency (CNRS), a private non-profit research centre (CNC), large companies – ZEISS for high-tech equipment, the pharmaceutical Lundbeck, the contract research organization Eurotrials and the Coimbra University Hospital (CHUC)–, a Federal Institute of Technology (EPFL, a main player in Switzerland's entrepreneurial power), a share-limited company in the health-care sector (PIN), and a small theatrical company. It is a well-balanced consortium spanning a diversity of sectors for the ESRs to interact with, be it during their secondments or in the network-wide events. They will be amply exposed to different approaches to the research process (academia vs. industry vs. a clinical environment) and practice distinct ways of presenting their research outcomes, guided by the leaders in the field, with whom they will be able to learn and exchange ideas face-to-face. They will experience distinct (research) working environments and their background and cultural differences (private vs. public, academic vs. entrepreneurial, profit vs. non-profit.) and get used to work in an intersectoral and international collaborative context; the fellows will be competent in key fundamental topics of neurobiology and skilful in a variety of associated research methodologies as well as in scientific dissemination/communication aspects, while being aware of the aims and goals of the pharma-industry and medical/patient community in the area of neuropsychiatric treatments.

2. Impact

2.1 Enhancing the career perspectives and employability of ESRs and their skills development

Syn2Psy provides unique "hands-on" research training to 14 ESRs with focus on understanding neuropsychiatric disorders, and advancing novel therapeutic approaches for alleviating these leading causes of disability worldwide. Syn2Psy will promote that ESRs develop skills and experiences to enhance their career into wider contexts and perspectives, but also successfully cope with change throughout their working life. The individual gains to all ESRs include: **1) To be trained through interconnected and well-balanced projects in cutting-edge methods** in neuroscience and biomedical research, ranging from molecular and cellular studies to neurophysiology, neuronal circuits, neural dynamics and behaviour; training will be interdisciplinary, intersectorial, and in an internationalized

environment (**the «*triple i*»**). **2) To experience international mobility** through secondments. **3) To develop complementary competences in clinical research and in the industrial sector** [including in procedures of clinical research (CHUC), dealing with IPR and confidentiality within the private sector (Lundbeck, Eurotrials) and regulatory affairs concerning clinical trials (Eurotrials)]. **4) To develop innovative D&C skills** from writing to the media to organising outreach initiatives (with PIN and Marionet). **5) To acquire competences in project managing and networking** (writing project reports, organising scientific meetings and identifying funding opportunities). **6) To be prepared for assuming leadership in their future careers**, by acquiring skills to identify synergetic possibilities and to interact successfully with both academic and non-academic sectors, ensuring a long-term attractiveness of the their careers; attention will be given by the supervisory board to whether ESR research projects can lead to valuable outcomes to non-academic Syn2Psy partners. **Our ESRs will be leading-edge researchers and clear-thinking experts in neuroscience and biomedicine, and future highly skilled employees** both at the academic and private sectors, **devoted to novel therapeutic approaches and health innovation**. Furthermore, our ESRs will be **remarkable communicators** of science to their peers, multiple target audiences, policy makers and the general public.

2.2 Contribution to doctoral/ESR training at EU level and to strengthening EU innovation capacity

- **Contribution to structuring doctoral/early-stage research training at the European level**. Traditional doctoral training is offered by local programmes with fellows almost entirely focused on a single study scheme that is limited to the resources and facilities of the hosting units, with little or no external guidance experience. Syn2Psy introduces a well-balanced pan-European structure, involving 6 PhD programmes from 6 top-level research centres and universities, in close cooperation with 6 non-academic organisations, across 7 countries, offering training that features *"a multi-disciplinary and collaborative activity focused not just on local/national goals, but those of Europe positioning itself in a competitive global environment*" (European Higher Education Area). Syn2Psy will help to boost neuropsychiatric and neurobiology research in a wider employment market in Europe, fully aligned with the reform and modernization of European Doctoral Programs (Salzburg II Recommendations, 2010) that includes the **EU Principles for Innovative Doctoral Training**. Syn2Psy offers a unique combination of "hands-on" research training underpinned by interdisciplinary, intersectoral mobility and international collaboration (see Fig. 3), with mutual benefit of all partners, and the appropriate professional career development opportunities, which include the development of individual transferable skills to all ESRs. Finally, by bringing together supervision experience of several top European research centres, the potential impact and outcome of Syn2Psy research will be magnified by continued support for successful projects.

- **Meaningful contribution of the non-academic sector to the doctoral/research training.** As exposed in sections 1.2.2. and 1.5, the Syn2Psy non-academic partners intervene in several selected steps of the training process, to extend the ESRs competencies beyond the pure academic PhD-training. The most meaningful contributions from the non-academic sector are: **a)** the bioimaging technical component supported by ZEISS, that grants the fellows with an insightful knowledge of a key technology critical to biomedical research, opening the door to future careers in the sector (e.g., technical communication, product management); **b)** the drug discovery and development component from Lundbeck, introducing the fellows to RD&I entrepreneurship in the pharmaceutical industry; **c)** direct contact with Eurotrials, a contract research organization proficient in the organization of clinical trials among other steps of drug development services; **d)** the clinical research component supported by the Autism Unit at the Coimbra University Hospital (CHUC); and **e)** direct engagement, through outreach activities, with the medical/patient community (via PIN) and the more general public (Marionet), in compliance with the EU Charter for Researchers, for the ESRs to gain a better understanding of public interest, concerns and priorities for science and technology.

Strengthening European innovation capacity. The EC has supported research focused on understanding the neurobiology of neuropsychiatric, but the challenge is far from being met. IMI, Europe's public-private partnership for Health focused on unmet medical needs, launched a H2020 call (SC1-HCO-10-2018): *Coordinating European brain research and developing global initiatives* emphasizing the need to "*understanding of diseases, innovation and accelerate innovation through the development of new diagnosis, prevention and treatment options in areas of high and unmet medical needs*". This is precisely the driving idea underlying the Syn2Psy training programme, which proposes a unique, integrative strategy that considers a wider set of neuropsychiatric disorders and covers innovative and state-of-the-art approaches to unravel the causes, mechanisms and neuromodulatory processes associated with them, towards finding their overlapping synaptic determinants. The scope and strategy is in line with the H2020 framework programme. Ultimately, our approach will lead to a more rational patient stratification and the development of novel diagnostic and treatment strategies, paving the way to innovation in the biomedical/pharmaceutical industry. Besides research-specific skills, the Syn2Psy trainees will acquire a keen understanding of the market needs, and a perception of drug development, clinical trials and clinical research procedures, as well as of the importance of raising social awareness to research on neurological disorders,

positioning themselves at the forefront of pioneer research and innovation in the area of mental health. The Syn2Psy project will thus help boost neuropsychiatric research in the EU, drive innovation and plant seeds that may shape the landscape of neurobiology research in Europe, as it is expected to significantly contribute to the advance of the state-of-the-art.

2.3. Quality of the proposed measures to exploit and disseminate the project results

- **Dissemination of the research results.** The dissemination activities will provide target information to multiple audiences: scientific community, students, patient associations, entrepreneurs, and society (Table 2.a). Engaging with the society is simultaneously important to inspire the next generation of neuroscientists, biomedical researchers and clinicians, but is also fundamental to promote awareness and informed decisions. The consortium will follow the Green Road to Open Access publication to disseminate results from this project. Scientific publications will be stored in free-access on-line repositories and/or on the electronic libraries of the involved research institutions. Supervisors have personal pages on scientific social networking sites like ResearchGate. The Syn2Psy website will include a complete list of publications with links for downloading. In the case of an embargo period, a substitute version will be made available without compromising the copyright law.

Table 2.a Target audiences, actions and indicators of the Syn2Psy dissemination plan.

Target group	Actions	Indicators
Scientific community	**Scientific publications in high impact peer reviewed journals** (e.g. Nature, Science, Neuron, Nature Neuroscience, PNAS, Cell, J Neuroscience, eLife) following the Green Road to Open Access publication; **Oral/Poster presentations during scientific conferences** (e.g. Society for Neuroscience, FENS-Federation of European Neuroscience Societies); **Design/maintenance of the Syn2Psy website**; **Organizing workshops, annual symposia, seminars and final conference**; **Publish on EU newsletters**, e.g. Marie Skłodowska-Curie actions, **online journals and existing newsletters and websites of beneficiaries and partners**; **Communication articles shaped for younger audiences** (e.g. Frontiers for Young Minds); **Establish links to in-house PhD programmes and other ITNs**. These actions will be revised in the kick-off meeting, and supervised by the D&C committee.	-Number of peer reviewed scientific publications; - Number of researchers addressed through oral/poster presentations; -Number of scientific events in which Syn2Psy is represented; -Number of visits to website, Facebook page; -Number of news/articles published on online EU-newsletters and journals, and other existing newsletters and websites; -Number of science communication news/articles; -Number of new research projects and collaborations.
Undergraduate and post-graduate students	**Creation and maintenance of e-newsletters, website and social media**, including e-newsletters from beneficiaries and partners and EU-newsletters, making links to other ITNs and EC-funded projects; **Conducting meetings and workshops**.	-Number of articles published on online EU newsletters and journals, and other existing newsletters and websites; -Number of new collaborations and interactions arising between ESRs and other students.
Younger audiences, patient organisations/ General public	Information articles on neuropsychiatric disorders will be produced by ESRs in collaboration with PIN. These articles will be written in English and translated to national languages of the consortium with the participation of the researchers from the network **Communication through direct contact**; **Organizing workshops**; **Publishing information/ awareness e-newsletters**. **Theatre performance.**	-Number of articles published at the Syn2Psy, PIN and other patient organisations websites (e.g. Phelan-McDermid syndrome Foundation); -Number of meetings/interviews; -Number of e-newsletters/on-line journals/websites news in which Syn2Psy is mentioned; -Number of outreach events at hospitals, museums, schools, shopping centres, and public talks given at medical centres and science cafes; -Number of visits to website/social media; -Number of articles published online.

The dissemination activities shall be compatible with the legitimate interests of the owner(s) of background and results, defined in the H2020 Rules for Participation, and the Syn2Psy consortium agreement. The dissemination plan will be defined in the kick-off meeting. The short time of research training programme, 36 months, will be limiting to assess the real impact of all initiatives taken by Syn2Psy, but some data on feedback/engaging actions and immediate impact is expected. Each planned dissemination activity will be sent to the D&C committee in advance and approved by the management board before implementation. The dissemination activities shall be all compatible with the legitimate interests of the owner(s) of background and results, defined in the H2020 Rules for Participation, and Syn2Psy consortium agreement.

- **Exploitation of results and intellectual property**. The general rules for access, use and dissemination of Intellectual Property Right (IPR), defined in the **H2020 Rules for Participation**, will be applicable to Syn2Psy. The rights of beneficiaries and partner organisations to use the knowledge produced within Syn2Psy (Table 2.b) will be subjected to IPR clauses in the **consortium agreement** that will be signed by all parties immediately after the grant agreement. In specific cases, such as researchers collaborating with non-academic sector during secondments, a nondisclosure agreement may be requested, to protect designs/ know-how/ procedures of the owner(s). As the ETN beneficiaries, all participating organisations shall ensure that the project results D&C is possible. The Syn2Psy consortium will examine and operate any potential IPR issues as they happen; CNC and the University of Coimbra have a highly-qualified Contract and Research Commercialisation team.

Table 2.b Main results with exploitation potential (see 3.2.6).

Results	Exploitation target	Expected Impact	Months After*	Partner(s)**
New models of disease	Pharmaceutical companies	Use new models of neuropsychiatric disorders for testing potential therapies	36	CNC, BMI-EPFL, ICL
Identification of new therapeutic targets	Pharmaceutical companies	Drug design toward newly identified therapeutic targets	36	All partners
Mesoscopic analysis of cortical dynamics	Pharmaceutical companies	Use of this method to evaluate efficacy of therapies in animal models of disease	36	ICL
Advances in microscopy techniques and image analysis methods	Optics industry	Development of new optical systems	36	IINS-CNRS

*=Timing after project end (months); ** Partner(s) responsible for exploitation

2.4 Quality of the proposed measures to communicate the project activities to different target audiences

- **Communication and public engagement strategy** Syn2Psy activities and results will be communicated to multiple audiences, including clinicians, patients and their families and the general public (Table 2.c). The communication plan is directed to: 1) raise awareness of the importance of research on synapse biology and neuropsychiatric disorders; 2) produce data that can inform regarding priorities to improve health and well-being in EU; 3) promote publication in open format; and 4) promote the possibilities offered by the MSCA. Syn2Psy will have access to the media (radio, WebTV, website, newsletters) of beneficiaries and partners organisations. We are very inspired by the possibilities offered through science writing and art collaborations, by Marionet. The communication officer at the CNC will help in the implementation and evaluation of the communication plan. All ESRs will have their own opportunity to orchestrate their communication activities; the D&C committee will monitor the progress of communication activities, approved by the supervisory board.

Table 2.c Communication and public engagement strategy.

Syn2Psy project identity	[mo1-6] The project identity will be created to reinforce the project's image and to ensure transdisciplinary coherence amongst all project communication channels.
Syn2Psy website	[starting at mo1] will be a central dissemination tool for the network (password protected for internal use), and one main open portal (with Open Access) for different audiences (scientific community, hospital, patient associations and families) and the general public. The website will provide information on the Syn2Psy network, the work in progress (results, presentations, publications, social media), e-news, awards, *press releases*, upcoming meetings and training activities, articles about neuropsychiatric disorders produced in collaboration with PIN, among others. We will distribute the web address to research institutions and universities and other relevant organisations in Europe to assure visibility.
Media activities	[starting at mo6] We will produce video-clips with research contribution of the network. We will embed a YouTube multimedia channel in the Syn2Psy website where video-clips, podcasts, and interviews will be available; this action will be carried out under CNC coordination. The beneficiaries and partners organisations have relevant experience with local and national media. All ESRs will be encouraged to participate actively in media activities that will deliver project messages with an important impact on the society.
Social networks	[starting at mo6] ESRs will create an account in the major social networks, such as Twitter; [starting at mo9], Syn2Psy will have a public blog in which all ESRs will write at least one blog post per year about their investigation, career progress or other experiences in the project. This activity will be carried out under CNC coordination.
Open dissemination sessions	[starting at mo9, every year] Selected students from high-schools and universities will be invited by each partner to spend one day in the lab. ESRs will present and illustrate specific Syn2Psy activities and laboratory experiments. This activity can be linked to other national initiatives (e.g. CNC collaborates regularly with Summer with Ciência).

Open science discussions	[starting at mo18] ESRs will participate or organize open science discussions, with the aim to demystify scientific research and incline the general public, including patients, towards research on neuropsychiatric disorders.
Scholars, Undergraduate students, Society	[mo9, every year] **summer with science**: Most participating Universities and Research Institutions run regular Summer Science Programmes during which undergraduate students receive a first-hand research and training experience in the lab. Selected students form high schools and universities will be invited by each partner to spend one day in the lab. ESRs will present and illustrate specific Syn2Psy activities and laboratory experiments. This activity can be linked to other national initiatives (e.g. CNC collaborates regularly with Ciência Viva). [mo12-42] **Collaboration with local schools and science centers**: ESRs and supervisors will organize sessions in the local schools and science centers dedicated to increase public awareness of the progress and benefits of brain research from the basic science to pharma-industry, to medical providers and to society. CNC collaborates regularly with the science museum of university of Coimbra, science Center exploratório (Coimbra), the science center Rómulo de Carvalho (Coimbra), and instituto para a educação e cidadania (Cantanhede).
PIN, patient organisations/public	ESRs will work with PIN with the objective of producing proper science contents to medical/patient community and society, beginning from young publics. The documents will become available at Syn2Psy and PIN websites.
Theatre and performance	ESRs will write the script and perform a play under the guidance of Marionet, on the activities of Syn2Psy. The play will be performed in Syn2Psy final meeting but also in other dissemination events, such as the European Researchers Night (ERN) and Brain Awareness Week (BAW). A Portuguese version of the script (to be played at the EIN and BAW) will be produced by the CNC science communication office, in collaboration with students of the CNC PhD programme.
Syn2Psy day	In the final year of Syn2Psy each ESR will organize a one-day workshop in their host institution, integrated in the Brain Awareness Week. This workshop should involve local patients associations and schools.

3. Quality and efficiency of the implementation

3.1 Coherence and effectiveness of the work plan

- **Fellow's individual projects**

Table 3.1 d Individual Research Projects [Host supervisors in bold letters at "Secondments" line]

Fellow **ESR1**	Host institution **CNC** Host supervisor **AL Carvalho**	PhD enrolment **YES**	Start date **Month 6**	Duration **36 months**	**DS1**; **D1-D4**
Cognitive disorders as defects in synaptic function: insight from human mutations in the CACNG2 gene encoding Stargazin; CNC + ICL + Eurotrials; **WP1**					
Objectives: Alterations in neuroplasticity and glutamatergic hypofunction are prominent features of cognitive disorders like intellectual disability (ID) and schizophrenia. One working model for these disorders is based on the disruption of normal homeostatic adaptation of neuronal circuits to changes in the environment, as a consequence of impaired synapse function. The *CACNG2* gene encodes the synaptic protein stargazin, an AMPA receptor auxiliary protein for which we have recently uncovered a role in homeostatic synaptic plasticity mechanisms. The recent finding of ID- and schizophrenia-associated mutations in the stargazin gene prompts the analysis of their functional impact. We have generated knock-in mice expressing a stargazin ID variant and propose to generate mice expressing a schizophrenia-associated mutant form of Stargazin (Stg-KI). We will perform morphological, electrophysiogical and behavioural analyses of Stg-KI mice, and image neural circuit dynamics with a voltage-sensitive fluorescent protein. These analyses will allow identifying a neural signature of illness associated with stargazin mutations, and compare shared and distinct defects triggered by stargazin variants associated with ID and schizophrenia. Guided by a specific hypothesis, we will test the potential therapeutic effects of an antidepressant drug using the knock-in models of disease.					
Expected results: Using knock-in mouse lines expressing the ID- and schizophrenia-associated mutant forms of stargazin (Stg-KI), we propose to use a multi-level approach to characterize shared and distinct in vivo neuronal effects of disease-associated stargazin mutations. **Task 1.1 In vivo evaluation of the effect of ID- and schizophrenia associated CACNG2 mutations**. Given our preliminary data implicating stargazin in regulating dendritic arborisation and synapse density, we propose to analyse cellular and spine morphology in vivo in the hippocampus and medial prefrontal cortex (mPFC) of Stg-KI mice, and expect to unravel whether mutations in stargazin have a neuromorphological effect. Severe behavioural deficits in cognitive disorders have been hypothesized to arise from alterations in the cellular balance of excitation and inhibition (E/I balance) within neural microcircuitry. Analysis of the functional effect of stargazin mutations so far has pointed to deregulated AMPA receptor traffic and synaptic plasticity. Thus, we propose to study hippocampal and mPFC function in Stg-KI mice by performing field and whole-cell electrophysiology recordings. Neuronal excitability, E/I balance, long-term potentiation and long-term depression will be assessed. We expect to pinpoint modifications in synaptic properties associated with the different stargazin mutations. **Task 1.2 Behaviour and cortical dynamics in Stg-KI mice**. Given the importance of stargazin and plasticity mechanisms to brain function, it is possible that mutations in stargazin may have pleiotropic effects, contributing not only to ID- and Schizophrenia-like phenotypes but also conferring risk to other psychiatric disorders. Therefore, comprehensive assessment of neurobiological outcomes in Stg-KI mice will be performed					

using a battery of behaviour tests to fully characterize these animals. We will analyse emotion/affective behaviour, as well as perform cognitive/memory tests. Given the high expression levels of stargazin in the cortex, we will use a voltage-sensitive fluorescent protein to image cortical neural circuit dynamics in vivo in Stg-KI mice, and unravel alterations in cortical dynamics associated with stargazin mutations. **Task 1.3 Stargazin-directed therapy: tianeptine**. Our preliminary data indicate that stargazin mutations render the protein dysfunctional, affecting AMPAR synaptic levels. We therefore searched for drugs that could rescue stargazin's function in neurons, namely normalize AMPAR. Tianeptine acts as a memory enhancer and antidepressant drug, which modulates the surface diffusion of AMPAR through a mechanism that favours the binding of stargazin to PDZ scaffold proteins, trapping AMPAR at synaptic sites. Therefore, here we will test whether tianeptine can rescue the behavioural, morphological and functional phenotypes found in Stg-KI mice.

Planned secondment(s): **ICL**: Imaging cortical dynamics with a voltage-sensitive fluorescent protein (Thomas Knöpfel, 4 months); **Eurotrials**: Medical writing, clinical trials development and regulatory affairs (3 months).

Fellow	Host institution BMI-EPFL	PhD enrolment	Start date	Duration	**DS2**; **D1-D4**
ESR2	Host supervisor **Carmen Sandi**	**YES**	**Month 6**	**36 months**	

Role of mitofusins in neurodevelopmental trajectories of psychopathology;
BMI-EPFL + IINS-CNRS + UEDIN; **WP1**

Objectives: Emerging evidence points to a critical role of mitochondrial dysfunctions in the pathophysiology of psychiatric disorders, including anxiety and depression, but the mechanisms mediating mitochondrial effects remain understudied. Recent findings highlight reduced brain expression of the mitochondrial GTPase Mitofusins 1 and 2 (Mfn1 and Mfn2; molecules critically involved in mitochondrial fusion and other functions) in depression and stress-related psychopathologies. The nucleus accumbens is a critical hub for motivated behavior and its function is altered in anxiety and depression. This project will use mouse genetics and gene delivery to examine the contribution of Mfn deficiency in specific accumbal medium spiny neurons for the production of motivated behaviors related to anxiety and depression. The final goal is to identify the circuitry engaged in dysfunctional behaviors produced by impaired mitochondrial dynamics in specific nucleus accumbens neurons and uncover relevant treatment targets for neuropsychiatric alterations.

Expected results: **Task 2.1 identification of nucleus accumbens efferent targets for psychopathological impact of Mfn loss of function.** Fiber photometry and calcium imaging through mini-endoscopes will be applied in vivo to identify target brain regions involved in the impact of Mfns loss of function and psychopathological alterations (i.e., depression-like behaviors, dysfunctions in social behavior). To this end, we will use Mfn2loxp/loxp mice and Mfn1loxp/loxp mice combined infusion of adeno-associated virus (AAV) expressing Cre for specific accumbal cell types. Given the role of accumbal-ventral pallidum projections in the regulation of motivated behaviors, we will focus on this projection to disentangle the role of dopamine 1 (D1) and dopamine 2 (D2) receptor-containing neurons in the regulation of the different behaviors under study. These experiments will be followed up by optogenetic approaches to establish the causal involvement of specific projection neurons. Based on the preliminary evidence, we predict that reduced Mfn1 or Mn2 in the NAc will enhance depression-related behavior in a cell type specific manner. Although unknown, we hypothesize the involvement of accumbal-ventral pallidum projections in these effects. **Task 2.2 Excitation/inhibition (E/I) balance in target areas following accumbal Mfn loss of function in specific cell types.** The impact of Mfn deficiency in specific cell types for E/I balance will be monitored *in vivo* and its synaptic consequences *in vitro*. These experiments will be complemented with molecular analyses of the expression level of genes and proteins involved in excitation/inhibition, including neuroligins and other synaptic markers. **Task 2.3 Impact of accumbal Mfn deficiency for the regulation of single NMDA receptor dynamics.** Preliminary work indicates that accumbal Mfn2 deficiency leads to a reduction in medium spiny neuron dendritic complexity and reduced excitatory inputs. Here, we aim at understanding how Mfn2 loss of function in specific cell types may affect NMDA receptor dynamics. To this end, we will track NMDAR subtypes at the surface of accumbal medium spiny neurons in accumbal acute brain slices using single nanoparticle (Quantum Dot) tracking. Subsequently, we will examine the implication of specific findings by manipulating NMDA receptor surface dynamics in Mfn2 deficient mice in accumbal D1 or D2 receptor-containing neurons and assess the impact of this manipulation in neurotransmission and psychopathological (i.e., depression-like and dysfunctional social) behaviors.

Planned secondment(s): **IINS-CNRS**: Measure dynamics of synaptic NMDA receptors in the nucleus accumbens following Mfn2 loss of function in D1- or D2-mice (Laurent Groc, 3 months); **CIP-UEDIN:** Investigate the impact of Mfn2 deficiency in accumbal neuronal subtypes on protein translation using TRAP (Emily Osterweil , 4 months).

Felow	Host institution CNC	PhD enrolment	Start date	Duration	**DS3**; **D1-4**
ESR3	Host supervisor **João Peça**	**YES**	**Month 6**	**36 months**	

Production and testing of human-derived neurons and brain organoids: advanced model probing in neurodevelopmental disorders; CNC+ CIP-UEDIN + Lundbeck + CHUC; **WP1**

Objectives: Autism and associated neurodevelopmental disabilities are chronic disorders that afflict 1 in 68 children. Not only there is no cure for these conditions but there is also an overall lack of knowledge regarding the precise neurobiological underpinnings leading to synaptic and cellular alterations in human tissue. To better understand these disorders, directly accessing neural cells to probe cellular and circuit dysfunctions is both critical and challenging. Current strategies suffer from drawbacks that include heterogeneity in reprogrammed induced pluripotent stem cells and the limited access to biopsies or post-mortem brain samples. Importantly, however, recent evidences have shown that neuronal populations can be differentiated from specific postnatal niches. Dental stem cells are a particularly relevant population since they derive from the neural crest and have been shown to readily differentiate into neurons. As such, there is great potential for the application of dental stem cells in the development of human culture models and cerebral organoids that can provide a breakthrough in understanding disease mechanism.

This project aims to create patient-derived neurons to be used in the understanding of the fundamental characteristics of neurodevelopmental disorders and to identify the neurobiological changes caused by mutations present in autism patients. A secondary objective is to probe the potential for organoid development from dental stem cells to follow the impact of patient associated mutations during cerebral formation. The objective of this work is to study what are the synaptic, neuronal morphology and electrophysiological properties changes that occur in neurons from individuals with defined neurodevelopmental disorders.
Brain organoids from dental stem cells offer considerable potential impact as biomedical and biotechnological platform with potential for translational research with personalized medical applications. The usage of dental derived neurons displays potential to dampen the need for animal studies, reduce and contain costs associated with drug development and may provide personalized testing devices with minimally invasive strategies.

Expected results: **Task 3.1. Enlarge the dental stem cell biobank from autism patients and from healthy controls:** Since there is detailed clinical and genetic information available from several of the patients consulted in the specialized neurodevelopmental and autism unit (UNDA) at the Paediatric Hospital of Coimbra, we have prioritized tooth collection (deciduous teeth – "milk teeth" and third molars – "wisdom teeth") from patients with known genetic alterations. Stem cells are obtained from the root apical papillae or from the dental pulp of impacted third molars with incomplete rhizogenesis which are extracted when there is therapeutic indication. Age- and gender-matched controls are also recruited in our study. This work has been approved by the Ethical Committee of the Faculty of Medicine, University of Coimbra. Upon joining the project, the ESR will participate in tissue processing, cellular expansion and storage of new samples as they become available. **Task 3.2. Characterization of patient specific stem cells**: Dental stem cells from the apical papilla (SCAPs) will be expanded and characterized by flow cytometry, using cell surface markers and further assessed for the expression of pluripotency markers by qRT-PCR and immunocytochemistry. The ESR will be actively engaged with a particular subset of patients and perform characterization work to determine state of differentiation, which will later inform on the outcome from the differentiation protocols. **Task 3.3. Develop neuronal cultures from dental stem cells to determine electrophysiological** and synaptic properties in patient cells: We will coax the differentiation of the dental stem cells into neuronal cultures and perform characterization work in vitro. This will include staining for synaptic markers, assessing neuronal morphology and electrophysiology characterization of basic membrane properties as well as recording excitatory and inhibitory currents. The ESR will be involved in the characterization of neuronal cultures from specific patients and corresponding controls. **Task 3.4. Probe neurophysiological, morphological and network activity properties in patient derived brain organoids:** There is currently limited information of the neuronal properties in patient derived brain organoids. In conjunction with aim 3, we will attempt to create brain organoids from dental stem cells to study synaptic properties via whole-cell patch clamp to determine spontaneous and network activity. We will specifically probe for inhibitory and excitatory neuronal activity and determine if there are changes in E/I ratio in patient-derived organoids. We will also evaluate morphology using two-photon microscopy to reconstruct neuronal morphology and assess network dynamics in live tissue. With this characterization, we will determine patient-specific neuronal phenotypes. Due to the ambitious nature of this aim, if the ESR encounters problems in generating organoids from dental stem cells, there is a contingency plan to generate organoids via conventional methods by first producing iPSCs. **Task 3.5. Proof-of-concept applications of brain organoids as a biomedical platform to test drugs:** As a proof of principle, aimed at future large-scale pharmacological manipulation, we will treat organoids from patients and controls with drugs (specifically related to the patient underlying condition) to determine their effects on organoid formation, network activity and neuronal morphology.
The aggregate knowledge produced in this research project will give new insight into the basic disease mechanism in genetically defined cases of autism and produce a new framework to test drug efficacy in advanced disease models.

Planned secondment(s): CIP-UEDIN: Characterisation of electrophysiological properties in patient-derived brain organoids in the context of mGluR signalling modulation (Peter Kind/Emily Osterweil, third year, 3months); **Lundbeck**: Characterization of interneurons in brain organoids (Niels Plath, 3 months); **CHUC**: exposure to clinical research (Guiomar Oliveira, 3 months).

Fellow	Host institution **IINS-CNRS**	PhD enrolment	Start date	Duration	**DS4**; **D1-D4**
ESR4	Host supervisor **Daniel Choquet**	**YES**	**Month 6**	**27.6 months**	

Linking autism related mutations in Shank3 over synaptic, network and behaviour defects; IINS-CNRS + UEDIN + Eurotrials; **WP2**

Objectives: Alterations in glutamatergic synaptic transmission are a prominent feature of numerous forms of ASD. In particular, numerous mutations in synaptic protein genes have been identified as risk factors for ASD with almost half of ASD being now recognized as synaptic diseases. The majority of these synaptic protein mutations concerns proteins that molecularly organize the synapse such as trans-synaptic proteins or scaffolding proteins. Among these, *SHANK3* has been highlighted as responsible for more than 1% of ASD cases. Despite numerous studies on *Shank3* mutant mice, surprisingly little is known yet on the mechanistic links between the molecular impact of *Shank3* mutations on synapse organization and the effect of such dis-organization on circuit and behavioural phenotypes. This originates in large part from our lack of knowledge of Shank3 precise role in organizing synapses and controlling their function. In this project, we will build on our unique joint expertise on high-resolution imaging of synapse organization, analysis of synapse function, circuit properties and behavioural phenotyping to unravel the multiscale consequences of *Shank3* mutations. We will perform a nanoscale dynamic analysis of glutamatergic synapse organization in hippocampal neurons in primary culture and organotypic slices, in various models of *Shank3* related ASD, such as models of Phelan-McDermid syndrome through *Shank3* KD or KO mice, and in human patients derived IPS cells. We will correlate these studies to analysis of circuit properties at the level of the

hippocampus-medial pre-frontal cortex connections (Hipp-mPFC), which have been involved in behavioural learning, and also to spatial working memory, and in which Shank3 expression will be specifically affected. These analyses will allow linking synapse organization to behavioural defects of *Shank3* mutation mediated ASD. We will test the potential therapeutic effects of new molecules that can regulate glutamate receptor trafficking in the *Shank3* KO model of disease.

Expected results: Using a KO mouse line of *Shank3*, or expression of a *Shank3* shRNA and patient derived IPS cells altered in Shank3 expression, we propose to use a multi-scale approach to link the nanoscale synapse disorganization to synapse function, circuit properties and behaviour in models of ASD. **Task 4.1 Impact of Shank3 mutations in excitatory synapse nanoscale dynamic organization:** The two central objectives of this task are 1) to depict the nanoscale molecular organization and dynamic of major excitatory synapse components (AMPA and NMDA receptors, scaffold and adhesion proteins such as PSD95, SynGap, neuroligins) at the basal state and when a specific form of ASD (Phelan McDermid syndrome) is triggered by decreasing *Shank3* level of expression. 2) To identify the difference in induction of long term plasticity events on AMPAR organization and synaptic response on these specific ASD types. Those questions will be approached by using a combination of innovative super-resolution imaging methods (PALM, 2-color 3D Storm, UPaint, to map AMPAR and scaffolding proteins re-organization and mobility, coupled to electrophysiology). These techniques will be applied both to neuronal cell cultures (primary neurons and patient derived IPS cells) and organotypic brain slices. To link modification of synapse organization and synaptic physiology, the effect of the various *Shank3* mutations on synaptic currents will be recorded with electrophysiology on cell culture. **Task 4.2 Impact of Shank3 mutations in hippocampal-medial prefrontal cortex circuit function:** To test for the impact of *Shank3* mutations at synaptic projections that have been involved in behavioural learning, we will use a double viral strategy (CAV-Cre/AAV) allowing the expression of both Shank3 shRNA (or control constructs) and of channel-rhodopsins (floxed constructs) in neurons from the ventral part of the hippocampus (vHPC) projecting to the mPFC. Then, synaptic efficacy and plasticity will be tested in vHPC acute slices by recording labelled and un-labelled neuronal cells, and also in mPFC slices by light stimulating axonal projections from shRNA/ChR2 and control/ChR2 injected mice. **Task 4.3 Impact of Shank3 mutations in behavioural tasks:** The consequences of these defects will be tested using spatial working memory tests such as Delayed Spatial Alternation (DSA) tasks that are currently used in the laboratory, and that are highly depending in the functionality of vHPC-mPFC afferents. To restrict genetic modifications to these specific afferents, the same CAV-cre/AAV) strategy will be used. **Task 4.4 Developing new approaches to correct Shank3 mutation induced defects:** The defects in synaptic transmission secondary to *Shank3* mutations converge to a loss in AMPA type receptors from the synapse. We are developing protein ligands that have the potential to increase AMPA receptor stabilization by modulation the TARP-PSD95 interaction. We will evaluate whether increased AMPA receptor stabilization can restore normal synaptic transmission and plasticity, and eventually behaviour, in *Shank3* mutant models.

Planned secondment(s): **UEDIN:** Testing gene therapy for Fragile X Syndrome (Emily Osterweil, 2.5 months); **Eurotrials**: Medical writing, clinical trials development and regulatory affairs (2 months).

Fellow	Host institution **ICL**	PhD enrolment	Start date	Duration	**DS5**; **D1-D4**
ESR5	Host supervisor **Thomas Knöpfel**	**YES**	**Month 6**	**36 months**	

Mesoscopic monitoring and analysis of cortical excitation/inhibition balance in an animal model of synaptic dysfunction; ICL + IBPS-CNRS + CHUC; **WP2**

Objectives: A tight balance of excitatory and inhibitory synaptic inputs (E/I balance) to neurons and circuits is crucial for brain development and function. Disturbed E/I balance is implicated in conditions such as ASD with diverse behavioural abnormalities including stereotyped behaviours, and atypical social and cognitive abilities. Sensitivity in multiple sensory domains - involved in refinement of motor skills and social behaviours - is also affected. Shank is a family of scaffold proteins localised to the postsynaptic sites of excitatory synapses, and transgenic mice with a deletion of the *Shank3* gene display ASD-like behaviours including social interaction deficits and repetitive grooming. How the E/I balance at resting awake state is affected at the population level by the *Shank* mutation to cause these behavioural aberrations is unclear, and how sensory processing is affected is also unknown. Additionally, how neuromodulatory mechanisms (e.g. 5HT) are affected by such postsynaptic dysfunction is also unclear, and would have novel therapeutic potentials. Monitoring E/I balance at the population level (beyond a selected few cells simultaneously) had been technically challenging due to both spatial coverage of monitoring and specified cell identity (e.g. GABAergic populations). Overcoming this technical limitation, voltage sensitive fluorescent proteins (VSFPs) are genetically encoded voltage indicators that can be selectively expressed in identified cell classes for direct neuronal activity monitoring. Here, we will perform optical voltage imaging of *Shank3B* KO mice with restricted VSFP expression in either pyramidal or GABAergic neuronal population to characterise how dysfunctional synaptic communication disturbs E/I balance at the population level in vivo, both during stimulus-free spontaneous activity and during sensory processing of somatosensory/whisker and/or visual stimulation. We will then explore how the neuromodulator 5HT affects this anticipated E/I balance disturbance.

Expected results: We will use the following combinations of transgenic animals expressing the voltage indicator chimeric VSFP Butterfly (chiVSFP) in identified cell classes, and perform mesoscopic optical voltage imaging to achieve large-area population monitoring of E/I balance in *Shank3*-deficient mice. By comparing the neuronal dynamic properties from these *Shank3*-deficient mice with our existing data from the control indicator-expressing mice, we can deduce the influence of postsynaptic dysfunction on cortical E/I balance.

-**Shank3B-/-**; **CaMK2A-tTA**; **chiVSFP** chiVSFP expressed in pyramidal neurons across all cortical layers, with *Shank3B* KO

-**Shank3B-/-; VGAT-Cre;ztTA; chiVSFP** chiVSFP expressed in GABAergic neurons across all cortical layers, with *Shank3B* KO

-[*Control*] **CaMK2A-tTA;chiVSFP** chiVSFP expressed in pyramidal neurons across all cortical layers
-[*Control*] **VGAT-Cre;ztTA;chiVSFP** chiVSFP expressed in GABAergic neurons across all cortical layers
We will perform head-fixed mesoscopic voltage imaging, where large cortical areas across both hemispheres will be dorsally monitored simultaneously during stimulus-free spontaneous activity and stimulus-evoked sensory processing (Task 5.1). We will also apply 5HT2AR ant/agonists in combination with voltage imaging and observe the neuromodulatory effects on E/I balance during sensory processing (Task 5.2). **Task 5.1 In vivo monitoring of cortical E/I balance:** We will first monitor stimulus-free spontaneous activity for both cell types. Sensory stimulation (somatosensory/whisker and visual) will then be applied during optical voltage imaging, and the response dynamics will be characterised. Our preliminary data indicate that sensory evoked activity propagates across large cortical space between anatomically defined cortical regions in different patterns between the excitatory and inhibitory networks of the control indicator mice. In *Shank3*-deficient mice, we expect to observe different dynamics in both local sensory processing and neuronal activity spread for both cell types, and we also anticipate altered E/I balance relationships. In addition, we will characterise the relationship between spontaneous activity prior to stimulus onset and sensory stimulus evoked activity for both cell types. Temporal binding deficit (with abnormal gamma activity) has been speculated in ASD, thus we also expect to observe different regional oscillatory properties in the *Shank3*-deficient mice compared to our existing control data. **Task 5.2 5HT neuromodulatory effects on E/I balance during sensory processing**: Neuromodulatory mechanisms, such as 5HT, is also expected to be affected by aberrant postsynaptic functions, but how this is affected per se and in the context of E/I balance are both unknown. We will explore this by applying 5HT2A receptor ant/agonists to these Shank3-deficient mice both during monitoring of stimulus-free spontaneous activity and stimulus-evoked sensory processing and findings are expected to have novel therapeutic potentials.

Planned secondment(s): **IBPS-CNRS**: Development of behavioural tests that can then be performed during *in vivo* optical imaging (Catalina Betancur, first year, 6 months); **CHUC**: exposure to clinical research (Guiomar Oliveira, 3 months)

Fellow	Host institution **IINS-CNRS**	PhD enrolment	Start date	Duration	**DS6**; **D1-D4**
ESR6	Host supervisor **Laurent Groc**	**YES**	**Month 6**	**36 months**	

Physiopathological regulation of single NMDA receptor dynamics in psychosis; IINS-CNRS + CNC + Lundbeck; **WP2**

Objectives: Most of the maturation and plasticity of glutamatergic synapses rely on the postsynaptic activation of N-Methyl-D-Aspartate receptor (NMDAR). In addition, a dysregulation of the NMDAR signalling has been proposed to play a direct role in the emergence of psychotic disorders, such as schizophrenia. Thus, understanding the physiopathological regulation of NMDAR signalling has captured a lot of attention and major advances have been made in recent years. Among these, the *set-in-stone* dogma that NMDAR are stable in synapses has been shattered, opening a new conceptual framework. These seminal studies unveiled that NMDAR surface trafficking is regulated by molecular pathways located in the intracellular compartment, within the plasma membrane, as well as in the extracellular environment. However, our current understanding comes from *in vitro* investigations using mostly primary cultures of neurons. Central questions related to the complexity and regulation of NMDAR surface distribution and dynamics thus urgently need to be tackled in intact brain tissue. This represents a particularly obvious challenge since the interplay between the extracellular environment and NMDAR dynamics now needs to be explored. Accessing this process in physiology will also allow us to directly address one of the hypotheses for schizophrenia, proposing that the NMDAR transmission deficit on pyramidal and/or GABAergic interneurons is due to an altered extracellular environment, such as the reduced extracellular matrix and perineuronal net observed in schizophrenic postmortem brains. Thus, understanding how membrane NMDAR are organized and trafficked in principal cells and interneurons in health and schizophrenia will surely break our current frontier knowledge. **The main objective of this proposal is to measure NMDAR surface dynamics in intact tissue and define the regulatory properties of the extracellular environment on this cellular pathway in health and models of psychosis. We hypothesize that the spatio-temporal dynamics of NMDAR and extracellular environment components are intimately entangled and play a pivotal role both in physiological conditions and schizophrenic brains.**

Expected results: Understanding this complex dynamic interplay requires first dedicated investigation strategies. An ultimate strategy for imaging and understanding biological phenomena in living cells or cell assemblies relies on single-molecule microscopy since it has the advantage to extract and identify the molecular behaviour of receptor sub-populations while retrieving molecule localizations with sub-wavelength precision. Based on our past experience and preliminary data, we are now in a unique position to track NMDAR subtypes at the surface of pyramidal cells and interneurons in hippocampal acute brain slices using single nanoparticle (Quantum Dot) tracking. To complement this first approach to study single NMDAR dynamics, we will also apply super-resolution approaches (uPAINT and STORM) in order to provide the first high-density quantitative map of surface NMDAR subtypes in pyramidal cells and interneurons from brain slices. With these, we will study the physiological impact of the extracellular environment on the NMDAR dynamic, both in pyramidal cells and interneurons. Then, we will use rodent models of schizophrenia to determine the alteration of NMDAR surface distribution, dynamics and transmission in this disorder. Finally, we will manipulate the NMDAR surface dynamics in schizophrenia models in order to restore the proper transmission and prevent the behavioural deficits

Planned secondment(s): **CNC**: Performing experiments using genetically-modified animals (Ana Luísa Carvalho, 7 months); **Lundbeck**: Characterising excitatory/inhibitory balance and gamma osscilations in hippocampal networks (Kjartan Herrik, 3 months).

Fellow	Host institution **CNC**	PhD enrolment	Start date	Duration	**DS7**; **D1-D4**
ESR7	Host supervisor **Carlos Duarte**	**YES**	**Month 6**	**36 months**	

FMRP regulation of synapse dynamics; CNC + ICL + Lundbeck; **WP2**

Objectives: Fragile X syndrome is caused by the loss of expression of the fragile X mental retardation protein (FMRP), an

mRNA binding protein. The absence of FMRP leads to translational abnormalities, which might underlie the cognitive dysfunctions observed in intellectual disability. mRNA profiling studies identified over a hundred distinct mRNAs that are associated with FMRP, including many synaptic proteins. Additional studies demonstrated that FMRP exerts translational control of synaptic proteins such as PSD95, CaMKIIα and NMDAR subunits, suggesting the importance of this protein in synapse regulation. However, most studies have focused on the role of FMRP in synaptic plasticity. The aim of this project is to investigate how FMRP regulates synapse dynamics. We will perform in vivo analysis of presynaptic bouton assembly, study possible interactions with the exocytotic machinery and their functional outcomes, and real-time imaging of AMPA and NMDA receptor dynamics to understand how FMRP-deficient synapses lead to cognitive dysfunction. In additional studies we will characterize the structural alterations in interneuron inhibitory synapses.

Expected results: **Task 7.1 In vivo evaluation of presynaptic bouton formation and dynamics in *Fmr1* KO mice**: FMRP has been shown to transport specific mRNAs to neuronal subdomains controlling growth cone dynamics, spine morphology as well as other neuronal development processes. FMRP has been better studied in the context of the post-synapse but it remains to be fully elucidated if FMRP regulates presynaptic bouton formation. Interestingly we have recently shown that local protein synthesis is required for presynaptic differentiation, suggesting that mRNA binding proteins might have a role in this process. In this task we aim to determine if presynaptic differentiation is affected in neurons derived from *Fmr1* KO mice. We will perform a detailed characterization of presynaptic formation in hippocampal neurons (cultured in microfluidic chambers) by analysing the number and morphology of pre-synapses. Synaptic vesicle clustering and active zone formation will be examined and compared to wild-type animals. Next, using two-photon imaging we will analyse in vivo presynaptic bouton formation in *Fmr1* KO mice. This will allow determining the role of FMRP in presynaptic bouton assembly and dynamics. **Task 7.2 Study the interaction of FMRP with exocytotic proteins and in regulating pool release and recovery**: FMRP affects presynaptic short- and long-term synaptic plasticity, modulates neurotransmitter release by acting on N-type calcium channels and BK channels, and affects release probability and vesicle dynamics. However, a direct effect of FMRP on the release machinery and on proteins involved in vesicle priming and pool replenishment has not been investigated. Therefore, we will study if FMRP can directly interact with exocytotic proteins, namely SNAREs, Munc13, Munc18, CAPS, Doc2B, synaptotagmins and complexin. We will also investigate if the absence of FMRP compromises the size of vesicle pools by performing hypertonic sucrose applications in neurons and calcium uncaging in chromaffin cells. We will also evaluate pool release and refilling kinetics. These studies will clarify whether FMRP can change neurotransmitter release by directly affecting vesicle release and/or pool refilling and identify possible target proteins. **Task 7.3 Analyse AMPA and NMDA receptor dynamics in Fmr1 KO mice**: *Fmr1* KO mice showed reduced levels of GluA1 AMPA receptor subunits in synaptosomal fractions isolated from the hippocampus, and the levels of the receptor subunit were normalized following administration of a TrkB receptor agonist. However, whether the dynamics of the plasma membrane associated GluA1-containing AMPA receptors is affected in hippocampal neurons of *Fmr1* KO mice is not known. Furthermore, it remains to be investigated whether BDNF-TrkB signalling changes the dynamics of AMPA receptors at synaptic and extrasynaptic sites. This will be investigated in this proposal, together with a detailed analysis of the signalling pathways involved, using real-time quantum dot tracking of single receptors. The hippocampal PSD of *Fmr1* KO mice also shows changes in the total amount of GluN1 and GluN2B subunits of the NMDAR, as well as alterations in several scaffold proteins. This suggests that the surface expression of NMDAR may also be changed in *Fmr1* KO mice. However, the alterations in the surface dynamics of NMDAR in KO mice have not been investigated. This question will be addressed in the proposal using real-time quantum dot tracking of single receptors. In these studies, we will also evaluate the effects of BDNF stimulation on the changes in surface dynamics of NMDAR in cultured hippocampal neurons from *Fmr1* KO mice. **Task 7.4 Alterations in interneuron inhibitory synapses in *Fmr1* KO mice:** Recent studies reported an impairment of GABAergic inhibition in the hippocampus of *Fmr1 KO* mice. This has been attributed to alterations in the surface expression of $GABA_A$ receptors, but whether morphological alterations also take place has not been investigated. To address this question, organotypic slice cultures will be prepared from WT and *Fmr1* KO mice, and GABAergic synapses will be identified by transfection with anti-gephyrin intrabodies, which allow visualizing inhibitory synapses in real-time, in living neurons, with high fidelity and without affecting neuronal function; interneurons will be labelled by immunocytochemistry, with antibodies against parvalbumin and somatostatin. The shape, conformation, size and abundance of interneuron inhibitory synapses will be compared in WT and *Fmr1* KO mice, and the alterations resulting from neuronal activity will also be investigated.

Planned secondment(s): **Lundbeck:** Alterations in interneuron inhibitory synapses in *Fmr1* KO mice (Niels Plath, second year, 1 month); **ICL**: *In vivo* imaging of presynaptic bouton dynamics in *Fmr1* KO mice (Vincenzo De Paola, third year, 9 months)

Fellow	Host institution: **ICL**	PhD enrolment	Start date	Duration	**DS8**; **D1-D4**
ESR8	Host supervisor: **V De Paola**	**YES**	**Month 6**	**36 months**	

Illuminating the mechanisms of synaptic and neural network dysfunction in a new *in vivo* model of Down's syndrome; ICL + IINS-CNRS + CHUC + Lundbeck; **WP2**

Objectives: Down's syndrome (DS) is a genetic disorder caused by trisomy of chromosome (Chr) 21 (Ts21). It is the most frequent cause of genetic intellectual disability, but the underlying synaptic and neural network mechanisms remain poorly understood. Most studies looking into the mechanisms of DS have been performed using mouse models. However, these models can only partially recapitulate the chromosomal abnormality present in DS patients. First, rodents do not have a Chr 21 and the > 200 genes contained in the human Chr21 are distributed into 3 sections of the mouse genome. Therefore, different transgenic mouse models are partially trisomic for a distinct set of genes present in the human Chr 21. In addition, there is evidence that also other chromosomes contribute to the disease. Because of these limitations, human induced

pluripotent stem cells (iPSCs) hold great promise for modelling neurodevelopmental brain disorders such as DS.
We have recently developed a radically new paradigm to model the synaptic and functional network phenotypes of DS, by transplanting human iPSC-derived neurons from healthy and DS donors in the adult mouse brain (in collaboration with Dr. Rick Livesey, Cambridge University). This approach combined with longitudinal structural and functional multiphoton imaging allowed us to study human neuron synaptic and calcium dynamics *in vivo* for the first time (Real et *al*., under review). We discovered that synapses are denser and more stable on Ts21 neurons, as well as a defect in the ability to build functional neural networks *in vivo* (Real et *al*., unpublished). The objectives of this project are, therefore, to 1) Dissect the mechanisms of the increased synaptic density in DS, and 2) Dissect the mechanisms of the functional network defect in DS.

Expected results: This project is expected to yield insights into the mechanisms controlling synaptic organisation and plasticity and lead to a deeper understanding of its regulation in DS. An important unresolved issue is how the synaptic phenotypes arise. Do they result from aberrant rates of synapse formation, elimination or both? And where are they initiated: in the pre- or post-synaptic side of the synapse or both? The standard approach in the field to detect synaptic defects (i.e. post-mortem studies of spine synapses), does not allow to address these questions. The direct visualization of synaptic connectivity in a novel *in vivo* model of DS will provide important mechanistic insights into the precise nature of synaptic deficits. Ultimately, with a better understanding of how synapses are formed and eliminated in the brain, we will obtain more refined tools to target synaptic reorganization for neurological intervention in DS. **Task 8.1 Dissecting the mechanisms of the increased synaptic density in DS**. In our previous work, the extended survival of the human grafts allowed human neurons to mature *in vivo* over several months, as evidenced by morphological criteria and expression of deep and upper cortical layer-specific neuronal markers. Ts21 neurons developed neurites through a normal process of developmental pruning and formed pre- and post-synaptic structures that were plastic over time (Real et *al*., unpublished). However, synapse density was higher in Ts21 neurons than in control neurons. This increase in synaptic density could be due to alterations in the rate of synapse formation, elimination and/or stabilization. To distinguish among these possibilities, we will engineer human iPSCs neurons to express GFP via lentiviral (LV)-mediated transduction and transplant them in 1 month old mice for 2-photon *in vivo* imaging, which will be performed at 3, 5 and 7 months post-transplantation. We will measure the rate of formation, elimination and stabilisation of both dendritic spines and axonal boutons, as well as the size (i.e. strength) change of the presynaptic boutons. *Ex vivo* slice electrophysiology will be used to study biophysical properties and synaptic input to the transplanted human neurons. **Task 8.2 Dissecting the mechanisms of the functional network defect in DS.** Remarkably, although human neuron grafts from two DS patients showed spontaneous calcium activity *in vivo*, could fire action potentials and received both excitatory and inhibitory input, they consistently failed to synchronise network activity *in vivo*, contrary to control grafts (Real et *al*., unpublished). To further understand the cellular mechanisms for this network deficit, we will study synaptic input to the human neurons with monosynaptic retrograde tracing using a modified rabies virus. We expect to find no difference in synaptic input between DS and control grafts, as previously uncovered with electrophysiological recordings. We will also perform RNAseq analysis of transplanted Ts21 and control neurons to confirm preliminary results, which identified several potassium channel expression alterations (Real et *al*., unpublished), potentially mediating the defective burst activity in DS. Finally, we will perform immunohistochemistry for presynaptic components, i.e. active zone proteins, synaptic receptors, synaptic vesicles and the axonal cytoskeleton, together with postsynaptic markers to investigate associated axonal and synaptic molecular changes in DS using super resolution microscopy (with Groc/Choquet, IINS-CNRS).

Planned secondment(s): **IINS-CNRS**: Superresolution microscopy analysis of synaptic molecular alterations in control and Ts21 neurons (Daniel Choquet/Laurent Groc, second or third year, 4 months); **CHUC**: exposure to clinical research (Guiomar Oliveira, second or third year, 0.5 months); **Lundbeck**: pharmaceutical development learning (2.5 months).

Fellow	Host institution **IBPS-CNRS**	PhD enrolment	Start date	Duration	**DS9**; **D1-D4**
ESR9	Host supervisor **Catalina Betancur**	**YES**	**Month 6**	**36 months**	

Role of glycinergic signalling in autism spectrum disorder; IBPS-CNRS + ICL + CIP-UEDIN; **WP2**

Objectives: Recent studies of rare structural and sequence variants have identified hundreds of loci involved in ASD, but our knowledge of the overall genetic architecture and the underlying pathophysiological mechanisms remains incomplete. Our research focuses on the identification of genes involved in ASD and understanding the underlying neurobiological mechanisms. We participate in international consortia performing large-scale analyses of structural and sequence variants in ASD. For the strongest candidate genes harbouring potentially pathogenic mutations, we perform *in vitro* and *in vivo* functional studies in order to validate their role in the disorder and to gain insight into the cellular and molecular bases of ASD. Recently, we used a combination of genetic and functional studies to demonstrate that rare mutations in the X-linked gene *GLRA2*, encoding the glycine receptor α2 subunit, are associated with ASD, implicating altered glycinergic signalling for the first time in ASD [16]. Glycine receptors (GlyRs) are ligand-gated chloride channels that mediate inhibitory neurotransmission in the adult nervous system but exert an excitatory action in immature neurons. GlyRs containing the α2 subunit are highly expressed in the embryonic brain, where they promote cortical interneuron migration and the generation of excitatory projection neurons. Behavioural studies of *Glra2* KO male mice (*Glra2*$^{-/Y}$) performed by our group revealed cognitive deficits in object recognition memory, with preserved spatial memory, suggesting a distinct contribution of GlyR α2 to the brain circuits that underlie these forms of memory. *Glra2*-deficient mice also displayed impaired long-term potentiation (LTP) in the medial prefrontal cortex (PFC), a region involved in recognition memory and consistently implicated in ASD. Overall, these findings unveiled novel roles for the GlyR α2 subunit in synaptic plasticity and learning and memory [16].
Recently, we observed an increase in the number of dendritic spines and arborisation in pyramidal neurons of the PFC in *Glra2*$^{-/Y}$ mice, together with a selective reduction in inhibitory synapses in the same brain region. These findings are

expected to result in perturbations of synaptic function in the PFC, with subsequent excitation/inhibition (E/I) imbalance and disruption of normal cortical network dynamics, and could provide a substrate for the previously reported behavioural and electrophysiological deficits observed in *Glra2*$^{-/Y}$ mice. The aim of this research project is to continue to dissect and characterize the underlying neurobiological mechanisms that link GlyR α2 to ASD. We will explore: (1) the cellular and behavioural correlates of PFC synaptic dysfunction in *Glra2*$^{-/Y}$ mice, including various modalities of working memory and attention, 2) the neural correlates of hippocampal-dependent spatial memory, and 3) the activity of brain circuits under basal conditions and during cognitive tasks. The proposed studies will shed light on the role of glycinergic signalling in the pathophysiology of ASD and in the brain in general, and contribute to a better understanding of the molecular and cellular mechanisms of PFC function and dysfunction.

Expected results: This project will address the consequences of *Glra2* deficiency at the cellular, network and behavioural levels and provide insights into the role of *GLRA2* in inhibitory and excitatory cortical circuit dysfunction in ASD. **Task 9.1 Explore the cellular and behavioural correlates of PFC synaptic dysfunction in Glra2$^{-/Y}$ mice**: We will explore in detail the behavioural consequences of the synaptic dysfunction observed in the PFC of *Glra2*$^{-/Y}$ mice by studying various modalities of working memory and attention dependent on this region. These studies will be complemented by molecular and cellular studies in the PFC. We will study the expression of GlyR α2 and other α subunits (1, 3 and 4) in the PFC of WT animals using *in situ* hybridization (no subunit specific antibodies) and analyse the cell subtypes expressing GlyR α2 using immunofluorescence. In addition, we will use electrophysiology to explore the role of GlyR α2 receptors in the adult PFC. Although GABA is the primary inhibitory neurotransmitter in the cortex, a distinct role for glycine was observed recently in pyramidal neurons of the mouse and rat PFC, with extrasynaptically located GlyRs shown to be tonically activated by ambient glycine. Given that the resulting tonic inhibition can have an important influence on PFC excitability and function, we will replicate these experiments in *Glra2*$^{-/Y}$ and WT mice (collaboration with Peter Kind, CIP-UEDIN), to test whether the GlyRs mediating this effect involve the α2 subunit, which seems likely. **Task 9.2 Study the neural correlates of spatial memory deficits**: As noted above, *Glra2*$^{-/Y}$ mice exhibited a specific deficit in novel object recognition, whereas no hippocampal-dependent spatial memory deficit was observed in the Morris water maze and novel location recognition task. It is therefore interesting to study whether the deficits observed in the PFC, in terms of synaptic plasticity (LTP) (collaboration with Peter Kind, CIP-UEDIN), inhibitory synaptic transmission and dendritic morphology, are also observed in the hippocampus, to determine whether the effects of the absence of *Glra2* have a regional specificity, as demonstrated in several genetic models of autism. **Task 9.3 Analyse neural circuits under basal conditions and in an object recognition task**: In order to map the activity of the neuronal circuits involved in the object recognition memory deficit observed in *Glra2*$^{-/Y}$ mice we will study the expression of the immediate early gene transcription factor c-fos, following an object recognition task and compare the profiles of neuronal activity in the brain of WT and mutant mice. We will also carry out co-labelling with anti-VGLUT1 or anti-GAD67 antibodies, in order to specify the nature of the cells positive for c-fos. Given our previous findings on impaired synaptic plasticity, increased dendritic spine density and branching in pyramidal neurons and decreased inhibitory synapses in the PFC, we expect an hypoactivation of this region in *Glra2*$^{-/Y}$ mice. Finally, given that the brain expression of *GLRA2* was shown to be strongly correlated with the resting-state activity in the default mode network in humans, which has been shown to be disrupted in ASD, we will study the expression of c-fos in the basal state in *Glra2*$^{-/Y}$ and WT mice, in cortical and subcortical structures, particularly in limbic structures. In collaboration with Thomas Knöpfel at ICL we will analyse cortical dynamics in these animals, using VSFPs.

Planned secondment(s): **ICL**: *In vivo* imaging of cortical dynamics and E/I balance in the PFC (Thomas Knöpfel, 4 months); **CIP-UEDIN**: Electrophysiological analysis of GlyR α2-deficient in the PFC and hippocampus (Peter Kind, 4 months)

Fellow	Host institution **IBPS-CNRS**	PhD enrolment	Start date	Duration	**DS10**; **D1-D4**
ESR10	Host supervisor **Catalina Betancur**	**YES**	**Month 6**	**36 months**	

The endocannabinoid system as a therapeutic target in Shank3-deficient mice, a model of autism spectrum disorder; IBPS-CNRS + CNC + Eurotrials; **WP3**

Objectives: Many genes implicated in ASD and other neurodevelopmental disorders encode proteins that play a role in synaptic plasticity, especially at glutamatergic synapses, including some of the most frequent monogenic causes of ASD: fragile X syndrome, tuberous sclerosis, and Phelan-McDermid syndrome (PMS), caused by *SHANK3* haploinsufficiency. The synaptic dysfunction caused by these mutations creates an imbalance between excitatory and inhibitory (E/I) neurotransmission, which is thought to be at the origin of the neurobehavioural manifestations observed in affected individuals. Restoring a normal E/I ratio therefore constitutes a promising therapeutic approach to treat forms of ASD arising from multiple molecular/cellular mechanisms. The goal of this project is to assess whether the modulation of the endocannabinoid system (ECS) has beneficial effects in a mouse model of ASD. The ECS is a key modulator of neuronal excitability and synaptic plasticity, and has already shown promise as therapeutic target in some neurodevelopmental disorders. We will use *Shank3*-deficient mice, a well-known model of ASD characterized by synaptic dysfunction and E/I imbalance. Deletions and mutations of *SHANK3* cause PMS and are one of the most frequent causes of ASD. The aims are to investigate the role of the ECS in the alterations associated with *Shank3* haploinsufficiency, and to assess if the pharmacological modulation of the ECS has a beneficial effect on the synaptic and behavioural deficits of this mouse model of ASD. In particular, we will study the effects of a novel allosteric inhibitor of CB1R derived from pregnenolone, developed by Drs. P.V. Piazza and G. Marsicano (Neurocentre Magendie, University of Bordeaux) for clinical use.

Expected results: This research project will allow us not only to evaluate the therapeutic potential of modulating the ECS in a mouse model of ASD, but also to increase our understanding regarding the molecular mechanisms underlying ASD, and in particular the role of endocannabinoid signalling. The findings on *Shank3*-deficient mice could potentially be extended to

other mouse models of ASD with synaptic abnormalities displaying an alteration of the E/I balance, and ultimately to PMS patients and those with other genetic forms of ASD. **Task 10.1 Examine the role of the ECS in Shank3-deficient mice**: We will examine if *Shank3* deficiency is associated with biochemical and functional alterations of the ECS. The study will be performed using a new strain of *Shank3* mutant mice in which all *Shank3* isoforms have been disrupted. We will measure the brain levels of the major endocannabinoids (2-AG and anandamide), and the main enzymes implicated in their synthesis and degradation pathways, as well as the expression of the receptors CB1R and CB2R. We will also assess whether the ECS is altered at the electrophysiological level, by studying first the effects of cannabinoid drugs on excitatory and inhibitory neurotransmission in wild-type (WT) and mutant mice, and then analysing endocannabinoid-dependent synaptic plasticity, such as depolarization-induced suppression of inhibition or excitation, as well as long term depression in the prefrontal cortex. **Task 10.2 Assess the effects of administration of ECS modulators on the phenotype of Shank3-deficient mice**: We will evaluate ECS modulators as a novel therapeutic strategy to restore the E/I balance and reverse the synaptic and behavioural deficits observed in this mouse model. In particular, we will test a novel non-metabolisable pregnenolone derivative (NMPD; patent PCT/EP2012/059310), and compare its effects with those of CB1R agonists and antagonists. The compounds will be administered to *Shank3*$^{+/-}$ and WT mice, and we will conduct a detailed phenotypic analysis combining behavioural, electrophysiological and molecular approaches. We will evaluate whether the ECS modulators can reverse deficits observed in the new *Shank3* strain, including motor deficits (accelerating rotarod and open field), repetitive behaviours (excess grooming, and in the open field), and cognition (Barnes maze and reversal learning). Moreover, we will use electrophysiology techniques on brain slices to analyse the consequences of the administration of ECS modulators on two forms of synaptic plasticity, LTP in the hippocampus and LTD at excitatory synapses in the prefrontal cortex. We will also study the basal excitatory and inhibitory neurotransmission in these regions. Finally, this integrated phenotypic analysis will include an anatomical and biochemical approaches, in order to study the morphology of dendritic spines and the molecular composition of synapses. Based on the evidence for E/I imbalance in ASD and the critical neuromodulatory role of the ECS, we expect to see evidence of reversal of electrophysiological and behavioural deficits in the *Shank3*-deficient mice.

Planned secondment(s): **CNC**: Electrophysiological analysis of endocannabinoid-dependent synaptic plasticity (João Peça, 4 months); **Eurotrials**: Medical writing, clinical trials development and regulatory affairs (1 month).

Fellow	Host institution **Lundbeck**	PhD enrolment	Start date	Duration	
ESR11	Host supervisor **Kjartan F. Herrik**	**YES**	**Month 6**	**36 months**	**DS11**; **D1-D4**

Investigating the excitation/inhibition (E/I) imbalance hypothesis of neuropsychiatric disorders in the cortico-thalamic system with electrophysiological methods; Lundbeck + CIP-UEDIN + BMI-EPFL; **WP3**

Objectives: Understanding neural circuit function has recently been suggested as a pathway for developing diagnostics and therapeutics for neuropsychiatric disorders, as it is an intermediate level that links genes to behaviour (Krol et al., 2018). From this circuit perspective, it has been repeatedly hypothesised that neuropsychiatric disorders as schizophrenia (SCZ) and autism course with an imbalance between excitatory and inhibitory (E/I) networks (Gao and Penzes, 2015). Although the underlying mechanism remains elusive, an increased interest has been directed towards a dysfunction in the GABAergic interneurons (Ferguson and Gao, 2018). This is particularly important in the context of thalamocortical circuits, which play a fundamental role in sensory gating, memory consolidation and sleep (Manoach et al., 2016; Manoach et al., 2019). Importantly, the sleep spindle activity that is driven by the thalamic reticular nucleus (TRN) has been reported to be markedly reduced in schizophrenic patients and suggested to be an endophenotype of SCZ (Manoach et al., 2016; Merikanto et al. 2019). This reduction was correlated with thalamic hyperconnectivity in fMRI studies (Baran et al., 2019). Accordingly, postmortem studies reveal TRN abnormalities reductions in parvalbumin expressing neurons (PV) (Steullet et al. 2018). A consequent impairment of TRN-mediated inhibition of thalamocortical neurons could decrease the rebound bursting that generates spindles and impair the gating of information flow to the cortex. Treatments that target TRN interneurons would, therefore, be promising therapeutic strategies to restore E/I balance and could be relevant in the context of neuropsychiatric disorders as SCZ. The present PhD project aims to study the circuits and mechanisms that govern E/I balance in cortico-thalamic and thalamo-cortical networks, focusing in the interplay between TRN, mediodorsal (MD) thalamus and medial prefrontal cortex (mPFC). More specifically, the role of TRN neurons and ion channels involved in pacing thalamocortical activity will be addressed. We hypothesize that changes in TRN activity will lead to alterations in E/I balance in the thalamus and neocortex, with a strong implication in sleep and sleep-dependent memory consolidation.
Using a variety of electrophysiological methods and pharmacological and chemogenetic tools, the E/I balance will be studied in both brain slices and awake and freely moving rodents. With access to both reduced (slice) and intact (freely moving) systems, the PhD student gets a unique opportunity to study E/I-mechanisms at a broad range of levels. The ultimate goal is to advance our understanding of the importance of upholding an E/I balance in the cortico-thalamic system and study both single neurons as well as population activity. The electrophysiological biomarkers studied in the freely moving rats, may further translate to human electroencephalographic and polysomnographic markers.
The new Lundbeck supervisors as well as the supervisor from University of Copenhagen are experts in ex vivo slice electrophysiology (Hougaard, Kohlmeier), ion channel pharmacology (Hougaard, Kohlmeier, Herrik), rodent in vivo electrophysiology (Herrik) and polysomnography (Kohlmeier).

Expected results: This project is experimentally designed in a comprehensive manner, where thalamocortical system will be studied at single neuron and ensemble activity levels. Besides, by combining in vivo and in vitro electrophysiological approaches, E/I balance will be studied in both reduced (brain slices) and intact (freely moving rats) systems. **Task 11: Identify ion channels as potential pacemakers of thalamocortical activity and its impact on E/I balance**.

Pharmacological tools will be used to characterise those ion channels involved in pacing thalamocortical activity. Several compounds will be tested, targeting ion-channels that could potentially mediate E/I balance in the crosstalk between TRN and thalamus. **Task 11.2: Effect of chemogenetic modulation of TRN neurons on the corticothalamic loop.** Chemogenetics will be used to selectively enhance/silence activity of TRN neurons in order to study their contribution on oscillatory rhythms and E/I balance in the mediodorsal (MD) thalamus and medial prefrontal cortex (mPFC). **Task 11.3: Impact of TRN neurons modulation in thalamocortical rhythms during sleep and sleep-dependent memory consolidation.** Electroencephalographic (EEG) and electromyographic (EMG) recordings will be carried out during a behavioural task (place object recognition test) that is known to involve sleep-dependent memory consolidation (extended stay at BMI-EPFL in collaboration with Simone Astori and Carmen Sandi). Polysomnographic analyses will be crucial to characterize NREM, REM and intermediate sleep epochs and the underlying brain rhythms. Pharmacological and chemogenetic tools will be used in order to identify circuits, neuronal subtypes and ion channels involved in pacing thalamocortical activity. **Task 11.4: To study the thalamocortical system and E/I imbalance in a relevant model for SCZ and TRN dysfunction.** Ultimately, modulation of sleep spindles and corticothalamic networks will potentially be studied in a transgenic rat model of the disease in collaboration with Peter Kind (extended stay at UEDIN).

Planned secondment(s): **Planned secondment(s)**: **BMI-EPFL**: Learning of polysomnographic recordings and sleep scoring in freely moving rats before and after novel recognition test. (Carmen Sandi/Simone Astori 3 months). **CIP-UEDIN**: Generating a relevant transgenic model of TRN dysfunction (Peter Kind, 4 months).

Fellow	Host institution **CIP-UEDIN**	PhD enrolment	Start date	Duration	**DS12**; **D1-D4**
ESR12	Host supervisor **Emily Osterweil**	**YES**	**Month 6**	**36 months**	

Identifying convergent dysregulation of mRNA translation in multiple models of autism; CIP-UEDIN + CNC + IINS-CNRS; **WP3**

Objectives: Mutations in many genes that encode regulators of mRNA translation, such as *FMR1* gene encoding the translation repressor Fragile X Mental Retardation Protein (FMRP) and the *SYNGAP1* gene encoding the Ras-Erk 1/ 2 repressor SynGAP, are significant risk factors for ASD. Mutant models of these and other neurodevelopmental disorders exhibit excessive neuronal protein synthesis, suggesting the hypothesis that aberrant synaptic mRNA translation is a point of convergence for multiple genetic causes of Autism Spectrum Disorder with associated Intellectual Disability (ASD/ID). If dysregulated mRNA translation is a common contributor to ASD/ID, then the important long-term goal is to address how disruptions in local protein synthesis lead to cognitive and behavioural symptoms. An essential first step is to identify the mistranslating mRNAs that lead to altered function in brain circuits that are affected in ASD/ID models. In recent work we performed the first cell type-specific translation profiling screen of *Fmr1*$^{-/y}$ neurons using Translating Ribosome Affinity Purification and RNA sequencing (TRAP-seq, RNAseq). This study revealed over 120 mistranslating mRNAs in hippocampal CA1 neurons and identified muscarinic acetylcholine receptor 4 (M_4) as a novel target for the correction of biochemical, electrophysiological and behavioural phenotypes in the *Fmr1* $^{-/y}$ mouse. In this proposal, we will use TRAP-seq to interrogate mistranslating mRNAs in multiple circuits that contribute to pathological phenotypes in mouse models of FX and SYNGAP1 haploinsufficiency syndrome. Previous work shows that both protein synthesis and mGluR-LTD are excessive in the *Syngap*$^{+/-}$ hippocampus, similar to what is seen in the *Fmr1*$^{-/y}$ mouse and these phenotypes are corrected with mGluR5 antagonist or inhibition of Ras-ERK1/2. This correction will normalize a number of electrophysiological and behavioural disruptions throughout the brain, including altered hippocampal long-term depression (LTD), hyper excitability in hippocampus and cortex, increased susceptibility to audiogenic seizures, and deficits in contextual fear learning. In parallel to the ongoing cell-type specific approach through TRAP-seq, ESR12 will lead a new approach consistent in the establishment of a ribosome profiling protocol to monitor translation in *Fmr1*$^{-/y}$ and *Syngap* $^{+/-}$ rat models and get a new deep outlook of the translatome. This would possibly let new mistranslated RNAs emerge consistent and/or in opposite direction to what has been shown by our preliminary results. In addition, ESR12 will perform these experiments in rat models of disease. This will have high impact and will possibly enrich our knowledge about the topic. The working plan will include (1) a ribosome profiling analysis comparing the footprints derived from *Fmr1*$^{-/y}$ and the *Syngap*$^{+/-}$ rat models, (2) an assessment of the extent of mRNA mistranslation in behavioural phenotypes, performing paradigms such as fear conditioning, (3) possible validation of identified targets through means of viral injection leading to a possible rescue of the phenotype, (4) comparison of the ribosome profiling map of rat models and commercially available IPSCs derived from patients.

Expected results: **Task 12.1** Our preliminary data indicate that, TRAP-seq is a powerful approach that would allow us to identify mistranslating mRNAs in the *Fmr1*$^{-/y}$ and *Syngap*$^{+/-}$ mouse models. In this direction we would be very interested to deepen this exploration through means of ribosome profiling in a rat model of disease (*Fmr1*$^{-/y}$ and *Syngap*$^{+/-}$ rats) and parallel it to the TRAP-seq approach. ESR12 will analyse the footprints derived by ribosome profiling and align them to the relative genome to understand the exact portions that are mistranslated, hopefully confirming the preliminary results obtained by TRAP analysis in mouse models and show a conservatory pattern in other species, or coming up with new targets to be validated. **Task 12.2** Alterations in context discrimination and learned fear are notable phenotypes in both *Fmr1*$^{-/y}$ and *Syngap*$^{+/-}$ mouse models. The mechanisms underlying these disruptions have not been established, however there is a long-standing observation that learned fear and the formation of memory require new protein synthesis. Interrogating the mRNAs translated in the underlying hippocampal CA1, layer 5 mPFC, and BLA neurons during fear conditioning would therefore yield important and novel information regarding the processing of fearful memory in general. Thus, an important part of this project will be to assess mRNA translation in a learning context to see if it shows consistency. ESR12 will perform sampling at different time points after behaviour: precisely 30 minutes, 4 hours and 24 hours after conditioning. **Task 12.3** The sequencing data derived from a naïve and a learning context will show if there is a

convergence in the mistranslated mRNAs and this could be the starting point for a possible target validation strategy. The ESR12 will explore this by performing in vivo injections of a shRNA against a validated target to possibly see a rescue in the fear conditioning phenotype. **Task 12.4** Provided with patient-derived hIPSCs sent from collaborators, ESR12 will run a comparative ribosome profiling analysis and possibly show a reliability with the animal model. This will possibly convey outstanding insights in research

Planned secondment(s): **CNC**: Analysis of ribosome trafficking (Ana Luisa Carvalho, 4 months); **IINS-CNRS**: Super-resolution microscopy analysis of spine dynamics in *Fmr1* $^{-/y}$ versus *Syngap* $^{+/-}$ models (Daniel Choquet, Laurent Groc, 6 months).

Fellow ESR13	Host institution **BMI-EPFL** Host supervisor **Carmen Sandi**	PhD enrolment **YES**	Start date **Month 6**	Duration **36 months**	**DS13**; **D1-D4**

Effect of corticotropin-releasing hormone on a thalamic hub for neurodevelopmental disorders; BMI-EPFL + IINS-CNRS + ICL; **WP3**

Objectives: Recent literature identifies a circuit endophenotype for neurodevelopmental disorders in the Thalamic Reticular Nucleus (TRN), the principal source of inhibition to the thalamus. TRN neurons express several disorder-relevant genes identified through GWAS, such as the schizophrenia-related genes Cacna1i and Grm3, and the autism spectrum disorder-risk gene PTCHD1, suggesting that this structure may reflect a source of common vulnerability across neurodevelopmental disorders (Krol et al., 2018). Notably, SZ patients display reduced density of sleep spindles (Manoach et al., 2016), a thalamocortical sleep rhythm that is initiated by TRN cell bursting (Astori et al., 2013). Besides its recognized role as a sleep pacemaker, TRN is being increasingly implicated in sensory and cognitive processing, such as attention selection, and TRN function is found to be altered in models of pathology (Krol et al., 2018). Whether the development and function of the TRN are affected by environmental factors, such as stress, has not been addressed. Notably, TRN cells express high levels the corticotropin-releasing hormone receptor 1 (CRHR1) (Pett et al., 2000; Bender et al., 2015), but how this stress-released neuropeptide affects TRN function is fully unexplored. By combining ex vivo cellular analyses and polysomnographic recordings we will assess how the CRH system impinges of TRN excitability and thalamocortical sleep rhythms. We will further examine whether chronic exposure to CRH at early postnatal stages alters the expression of SZ- and ASD-risk genes in the TRN.

Expected results: Task 13.1 Impact of CRH on TRN cell excitability: Our preliminary data from patch-clamp experiments indicate that exposure the CRH in acute slices alters TRN cell firing, with tonic firing being promoted over burst firing. We will extend these results and explore the molecular mechanisms whereby CRH modulates TRN intrinsic excitability. We will examine whether cortical and thalamic glutamatergic inputs onto TRN are affected, as well as the intrathalamic spindle rhythmogenesis. **Task 13.2 Identification of the endogenous source of CRH onto TRN:** We will use retrograde labelling through viral infections in the TRN in order to identify the population(s) of CRH-releasing cells projecting to the TRN. The expression of opto- and chemogenetic tools in the identified cell population will allow us to examine the effects of endogenous CRH release on TRN excitability. **Task 13.3 Impact of CRH on thalamocortical sleep rhythms:** We will perform polysomnographic recordings in freely-behaving animals and examine the effects of CRH on sleep rhythms by gain-/loss-of-function experiments in which the TRN-projecting CRH-releasing cells will be activated/inhibited. **Task 13.4 Impact of stress on TRN gene expression profile:** We will assess whether chronic exposure to CRH or the repetitive stress exposure during early life affects the expression of SZ- and ASD-related genes in the TRN and alter the TRN cell development and function. We will attempt CRHR1-directed pharmacology to normalize the CRH-/stress-induced phenotype.

Planned secondment(s): **IINS-CNRS**: Measure dynamics of synaptic receptors in the TRN of mice exposed to CRH/stress (Laurent Groc, 4 months); **ICL**: *In vivo* monitoring of TRN activation with voltage/Ca2+ sensors during CRH/stress exposure (Thomas Knöpfel, 4 months).

Fellow **ESR14**	Host institution **UEDIN** Host supervisor **Peter Kind**	PhD enrolment **YES**	Start date **Month 6**	Duration **36 months**	**DS14**; **D1-D4**

Circuit deficits associated with ASD/ID; CIP-UEDIN + IINS-CNRS + Eurotrials; **WP3**

Objectives: While the genetic causes of neurodevelopmental disorders (NDDs) are complex, much is being learned by using models of rare, highly penetrant genetic mutations as prototypes of these disorders. Indeed, two areas of research have recently provided a sea change in how we envision potential treatments for ASDs and NDDs more generally. First, evidence suggests that genetically disparate ASDs *converge* on relatively few axes of pathophysiology that are susceptible to common therapeutic intervention. Second, at least some forms of these disorders may be *treatable throughout the lifespan*. We recently demonstrated that the hippocampal cellular phenotypes associated with models of fragile X syndrome (FXS) and *SYNGAP1* haploinsufficiency converge upon altered mGluR5 to ERK signalling and can be rescued by dampening this signalling pathway. We found similar convergence of cellular pathophysiology in the amygdala and prefrontal cortex. However, whether this convergence of cellular pathophysiology is mirrored by a convergence of treatment efficacy at a behavioural level is not known.

For decades it was believed that the adult brain is hard-wired, and that interventions for *neurodevelopmental disorders* would only be effective if implemented during the first few years of life. This dogma has recently been questioned by studies showing the near complete reversibility of phenotypes associated with the loss of MeCP2 (Rett syndrome) in adult mice. These studies have led to the growing belief that not all disorders that first present during development are true NDDs but instead may result from deficits in *Neural Maintenance (NMDs).* To address efficacy of pharmaceutical intervention strategies as a function developmental timing requires a detailed developmental trajectory of the phenotype being examined. We have been developing rat models to a range of "NDDs" to establish a robust developmental profile of behavioural and

cognitive phenotypes and the developmental emergence. We are now in a position to test the efficacy of a range of proposed therapeutic strategies for their ability to prevent and/or reverse behavioural phenotypes that depend on amygdala, hippocampus and/or prefrontal cortex function. By employing a systematic approach to reversibility, we will answer fundamental questions about the extent to which *"NDDs"* can be treated throughout lifespan.
Expected results: **Task 14.1 To determine whether behavioural phenotypes associated with *Fmr1*$^{-/y}$ and *SynGAP1*$^{+/-}$ rats show similar susceptibility to therapeutic intervention.** To look at complex association learning we will test rats on a battery of spontaneous recognition memory tasks. These tasks assess the ability to discriminate novel from familiar objects (OR), and novel from familiar object-context (OC), object-place (OP) and object-place-context (OPC) associations. Only the most complicated of these, the OPC task, is hippocampus-dependent and involves the associative recognition of objects, their spatial locations, and the local context. We find that *Fmr1*$^{-/y}$ rats show deficits in hippocampal-dependent, but not hippocampal-independent, forms of associative recognition memory indicating that the loss of FMRP causes defects in episodic-like memory. We have also demonstrated that both *Fmr1*$^{-/y}$ and *Syngap1*$^{+/-}$ rats show altered cued-fear conditioning and extinction, behaviours that are dependent on the amygdala and prefrontal cortex function, respectively. We will now examine whether chronic or acute treatment with modulators of the ERK pathway can prevent (early treatment) and/or reverse (late treatment) these behavioural deficits, thereby elucidating a critical period of therapeutic efficacy. **Task 14.2 To establish whether cellular phenotypes can be prevented or reversed in *Fmr1*$^{-/y}$ and *Syngap1*$^{+/-}$ rats**. We have found deficits in the intrinsic and synaptic properties of cells in the hippocampus, amygdala and prefrontal cortex of both *Fmr1*$^{-/y}$ and *Syngap1*$^{+/-}$ rats. Following the treatment strategies outlined in Task 14.1, slices from hippocampus, amygdala and prefrontal cortex that correlate with the observed behavioural deficits. More specifically, we have found deficits in the intrinsic properties and synaptic plasticity (either LTP or LTD) of neurons in all three brain structures. Finally, using glutamate uncaging and multiphoton microscopy, we have found a dramatic breakdown in the structure:function relationship of dendritic spines on cortical neurons of *Fmr1*$^{-/y}$ animals. This project will examine whether these correlations continue following therapeutic interventions.
Planned secondment(s): **IINS-CNRS**: Using Super-resolution to examine if the molecular structure of the synapses is altered and subsequently rescued in our models (Laurent Groc/Daniel Choquet, 6 months); **Eurotrials**: Medical writing, clinical trials development and regulatory affairs (2 months).

Fellow **ESR15**	Host institution UEDIN Host supervisor **Emily Osterweil**	PhD enrolment **NO**	Start date **Month 44**	Duration **7.6 months**	**DS4**; **D1-D4**
Testing gene therapy for Fragile X Syndrome; UEDIN; **WP3**					
Objectives: This project will examine the impact of genetic Fmr1 replacement on pathological phenotypes in the Fmr1-/y mouse and rat models of Fragile X Syndrome (FXS). FXS is the most common form of inherited intellectual disability and autism. Both mouse and rat models have been generated to study how loss of the Fmr1 gene results in altered synaptic and circuit function in the brain. A long-standing question is whether re-introduction of Fmr1 can restore function in the adult nervous system, and if so whether this replacement must occur early in development. To address this question, we will use a viral gene therapy vector (AAV9-Fmr1) that results in a stable re-expression of FMRP in adult brain after systemic injection in neonatal mice (unpublished data). This viral construct will be injected into specific regions of Fmr1 mouse and rat brains and characteristic phenotypes such as hippocampal protein synthesis, mGluR-LTD and audiogenic seizures assessed. Additionally, tissue will be harvested from injected animals in order to perform molecular investigation of FMRP target mRNA expression.					
Expected results: We propose that AAV9-Fmr1 injection will ameliorate the exaggerated protein synthesis/mGluR-LTD and AGS phenotypes when injected into the hippocampus and inferior colliculus, respectively. **Task 4.1** Inject virus intra-hippocampally at P21 and perform metabolic labelling after 1 week of re-expression. This will be done in both Osterweil (mouse) and Kind (rat) laboratories. **Task 4.2** Inject virus into inferior colliculus at P21 and perform AGS after 1-week expression. **Task 4.3** Perform qPCR analysis of tissue isolated from injected regions to assess levels of FMRP target mRNAs. Task 4. Repeat analyses of protein synthesis and AGS in animals injected at P60.					

3.2. Appropriateness of the infrastructure of the participating organisations. Syn2Psy consortium is fully committed with high quality doctoral-level training of 14 ESRs. The consortium will comply with the Erasmus Mundus Handbook of Excellence, namely "*We will formalise the partnership through a Consortium Agreement, and understand how we will deal with IPR issues. ESRs will be provided with an employment contract. When all is in place, we will market the programme professionally*."

- **Network organisation and management structure** of Syn2Psy is composed by the **Project Coordinator** (PC), the **Project Manager** (PM), and **three project committees**:

Project Coordinator (PC)	**Ana Luísa Carvalho** is Principal Investigator and group leader of the Synapse Biology Lab at the CNC, will be the intermediary between the Syn2Psy network and the Research Executive Agency. The PC will be responsible for: 1) scientific coordination, 2) ensuring that the project is executed and implemented according to the ETN Grant Agreement and the Consortium Agreement, 3) selection and hiring of the project manager, 4) monitoring overall contractual, financial and administrative management, 5) monitoring overall project activities and consortium communication; 6) submitting the reports, financial statements and deliverables to the EC and to

	communicate any deviation from the implementation and work plan to the Project Officer.
Project Manager (PM)	Based in Coimbra, will provide direct assistance to the PC and the consortium, namely: 1) the ESRs recruitment process, 2) the logistical preparation of network-wide training courses, 3) the monitoring of deliverables and milestones, 4) the administrative and financial tasks, including the production of technical and financial reports, 5) the organization of consortium meetings, 6) maintenance of the website and social media contents. A requirement for the PM position will be experience in management of EU funded projects; all beneficiaries will contribute to PM budget under the management costs of the programme.
Committees	Three project committees consisting of the beneficiary PIs will be established. The main objective of these committees is to redistribute managing duties from the PC to other consortium members. -The **Training/Doctoral Studies Committee** will: 1) implement the training program, 2) monitor the local PhD courses, 3) monitor the network-wide events, and 4) report periodically on training program progress to Supervisory Board (SB); -The **D&C Committee** will: 1) define and implement the D&C plan, 2) monitor the dissemination and communication activities, and 3) report periodically on D&C plan to the SB; -The **Research Coordination Committee (Supervisory Committee)** will: 1) advertise the ESR positions, 2) inform all selected ESRs and confirm the 14 contracts, 3) monitor the supervision and co-supervision of all ESRs, 4) monitor the secondments period of all ESRs, and 5) report periodically on individual research projects to SB.

- **Joint governing structure** of Syn2Psy is composed by the **Supervisory Board** (SB), **Management Board** (MB), the **ESR Board** (ESRB) and the **External Advisory Board** (EAB). The SB and MB completely manage the project and are the overseeing/advising (SB) and decision-making bodies (MB).

Supervisory Board (SB)	The **SB** is composed of the PC (who will chair it), the PM, the representatives of the three Committees, and one ESR (chosen by the peers via the ESRs board). The SB has complete responsibility for guaranteeing that high quality research and training is provided by the network, and for detecting and solving any difficulties with the supervision and work progress of ESRs. Specifically, the SB will: 1) define ESRs skill requirements, 2) overview the selection and recruitment made by the research coordination committee and MB, 3) formalise the work and skills expected from the each individual ESR, 4) outline the ESRs Personal Career Development Plan, 5) monitor all ESRs' training progress ensuring equal training between ESRs and hosts, 6) evaluate ETN training, 7) monitor progress in terms of timetable, deliverables and milestones, 8) to overview the three project committees. The SB will communicate with all ESRs aiming at providing feedback on the supervision arrangements, the training activities and the secondments. The SB will meet physically once a year during the life of the project, and regularly via e-mail and Skype. After reports from the MB, the SB will make the final decisions.
Management Board (MB)	The **MB** is composed of the PC and the PM. The MB is responsible for adopting main decisions regarding financial issues, work plan, intellectual property rights and the progress of the network consortium, after advice from the SB.
ESR Board (ESRB)	Feedback from each ESR will be obtained through the annual progress monitoring meetings and the **ESR Board** (ESRB). Three ESRs are annually elected to the ESRB and will participate in SB meetings. The ESRB will change annually, thus providing management experience to the largest possible number of fellows. The ESRB have an important role in the project as they are envisaged to help in the bridge between ESRs and the SB, regarding the research training programme, secondments, and any other issues of the network that may need dialogue. The ESRB will represent ESRs in all issues related to the work and contract conditions. The ESRB will be stimulated to create a forum online where all ESRs can put questions and comments.
External Advisory Board (EAB)	An **External Advisory Board** (EAB) consisting of two to four European and non-European top researchers in the research field of the project will be appointed to observe and advise on the strategic direction of Syn2Psy research training programme. The EAB will also embrace independent members to afford guidance on our transferable training skills, including our links with industry and technology. The EAB will be appointed at the kick-off meeting.
(i) ESR supervision. Each ESR will have a supervisor and a co-supervisor, complementary in expertise and merit. Each ESR will communicate weekly or daily if necessary with their main supervisor, and at least once a month with the co-supervisor via e-mail and Skype. When appropriate, adjusts to the working plan will be implemented. **(ii) Voting procedures within Syn2Psy consortium**. The SB shall not deliberate and decide validly unless a quorum of 2/3 of its members is represented. As a rule, strategic decisions will be made by the SB (one vote per member). However, authority for rapid decision-making in day-to-day routine activities will be delegated to the PC who will count with the dedicated assistance of the PM. Decisions will be pondered by a simple majority with the PC having the right to veto under exceptional circumstances that have to do with breaching the commitment and contract. If a conflict arises, the SB will organize a conflict resolution meeting and, if necessary, the PC shall designate a legal expert. **(iii) Communication within the consortium** will be mainly by mailing and Syn2Psy website (please see WP6). The website will have an internal access in which the consortium can deposit data, training activities, information, notes, instructions, etc. Other internal communication channels will be used on a regular basis for efficient coordination and planning of the envisaged activities and internal reporting, typically electronic/virtual meetings via e.g., WebEx/Skype. Researchers will also adopt regular video conferencing calls between ESRs, supervisors, partners, and collaborators, in academic and non-academic sectors, so that all aspects of tutoring, training and D&C can be discussed and planned thoroughly in advance, and the merit and distinction of Syn2Psy network-wide interaction monitored. **(iv) Financial management**: "*Management and indirect costs*" and "*Networking costs*" will not be allocated evenly, but matching to a relative estimation of the financial management responsibilities and tasks of the partners, according to the Proposal, that will	

be approved before signing the *Syn2Psy Consortium Agreement*. Individual participant organisations are responsible for managing their own involvement, distributing salaries to ESRs and reporting back to CNC and the EC.

- **Recruitment strategy**. The first mission of the project will be to hire the PM and to initiate the recruitment of ESRs that will follow the good practice procedures in the **European Code of Conduct for the Recruitment of Researchers**. The second mission will be to form the three project committees and the SB (in the kick-off meeting, month 1); the research coordination committee will oversee the recruitment with the MB and will report it to SB. The advertisements will be widely announced, e.g. in ERACAREERS and EURAXESS Jobs Portals, partner's mailing lists, partner's websites, scientific journals and international meetings. The ESRs will be offered work contracts. The advertisements will provide a description of knowledge and competences required, selection criteria as well as career development prospects and employment conditions. The candidates must have a degree in a relevant area and should present the *Curriculum Vitae*, a copy of the academic record with academic/education history, including a list of courses/exams and grades, two reference letters, and a letter of motivation explaining the interest in the project and the favoured position(s) within the Syn2Psy network. The principal additional admission requirements specific to the application are the Marie Curie mobility criteria.
Host institutions will not discriminate against researchers in any way on the basis of gender, age, ethnic, national or social origin, religion or belief, sexual orientation, language, disability, political opinion, social or economic condition. The selection should bring together diverse expertise and competences and should have an adequate gender balance. Whenever possible, a wide range of selection practices should be used, such as external expert assessment and face-to-face interviews (in particular to ESRs with the higher scores). The interview panel will be composed of members of the partner institutions working together in the project. ESRs will be selected based on the following criteria: Excellence, motivation, publications, degree and grades and previous experience. Recruitment will take place in the first six months after initiation of the network. All ESRs will be recruited for 36 months period allowing them to complete their individual projects ideally achieving PhD.
The MB is responsible for directing each individual research project proposed and agreed by the beneficiaries and their host institutes. The host institutions ensure open and transparent selection and recruitment procedures; the employment conditions are the best possible and in line with all legal requirements and standards of national legislation. The doctoral programmes in the partner institutions usually start during autumn with the admission assessments occurring in early summer. Thus, the projects will start in January (please see Gantt chart in section 4).

- **Progress monitoring and evaluation of individual projects** will be performed by the MB and SB. ESRs' Personal Career Development Plan will be the basis of the supervision process. The principal supervisor will take the first responsibility of daily monitoring of routine performance and research progress. The co-supervisor will follow the ESRs progress monthly (or weekly, during secondments). Evaluation procedures of individual projects will take into account the ESRs' overall research vision and research results, e.g. talks/posters presented, publications, national or international collaboration, mobility, management duties, outreach and public engagement activities. The monitoring and evaluation of the ESRs training programme will take place four times a year through the following indicators: ESRs rate of recruitment, ratio man-month achieved/offered, time, duration of individual appointment; number of secondments undertaken or organised by each ESR; participation to network-wide training events and inter/national conferences; participation/organization to outreach initiatives (e.g. including talks attended, courses, seminars, teaching/demonstrating activities, clinical and technological activity); acquisition of transferable skills; ESRs satisfaction; innovative know-how achieved. The project meetings (see Table 1.2c) will allow ESRs to present their individual research project results.

- **Intellectual Property Rights (IPR)**. Syn2Psy will develop an IPR protection policy following the guidelines outlined in H2020 DESCA Model. The management and technology transfer offices of parties will help the consortium at identifying "*Confidential information*" (that mean technical and/or commercial information, including but not limited to any documents, samples or prototypes disclosed or supplied by one party to another and identified as confidential or proprietary). The parties will respect the interest of another party to keep its own technical or commercial information confidential. Confidential oral information will be recorded in writing by the disclosing party within 30 days after disclosure, and the resulting document will specifically state the date of disclosure and designate the information as confidential or proprietary. Agreements will be concluded between participants and the non-academic/industrial partners after consultation with the SB and integrated into the activities of WP6.

- **Gender aspects** and equal opportunities are safeguarded by WP Leaders and will be ensured at all levels: recruitment of ESRs, staff involved, Board and Committee composition. Syn2Psy will also support ESR(s) in case of pregnancy during the project time; SB will discuss alternative ways to decrease the delay in the project.

- **Data management plan** and scientific misconduct. Syn2Psy network will establish a data management plan (DMP; e.g., Green Open Access, Knowledge transfer and IPR) within the first 6 months of the project.

Syn2Psy will take advantage of a data repository that will be created at CNC to develop a unified storage and data exchange platform. The strategy set in the data management plan will follow the Open Access to Research Data in Horizon 2020. Syn2Psy will inform students about ethics in science, to prevent scientific misconduct. However, a strategy is necessary to handle unexpected cases of scientific misconduct within the network. At the kick-off meeting, the Supervisory Board will define a strategy to prevent, monitor and counteract scientific misconduct, guided by the ERC Scientific Misconduct Strategy that includes the following points: (i) Initial information: The Supervisory Board will elaborate a text that will be given to all ESRs in the kick-off; every member will be asked to report to the Supervisory Board all cases of scientific misconduct. (ii) Persons suspected of misconduct will be treated with confidentiality and fairness as long as the allegation is not proven, (iii) Assessment of the allegation through the Supervisory Board including eventual notification to European Anti-Fraud Office (OLAF) and hearing of concerned parties involved.

3.3 Appropriateness of the infrastructure of the participating organisations. The infrastructure of each partner is well fitted to the given ESRs projects and the Syn2Psy as a whole (please see **Syn2Psy chart** and **section 5**). The academic institutions have wide-ranging experience in supervising PhD projects and organising conferences. All institutions have laboratory space with equipment and logistics, classrooms and audio-visual facilities, appropriate for research project development and training. The non-academic institutions have extensive experience in interaction with academic institutions. The organizations have dedicated offices to welcome incoming students, and help ESR establish in the host institutions, helping them find housing and granting them access to institutional facilities through ID cards.

3.4 Competences, experience and complementarity of the participating organisations and their commitment to the programme

- **Consortium composition and exploitation of partners' complementarities**. The consortium consists of 7 beneficiaries (6 academic and 1 non-academic), in addition to 5 non-academic partner organisations. This ETN creates a well-balanced international, intersectoral and interdisciplinary research training in Neuroscience, with expressive collaboration between all institutions through shared researchers' supervision and secondments, and equitable distributed per work package. Our research topics and projects are ambitious and cutting-edge, and commit on complementary and synergistic expertise described in Fig. 3 (please also see section 5). Each Syn2Psy beneficiary and partner organisation offers excellence expertise and experience, and each project contributes to ESRs earning notable transferable skills. There are already links between beneficiaries, based on previous research training of students (namely within the Neurasmus-Erasmus Mundus programme, the European Neuroscience Campus Network and individual collaborations) as well as joint publications. Because of the collective strength of the consortium, future plans include application to other types of funding schemes to complement funding for the different projects or to develop new research projects.

- **Commitment of beneficiaries and partner organisations to the programme**. All beneficiaries and partner organisations will be highly active in the Syn2Psy research and training programme (please see Table 3.1 d), by either organizing courses/workshops or by providing their expertise at secondments, as well as in the D&C strategy and impact. All beneficiary organisations will recruit at least one ESR and receive at least one ESR from another organisation. This proposal has been written with joint collaboration of the Syn2Psy consortium. Different rounds of corrections were performed, with all parties providing input to design the individual research projects, the work packages, and the D&C strategy and impact. All beneficiaries and partner organisations will be in the supervisory board and the three committees, and will participate in the four network schools and project meetings.

i) Funding of non-associated third country. Not applicable.

ii) Partners organisations. **ZEISS, CHUC, Eurotrials**, **PIN** and **Marionet will provide a unique training and secondment opportunities to all ESRs.** The 3 partners will participate actively in all project meetings and will be represented in the supervisory board. The **Letters of Commitment** from the 5 partner organisations are annexed in section 7.

4. GANTT Chart

	Months	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
ESR Individual project	ESR1 (**CNC**+ICL+Eurotrials; WP1)							•																						s1	s1	s1	s1	s2	s2	s2																					☺
	ESR2 (**BMI-EPFL**+IINS-CNRS+CIP-UEDIN; WP1)							•																						s1	s1	s1	s2	s2	s2	s2																					☺
	ESR3 (**CNC+**CIP-UEDIN+Lundbeck+CHUC; WP1)							•																							s1	s1	s1	s2	s2	s2	s3	s3	s3																			☺
	ESR4 (**IINS-CNRS**+UEDIN+Eurotrials; WP2)							•																																			s1/2	s1/2	/													
	ESR5 (**ICL**+IBPS-CNRS+CHUC; WP2)							•																		s1	s1	s1	s1	s1	s1	s2	s2	s2																							☺
	ESR6 (**IINS-CNRS**+CNC+Lundbeck; WP2)							•																		s1	s1	s1	s1	s1	s1	s1	s2	s2	s2																					☺
	ESR7 (**CNC**+Lundbeck+ICL; WP2)							•																		s1	s2	s2	s2	s2	s2	s2	s2	s2	s2																					☺
	ESR8 (**ICL**+IINS-CNRS+CHUC+Lundbeck; WP2)							•																				s1	s1	s1	s1	s2	s3	s3																					☺
	ESR9 (**IBPS-CNRS**+ICL+CIP-UEDIN; WP2)							•																				s1	s1	s1	s1	s2	s2	s2	s2																					☺
	ESR10 (**IBPS-CNRS**+CNC+Eurotrials; WP3)							•																				s1	s1	s1	s1	s2																							☺
	ESR11 (**Lundbeck**+BMI-EPFL+CIP-UEDIN; WP3)							•																				s1	s1	s1	s2	s2	s2	s2																					☺
	ESR12 (**CIP-UEDIN**+CNC+IINS-CNRS; WP3)							•																				s1	s1	s1	s1	s2	s2	s2	s2	s2	s2																			☺
	ESR13 (**BMI-EPFL**+IINS-CNRS+ICL; WP3)							•																				s1	s1	s1	s1	s2	s2	s2	s2																					☺
	ESR14 (**CIP-UEDIN**+IINS-CNRS+Eurotrials; WP3)							•																				s1	s1	s1	s1	s1	s1	s2	s2																					☺
	ESR15 (**CIP-UEDIN**; WP3)																																											•												
Local training	Doctoral programmes							–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/												
	Course on animal experimentation							–	–	–	–	–	–	–	–	–	–	/																																						
	Other specialized courses							–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/								
	Seminars, journal clubs, thematic conferences							–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/								
Network-wide training	Network school 1							✓																																															
	Network school 2																																					✓																
	Network school 3																											✓																										
	Network school 4																																				✓																
	Specialized courses, transferable skills							–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/								
	Project meetings							**K**																				**I**																		–	–	–	–	–	–	–	–	–	–	**F**
Personal Career Development Plan								–	–	–	–	–	**P**	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/
Dissemination	Scientific community																		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/
	Undergraduate & Post-graduate students																		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/
	PIN and other patient organisations																		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/
	General public																		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/
Communication & Public engagement	Project identity						✓																																															
	Project website						–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/	–	–	–	–	–	–	/
	Media activities						–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/	–	–	–	–	–	–	/
	Social networks						–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/	–	–	–	–	–	–	/
	Open dissemination sessions						–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/	–	–	–	–	–	–	/
	Open science discussions						–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/	–	–	–	–	–	–	/
	Theatre script and Performance						–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	★
	Syn2Psy day																														–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	/
Management	Recruitment ESRs						**R**																																															
	Project monotoring and quality check												**R**												**R**												**R**																			

• Recruitment	– Time interval expected for the deliverable	**K** Kick-off meeting	**I** Intermediate meeting	**F** Final conference
P PCDP	✓ Network school event	**R** Report	☺ PhD thesis defense	★ Theatre / Concluded

5. Ethics Issues

The overall aim of **Syn2Psy** is to integrate molecules, synapses, neurons, circuits and behaviour to understand neuropsychiatric disorders, which is expected to contribute to the development of novel therapeutic strategies to treat those diseases. A multidisciplinary research team, involving scientists with a comprehensive know-how in the field of neuroscience, ranging from molecular and cellular studies to neurophysiology, neuronal circuits, neural dynamics and behaviour, complemented by leading non-academic partners, will participate in the proposal. The proposed work has implications on two different levels: the use of (i) laboratory animals and (ii) human-derived samples, from healthy volunteers and patients with *Shank3* mutations.

5.1 Experimentation with animals

All research groups belonging to the consortium have a long experience in research with rats and mice, the main models to be used in the proposed studies, and therefore are aware of the ethical implications of animal experimentation. The partner laboratories have been applying since several years the European Community guidelines for the care and use of laboratory animals, which have been acquired and transformed into operative rules by the national (Ministry of Health or Ministry of Agriculture) and local institutions (Health Services, Universities and their operative branches, the Departments and Institutes), and monitored by local Ethical Committees.

For research involving animals − small rodents in the case of the present project (all ESRs; approximately 100-150 rats/mice per year for each organization involved) − studies will be performed in compliance with Directive 2010/63/EU (revising Directive 86/609/EEC), that is transposed into the national law of all partners involved.

In **Portugal**, the above EU Directive is transposed to the law no. Decree-Law no. 113/2013, August 7 (Decreto-Lei n.º 113/2013 - Diário da República n.º 151/2013, Série I de 2013-08-07). An ethical approval is required and at **CNC** it needs to be submitted first to the Animal Welfare Body [ORBEA - *Órgão Responsável pelo Bem Estar Animal*] of the Animal House facility, which will then request final approval from the appropriate national authority (DGAV). Therefore, requests for the necessary approvals will be submitted in due time. An Animal Experimentation course (FELASA categories B-C) is mandatory for all CNC researchers/staff handling and/or experimenting on animals.

In **France**, experiments will be performed on mice in agreement with the 2010/63/EU directive relative to the "protection of animals used for scientific experiments". At IINS-CNRS (UMR5297), all projects involving laboratory animals are evaluated by the Ethics committee n°50 of Bordeaux, affiliated with the CNREEA (*Comité National de Réflexion Ethique sur l'Expérimentation Animale*). At IBPS-CNRS (CNRS UMR 8246, INSERM U1130), all projects involving laboratory animals are evaluated by the Ethics committee n°5 in Paris, affiliated with the CNREEA.

In **Switzerland**, the Federal Food Safety and Veterinary Office (FSVO) regulates the procedures for animal research. As indicated in their website (https://www.blv.admin.ch/blv/en/home/tiere/tierversuche/antrag-bewilligung-tv.html), "each individual animal experiment and laboratory animal facility must be approved". The legal requirements for the authorisation procedure for animal experiments and laboratory animal facilities are laid down in the Animal Protection Act (LPA) 16.12.2005 from the Swiss Federal Confederation Assembly (art. 80, al. 1 and 2, et 120, al. 2, of the Constitution) and the Animal Protection Ordinance (OPAn; 23.04.2008 law of 16.12.2005 of the Swiss Federal Council on animal protection, LPA, art. 19, al. 1, law of 21.03.2003 on genetic manipulations). Each application is assessed and approved very carefully and on a case-by-case basis. Various bodies are involved in assessing animal experiments and granting authorisations, and these bodies also run checks on each other. The cantonal committee on animal experimentation examines the application, clarifies any questions with the researchers and gives a recommendation to the cantonal veterinary office to grant or not the application. The licence is issued by the cantonal veterinary office. The FSVO then examines the cantonal veterinary office's decision and may request amendments. The period of validity of a license to conduct animal experiments is limited to three years (Art. 141 AniPO). Laboratory animal facilities must also be approved by the cantonal veterinary office. At the EPFL, the Veterinary from the Phenogenomics Center advices on animal ethical licenses. In addition, all EPFL animal researchers and staff from the Phenogenomics Center need to follow the DFE Ordinance 455.109.1, according to which “individuals who carry out or supervise animal experiments, must follow the introductory course in laboratory animal science (module 1; section 2: article 23; equivalent to the FELASA-B or EU directive function A). Principal investigators also have to attend a second course (module 2; section 3: article 27; equivalent to a FELASA-C course or EU directive function B), only following a mandatory 3-year period of animal experimentation, to acquire the expertise and techniques necessary to plan and supervise animal

experimental protocols. All FELASA-B and C trained experimenters must also follow 4-days of continuing education every 4 years.

In the **UK** animal research is performed under the Animal Scientific Procedures Act 1986 Amendment Regulations 2012 which amended the Animal Scientific Procedures Act 1986 (ASPA) to transpose European Directive 2010/63/EU. This involves a three tier licencing system which licences the Establishment (Establishment Licence - PEL), Body of work (Project Licence - PPL) and people performing scientific procedures (Personal Licence –PIL). Project Licences are renewed every 5 years and reviewed by an internal committee – the Animal Welfare and Ethical Review Body prior to submission for review and approval to the external licencing body, the Home Office in the UK. Personal Licence Holders undergo a formal training course approved by an external body and have ongoing competency assessed. In order to undertake an experiment, scientists must submit an Experimental Request Form describing the proposed study that is reviewed by the Named Veterinary Surgeons prior to being undertaken. Engagement with the 3Rs is encouraged at all stages of project preparation and during the lifespan of the Project Licence. A team of vets oversee animal care and welfare as well as experimental work and animal care is undertaken by trained animal technicians.

In **Denmark**, all experiments are carried out in accordance with the European Communities Council Directive (2010/63/EU) for the care and use of laboratory animals and the Danish legislation regulating animal experiments; Law and Order on Animal experiments; Act No. 474 of 15/05/2014 and Order No. 12 of 07/01/2016, and with the specific license for this experiment issued by the National Authority.

*

The **Syn2Psy** project will comply with the *Amsterdam protocol on animal protection and welfare*, which is characterized by the need to **Replace** animals whenever possible, to **Reduce** the number of animals used in experimental research, and to **Refine** procedures to minimize suffering (3Rs approach). The following principles will be implemented:

Reduction: While accepting the need for animal use to the advancement of scientific knowledge and for human and animal health and well-being, we will make all efforts to *reduce* the number of animals used in experiments to the minimum that is required for obtaining meaningful results. Adequate planning and exhaustive search of the available literature in the field will allow avoiding redundancy of experimentation, i.e., experiments that in all likelihood will not lead to meaningful results. Furthermore, whenever possible, preliminary in vitro experiments will be performed to determine the optimal conditions for animal experimentation in order to reduce the number of animals used. We will also work in close collaboration with in house statisticians to ensure that optimal (minimum) group sizes are chosen in all experiments performed. In order to reduce the number of animals used, we will also adopt the following measures: (i) pilot studies whenever appropriate to avoid unnecessary large-scale experiments, and (ii) a cumulative approach will be used to end animal experimentation as soon as statistical significance has been reached.

Replacement: A major effort will be made to keep animal experimentation to the minimum required and to *replace* the use of live animals by non-animal alternatives. The use of neuronal cell lines (e.g. differentiated HT22 cells) will avoid the use animals in several tasks of this proposal, and the use of primary cultures of neurons will also replace the use of live animals in several tasks. However, certain questions to be addressed in this proposal cannot be fully elucidated with *in vitro* systems and will therefore require the use of animal models of neuropsychiatric disorders, and the study of such models is an important aim of the project. In this case, utmost care will be taken in order to minimize the level of discomfort to the mice.

Refinement: Mice (wild type and genetically modified) will be housed in certified animal facilities at all participating institutions. Housing conditions will provide an adequate environment, water ad libitum and appropriate feeding, and the animals will receive all the care necessary for their well-being. Animal handling and all the experiments with rodents will be performed by trained investigators in order to ensure animal welfare. Furthermore, the use of animals in the project will be subjected to independent expert review, for both scientific and animal welfare considerations. Although some of the proposed studies may cause a certain level of suffering to the animals, all efforts will be made to keep this to an acceptable minimum. This will be ensured by monitoring clinical signs on a regular basis, and the animals will be sacrificed in case unintentional or accidental suffering is observed. It will be considered that experimental procedures that would cause pain in humans also cause pain in other vertebrates, unless there is evidence to the contrary. Therefore, any procedure that may cause more than momentary or minimal pain or distress to rodents will be performed, whenever appropriate, under sedation, analgesia, anaesthesia or any other suitable strategy to minimize pain or distress, in accordance with the best veterinary practice. The methodologies used in care and health monitoring of animals will be supervised by veterinarians or specialists in the field of laboratory animal science. Mice will be euthanized by CO_2 inhalation in

accordance with the American Veterinary Medical Association (AVMA) Guidelines on euthanasia (June 2007). This methodology does not cause the accumulation of exogenous chemical residues in the brain, and does not induce observable histological changes. CO_2 inhalation causes rapid depressant, analgesic, and anaesthetics effects, resulting from a direct depression of cerebral cortex and subcortical structures, and induces a direct depression of heart muscle, making this a safe and humane method of euthanasia. The euthanasia chambers available in all partner laboratories allow ready visibility of the animals, and are connected with a compressed CO_2 gas cylinder for a precise regulation of the gas inflow into the chamber. Animals will be left in the container until clinical death has been ensured. All individuals responsible for the euthanasia of mice are appropriately qualified. In order to ensure the best practice in experimental research with animals, all ESRs will be required to successfully conclude a FELASA course - Category B (for persons carrying out animal experiments).

5.2 Experimentation with human-derived samples

For research with patient derived cells (ESR3, 4, 8), the studies will be presented to the local Ethics Committee of the respective institutions and written informed consent will be obtained from all participants. For the patients who are unable to consent for themselves, a parent or legal guardian will consent to the study on their behalf. Concerning human data, we will follow the European Directive 95/46/EEC, Opinion 8/2010 on applicable law, adopted on 16 December 2010 by the Data Protection Working Party, the Directive 2009/136/EC of the European Parliament and of the Council of 25 November 2009 amending Directive 2002/22/EC, and the national laws. Data protection, confidentiality, and anonymity will be implemented. Informed consent will be obtained for all human-related material and data. Human patient data will be stored in a repository at the Universities/Clinical sites where the study is conducted. Access to the data will require approval of the coordinator and partners and a local ethical committee. Only Syn2Psy partners will have access to the experimental data. Data will be released to the public upon publication.

Human participants will be recruited to participate in ESR3 which involves the collection of personal data and tissues. No physical injury, financial, social or legal harm will be posed to the participants, and potential psychological risks will not exceed the daily life standard. We are not aware of and do not expect any potentially critical ethical implications of the research results such as the protection of dignity, autonomy, integrity and privacy of persons, biodiversity, protection of the environment, sustainability or animal welfare. The research will not involve stigmatisation of social groups, political or financial retaliation, benefit sharing or other malevolent use. The proposed research does not include research activity aimed at human cloning, is not intended to create human embryos, and does not involve the use of human embryos or embryonic stem cells.

ESR3 project involves the collection of human adult stem cells (from teeth) and fibroblasts (from gingival biopsy, associated with the tooth extraction) from patients and healthy controls. Of note, tooth collection for this project is secondary to standard dental treatment and will only be performed if deemed necessary by the patient/caregiver. All protocols will strictly adhere to the precepts set forth in the Declaration of Helsinki.

Patients and healthy volunteers will be referred from the Paediatric Services, namely from the Unit for Neurodevelopment and Autism of the Hospital Center of the University of Coimbra. For research involving human cells or tissue, law no. 12/2009, March 26 (*Lei n.º 12/2009 - Diário da República n.º 60/2009, Série I de 2009-03-26*) applies, which transposes to the national law Directive no. 2004/23/EU of the European Parliament and Directives no. 2006/17/CE and 2006/86/CE of the European Commission. This study and the associated Informed Consents have been approved by the Ethics Commission of the Faculty of Medicine, University of Coimbra.

Patient diagnosis will be assigned using gold standard instruments: including parental or caregiver interview (Autism Diagnostic Interview– Revised, ADI-R (Le Couteur et al. 2003; Lord et al. 1994)), direct structured proband assessment (Autism Diagnostic Observation Schedule, ADOS (Le Couteur et al. 2003; Lord et al. 1989; Lord and Rutter 1999), and clinical examination performed by experienced neurodevelopmental Paediatricians. The current diagnostic criteria for autism has been revised according to the Diagnostic and Statistical Manual of Mental Disorders 5, DSM-5 (American Psychiatric Association 2013). Only patients with positive results in the ADI-R and/or ADOS for autism or ASD, that meet the criteria for ASD from the DSM-5 will be included.

For this study (ESR3), prior to signing an informed consent form, participants and legal guardian will be informed of the study purpose, duration and possible adverse events of the study in a clear and unambiguous language and in terms understandable to the participants/legal guardian. Medical staff will clearly indicate that enrolment is voluntary, that refusal to participate would involve no penalty and that participation can discontinue at any time without penalty and without having to provide any explanation for the discontinuation. Written informed consent will then be obtained from the participants or their legal representatives. In cases where the recruited patient is a

minor, all data, informed consent and necessary claims shall be transmitted to the legal guardians. In addition, and whenever possible, verbal consent of the minor will be collected before the procedure.

This study (ESR3) will involve collection of samples from participants with ages from 5 to 12 years of age (for the collection of deciduous "milk" teeth) and of those with ages from 14 to 24 years of age (for the collection of third molars). There is no risk to the health of the volunteer/patient in participating in the study beyond the normal risks associated with dental treatment. Clinical procedures will be performed in a clinical setting and only if indicated by therapeutic indication (e.g. dental crowding; impacted third molars; orthodontic treatment etc…). If a participant abandons participation in the project, dental procedures will not be discontinued and all planned dental care will be administered to the patients.

The standard procedures of the dental extractions performed by the medical professional will include:

1. Collection of clinical history with indication of pathologies or medication of the participants.
2. Panoramic radiography (orthopantomography) for the evaluation and planning of the procedure.
3. Blood collection for clinical control, if necessary.
4. Dental extraction with infiltrative local anaesthesia, sedation or general anaesthesia, and surgical wound suture.
5. Gingival biopsy (during the dental extraction procedure) for collection of fibroblasts.
6. Suture removal and clinical evaluation 7 days after tooth extraction.

Dental derived samples will be stored at the Hospital Center of the University of Coimbra, which operates a licensed biobank. A governance system will be organized to determine access of other researchers to patient samples will be created and implemented to ensure the anonymity and confidentiality of data collected from all samples employed in this study.

Personal data, data protection and confidentiality

All personal data accessed by the researcher for the ESR3 research project is pseudoanonymised. **The confidentiality of participant information will be protected and the nature of the proposed studies does not give rise to stigmatization for those bearing the diseases under study.** Personal data of participants, including medical or health information collected or created as part of the study (such as medical records or test results) will not be required for this project after its collection, and should remain in the hospital's clinical registry in the Faculty of Medicine, University of Coimbra. The participants' clinical information will be used as follows:

1. The medical professionals at the Faculty of Medicine, University of Coimbra will collect the personal data in the clinical setting as standard procedure, by therapeutic indication.
2. Personal data will be associated with the participant's initials or another code that will not directly identify the participant and will be used by the researchers involved in the study.
3. The personal data, associated with the initials of the participant or another code that does not allow direct identification, may be communicated to national and international health authorities if needed.
4. The identity of the participant will not be disclosed in any reports or publications resulting from this study.
5. All individuals or entities with access to the participant's personal data are subject to professional secrecy.

For the ESR3 study, patient data collection for and processing will be performed according to standard clinical practice and all data will remain with the primary caregiver; scientific/academic researchers involved in the project will not have access to patient information (with exceptions highlighted below). Data protection is assured by the clinicians through the usage of the software "SClinico Hospitalar", which is maintained and certified by Portuguese Ministry of Health, via the office for Shared Services (SPMS, EPE) (http://spms.min-saude.pt/product/sclinicohospitalar/). Pseudoanonymization of samples will be performed by the primary caregiver. The research staff will not have access to patient data with the exception of a) sample code number, b) type of tissue collected (tooth number and cellular population) and all minimal relevant information such as: c) age, d) gender, e) neurodevelopmental diagnostics and co-morbidities and f) if the ASD is idiopathic or with known associated mutations or genetic syndrome.

Other relevant procedures and information, alongside with a declaration of compliance will be submitted as a deliverable to REA before the relevant work commences.

The participants in the ESR3 study will comply with:

1. The European Legal Framework and will apply its ethical standards and guidelines. Furthermore, the participants will comply to relevant EU legislation for human studies, including the Declaration of Helsinki in its latest version;
2. The EU Good Clinical Practice Directive (2001/20/EC);
3. The charter of fundamental rights of the EU (2000/C 364/01);

4. Directive 95/46/EC (amendment 2003) of the European Parliament and of the Council of 24 October 1995 on the protection of individuals regarding the protection of privacy, storing of personal data and on the free movement of such data;
5. Directive 95/46/EC on the protection of individuals regarding processing of personal data and on the free movement of such data; and
6. Council Directive 83/570/EEC of 26 October 1983 amending Directives 65/65/EEC, 75/318/EEC and 75/319/EEC on the approximation laid down by law, regulation, or administrative action relating to proprietary medicinal products.

The researcher and the beneficiary will ensure continuing compliance and will consider relevant revisions to the mentioned legislation and directives. Every periodic report and the final report will contain all ethical information related to the research completed and the research to come.

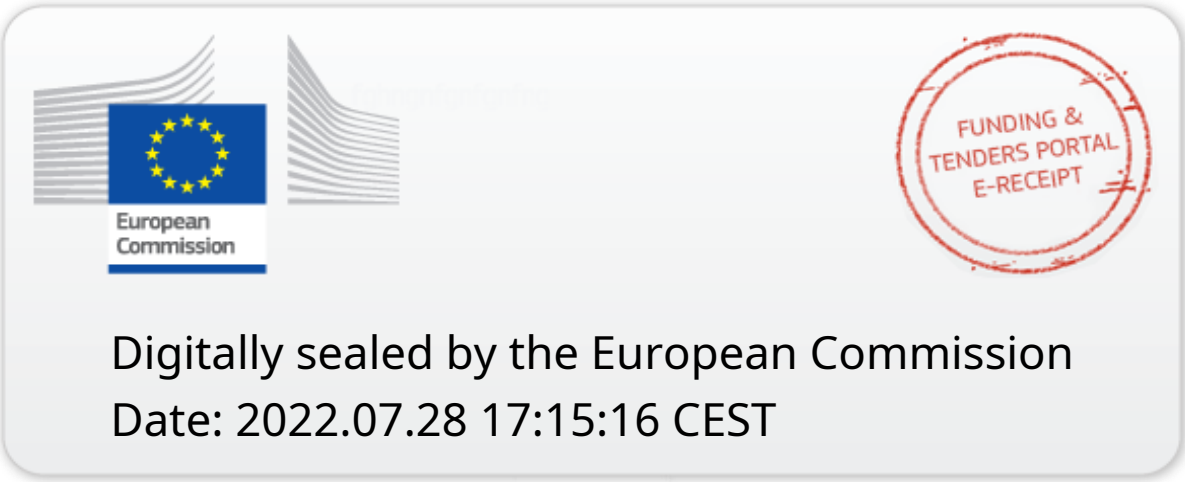
5.3 Ethics approval

The consortium confirms that all the proposed work will be conducted in accordance with the relevant national rules of the country where the research will be carried out. Whenever necessary, authorization will be requested by the competent research ethics committee or the medical ethical committee of the country where the work is conducted.

ESTIMATED BUDGET FOR THE ACTION

			Estimated eligible[1] costs (per budget category)											EU contribution		
			A. Costs for recruited researchers						B. Institutional costs				Total costs	Reimburse-ment rate %	Maximum EU contribution[2]	Maximum grant amount[3]
			A.1 Living allowance		A.2 Mobility allowance		A.3 Family allowance		B.1 Research, training and networking costs		B.2 Management and indirect[4] costs					
	Number of units (person-months)	Form of costs[5]	Unit		Unit		Unit		Unit		Unit					
			Costs per unit[6]	Total a[7]	Costs per unit[6]	Total b[7]	Costs per unit[6,8]	Total c[7]	Costs per unit[6]	Total d[7]	Costs per unit[6]	Total e[7]	f = a+b +c+d+e	g	h	i
1. CNC	108.00		2 753.34	297 360.72	600.00	64 800.00	250.00	27 000.00	1 800.00	194 400.00	1 200.00	129 600.00	713 160.72	100.00	713 160.72	n/a
2. CNRS	135.60		3 783.39	513 027.68	600.00	81 360.00	250.00	33 900.00	1 800.00	244 080.00	1 200.00	162 720.00	1 035 087.68	100.00	1 035 087.68	n/a
3. EPFL	72.00		3 963.24	285 353.28	600.00	43 200.00	250.00	18 000.00	1 800.00	129 600.00	1 200.00	86 400.00	562 553.28	100.00	562 553.28	n/a
4. Imperial	72.00		4 571.46	329 145.12	600.00	43 200.00	250.00	18 000.00	1 800.00	129 600.00	1 200.00	86 400.00	606 345.12	100.00	606 345.12	n/a
5. UEDIN	79.61		4 571.46	363 951.76	600.00	47 768.34	250.00	19 903.48	1 800.00	143 305.02	1 200.00	95 536.68	670 465.28	100.00	670 465.28	n/a
6. H. LUNDBECK AS	36.00		4 414.50	158 922.00	600.00	21 600.00	250.00	9 000.00	1 800.00	64 800.00	1 200.00	43 200.00	297 522.00	100.00	297 522.00	n/a
Total consortium	503.21		n/a	1 947 760.56	n/a	301 928.34	n/a	125 803.48	n/a	905 785.02	n/a	603 856.68	3 885 134.08	100.00	3 885 134.08	3 885 134.08

[1] See Article 6 for the eligibility conditions.
[2] This is the theoretical amount of EU contribution that the system calculates automatically (by multiplying all the budgeted costs by the reimbursement rate). This theoretical amount is capped by the 'maximum grant amount' (that the Commission/Agency decided to grant for the action) (see Article 5.1).
[3] The 'maximum grant amount' is the maximum grant amount decided by the Commission/Agency. It normally corresponds to the requested grant, but may be lower.
[4] The indirect costs covered by the operating grant (received under any EU or Euratom funding programme; see Article 6.3(b)) are ineligible under the GA. Therefore, a beneficiary that receives an operating grant during the action's duration cannot declare indirect costs for the year(s)/reporting period(s) covered by the operating grant (i.e. the unit cost for management and indirect costs will be halved for person-months that are incurred during the period covered by the operating grant), unless it can demonstrate that the operating grant does not cover any costs of the action.
[5] See Article 5 for the forms of costs.
[6] See Annex 2a 'Additional information on the estimated budget' for the details on the costs per unit.
[7] Total = costs per unit x number of units (person-months).
[8] The amount for the family allowance inserted by the system represents an average (with/without family). For the financial statements (Annex 4), this amount will be adjusted according to the actual family status of the recruited researchers (as specified in the 'researcher declaration').



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