



The Azrieli Neurodevelopmental Research Program
in partnership with
Brain Canada

Request for Applications Multi-Investigator Research Initiative (MIRI)

The Challenge

Developmental brain disorders are a leading cause of disability and impact not only the individuals affected, but also their family and the society in which they live. Autism Spectrum Disorders (ASD), Fragile X syndrome, fetal alcohol syndrome, cerebral palsy, schizophrenia, attention deficit disorder, dyslexia, epilepsy, intellectual disability, depression and neurological birth defects, among others, rob young people of the promise of a lifetime.

ASD now affects 1 in 88 children and 1 in 54 boys. The 2012 statistics reflect a 78% increase in reported prevalence in the last six years. More children will be diagnosed with autism this year than with AIDS, diabetes & cancer combined. There is no medical detection or cure for autism. Fragile X syndrome is the most common inherited form of mental impairment and affects 1 in 4,000 boys and 1 in 6,000 girls of all races and ethnic groups. While Fragile X individuals have a normal life expectancy, most will need support and care for their entire lives.

The Opportunity

There has never been a better time to invest in translational research on neurodevelopmental disorders. This has come about because of advances in genetics, genomics, structural biology, and neuroimaging, and the fruits of basic research such as better animal models of disease, insights into cellular neurobiology, and strategies for rational drug design. The result has been a dramatically improved understanding of the fundamental deficits in neuronal connectivity and communication in genetic disorders, including Fragile X syndrome and Rett Syndrome, and the rational application of drugs that may correct these deficits. Advanced and high-throughput genomic technologies are not only revolutionizing understanding and suggesting novel approaches to treatment: increasingly they are being used to provide an early molecular diagnosis for affected children. Early recognition of the specific problem permits the more effective application of behavioural therapies and provision of services, reducing the impact on the child and the family.

Fragile X syndrome (and other x-linked disorders) is a relatively under-researched area in Canada, despite being the most frequent form of inherited intellectual disability, and the Partners hope that this funding opportunity will encourage more talented research teams to apply their insight and imagination

to this particular class of neurodevelopmental disorder. Rapid advances are being made in the understanding of Fragile X syndrome, with new therapeutic opportunities arising from elucidation of the molecular pathways disrupted by the genetic alteration and their impact on synaptic function, leading in turn to neurobehavioural changes. For example, recent publications show that drugs affecting mGluR5 or 5-HT7 receptors are promising candidates for rational treatment of this syndrome.

While genetic research holds great promise for future interventions, improving current approaches to treatment of the behavioural and intellectual difficulties of children and adults with neurodevelopmental disorders must also be a priority. Recent well-controlled clinical trials have helped to identify effective antipsychotics for children with ASD, but better trials continue to be urgently needed to determine if other drugs commonly given, such as antidepressants, are truly effective, recognizing that underlying apparently similar behavioural problems may be a wide range of physiological defects. Randomized controlled trials of several behavioural therapies have also shown them to be of benefit to children with ASD, and there is enormous scope to build on this research to further refine behavioral interventions, and to increase their cost-effectiveness. With the better identification and diagnosis of ASDs and other neurodevelopmental disorders, an increasing population of affected individuals is moving into adulthood, and much more needs to be discovered about how best to support these individuals as they mature and age, helping them to enjoy satisfied and productive lives.

Canada has played a significant role in many discoveries about the neurodevelopmental disorders, and across the country there are leading laboratories and clinical research facilities able to contribute to the research effort. At the same time, there is a need to build capacity in this area of translational neuroscience, and to encourage collaboration with leading groups in other countries. Canada produces only about 3% of the research publications in this area, and our talented investigators and motivated trainees will benefit from stronger connections with the other 97% of the worldwide research effort.

The Initiative

The Azrieli Foundation and Brain Canada (the Partners), through this joint venture, wish to support excellent translational research in the area of neurodevelopmental disorders, with a special focus on ASD and Fragile X syndrome, through the efforts of Canadian research teams or teams involving Canadian and international scientists. By fostering collaboration between Canadian and international researchers working in this area, the Partners intend to accelerate research progress, and ensure the widest dissemination of the research outcomes. The ultimate goal of the initiative is to develop new diagnostics, treatment and prevention strategies for neurodevelopmental disorders, to reduce their economic and social burden on Canadians, and to improve the quality of life for those affected by neurodevelopmental disorders and their families. A secondary goal is to build Canadian research capacity in this area.

The Partners will support Canadian teams, or the Canadian components of international teams, proposing a **collaborative research project in the area of neurodevelopmental disorders, with specific focus on systems and/or translational approaches**. Systems neuroscience follows the pathways of information flow within the central nervous system, attempts to define the kinds of processing occurring there, and uses this information to help explain normal and abnormal behavioral

function¹. Translational research refers to studies conducted at the interface of fundamental and clinical research that transform scientific discoveries arising from laboratory, clinical, or population studies into clinical, behavioural or educational applications and interventions in order to reduce the incidence, severity and morbidity of neurodevelopmental disorders². Studies that integrate perspectives from cell biology, genomics, and behavioural sciences into systems or translational approaches are also welcomed. Proposals relevant to ASD or Fragile X syndrome are especially encouraged.

The Partners will each contribute \$750,000 a year, and other funding partners are encouraged to contribute to the initiative, possibly triggering additional matching contributions from the Canada Brain Research Fund³. It is expected that at least three teams will be funded, for five years (subject to satisfactory mid-term review in year 3), in the range of \$500,000 per year.

Funded MIRI teams may be invited to participate in an international symposium on progress in neurodevelopmental disorders organized by the Partners. This will provide an opportunity for interaction between the teams, for development of further international contacts and collaborations, and will assist the trainees in broadening their conceptual, technical, and professional horizons.

The Partners appreciate the effort involved in preparing multidisciplinary team applications. To encourage imaginative proposals from the widest range of multidisciplinary teams, this application process begins with submission of a simple letter of intent (LOI), and an expert review that focuses on innovative ideas with high potential impact, and the applicants' track record.

Brain Canada will operate the competition on behalf of both Partners, and both Partners will be involved in the selection of reviewers and will participate in the meetings of the selection committee. The Partners have agreed that their funding will flow only to applications that are recommended for funding by the selection committee, in descending order of merit until available funds are exhausted.

Scope and Focus

- Proposals that are relevant to ASD and Fragile X syndrome are especially encouraged, but they can also address any neurodevelopmental disorder if the outcome of the study is likely to have an impact also on ASD and Fragile X syndrome.
- Proposals should focus on systems and/or translational approaches,. The overall goal of proposals must be on the translation of scientific discoveries into interventions to reduce the incidence, severity and morbidity of neurodevelopmental disorders. Early-phase clinical trials can be included as a component of the project.
- The Partners will not support research projects that focus entirely on the fundamental biology and pathology of neurodevelopmental disorders and have no translational component, nor will they support requests for core facilities, research platforms, technology transfer, or business development activities.
- Proposals that describe an extension of the work of an existing team into a new area of

¹ Modified from the definition of the Department of Brain and Cognitive Sciences, MIT.
<http://bcs.mit.edu/research/systemsneuro.html>

² Modified from the National Cancer Institute Translational Research Working Group Definition of "Translational Research". <http://www.cancer.gov/trwg/TRWG-definition-and-TR-continuum>.

³ Interested potential partners are asked to contact Brain Canada (astride@braincanada.ca) to discuss how their funding could be matched.

translational research are acceptable.

- International collaboration is encouraged where it adds value to the efforts of the Canadian members of the team. The Partners' MIRI grants support the added costs of international networking, exchanges, and collaboration at a distance. However, the research activities of international collaborator(s) conducted outside Canada must be supported by other funds. Brain Canada will foster international partnerships to help provide these non-Canadian funds for successful international teams.
- The proposal must be feasible within the time and budget of a MIRI grant. One way of demonstrating feasibility is to provide preliminary data; however, for very novel proposals this may not be available, in which case applicants should explain carefully why the project is feasible.
- A MIRI grant will normally provide up to \$500,000 a year in each of five years for a total of \$2.5M. Applicants may provide a rationale for a different annual funding profile within the \$2.5M total if this facilitates their proposed research activities.
- MIRI grants may be used to support any aspect of the operating costs of the research project conducted in Canada or by researchers employed by a Canadian institution, including: supplies and materials; provision of special services and user fees; maintenance of essential equipment; travel of team members and trainees for collaboration and presentation of results; publication costs; salaries for technical personnel; stipends of trainees and funding of trainee exchanges with international collaborators; equipment that is currently unavailable but essential for the project. MIRI grants may not be used for salary payments to any team members who are eligible to apply for operating grants from the federal granting agencies, or who are resident outside Canada. MIRI grants do not provide institutional overhead.
- It is expected that data generated in these projects will be shared with and accessible to other researchers as soon as possible after it is generated, and in a form that respects the privacy of human subjects, in order to benefit the worldwide effort in neurodevelopmental research. This open sharing is subject to temporary confidentiality requirements necessary for protection and exploitation of intellectual property. Publications arising from Partner funding must be openly accessible within six months of the date of publication. This requirement can be met by depositing the final accepted manuscript in a major archive (such as PubMed Central) so that it can be located by the leading search engines.

Eligibility

- This competition is open to teams of two or more Canadian investigators in any scientific discipline, who are eligible to apply for research grants from the federal granting agencies (CIHR, NSERC, and SSHRC), and inclusion of international collaborators is encouraged. One of the Canadian team members will be the team leader, and will be the individual responsible for communication with the Partners.
- Teams must be multidisciplinary, and their members may be based in one or several Canadian and international research institutions. The team must include the range of expertise and experience required to carry out the proposed research.
- To build capacity and generate novel perspectives, Brain Canada encourages the formation of teams that include researchers at all stages of their careers, as well as researchers within and outside the neurosciences who wish to apply their expertise to problems of neurodevelopment.
- Participants from the government, industry, and the not-for-profit sectors are also welcomed in order to strengthen teams and facilitate the uptake of their research, but Brain Canada funds will

only support the portion of the work conducted in Canadian institutions eligible to receive funding from the federal granting agencies.

Criteria for Assessment

- **Innovation and originality.** Proposals which are solidly-based in scientific fact and offer new approaches to the translation of scientific discovery into novel and effective interventions for ASD, Fragile X syndrome or other developmental disorders. Since a track record of innovative and relevant research, appropriate for career stage, is a predictor of future performance, quality of the team and novelty of the proposal will both be critical components of the assessment.
- **Multidisciplinarity and teamwork.** Members from different disciplines contribute a specific value to the team, and the team as a whole achieves synergy of effort in order to accelerate research translation. International collaborators add value in terms of specific expertise, or access to unique research resources, or study populations.
- **Feasibility.** The goals of the project are attainable within the time and funding available, and the approach is realistic, ethical, and technically feasible.
- **Impact.** The proposed research has the potential to lead to new diagnostic, treatment and prevention strategies for neurodevelopmental disorders, in order to reduce their economic and social burden on Canadians, and to improve the quality of life for those affected and their families.

Sharing of Applications between the Partners

Brain Canada has to receive funds from the Azrieli Foundation in order to release matching funds from the Canada Brain Research Fund. Under confidentiality agreements, Brain Canada will share the full contents of relevant LOIs and applications with representatives of the Foundation, and may also share contents with other potential funding partners, in order to fund as many high-quality applications as possible. Applicants are advised to consult the Brain Canada website for details of how the Canada Brain Research Fund and partnerships operates.

Timeline

Call for Applications:	Dec 20, 2012
Deadline for Receipt of Letters of Intent:	16.00 EST April 5, 2013
Review of Letters of Intent:	April-May, 2013
Invitations to Apply sent:	May 27, 2013
Deadline for Receipt of Full Applications:	16.00 EDT August 16, 2013
Review of Full Applications:	August-September-October, 2013
Notification of Conditional Award sent:	October 14, 2013
Due diligence for removal of conditions:	Late October - early November 2013
Funding begins:	Earliest date, November 18, 2013

Letter of Intent (LOI)

Team leaders should contact Brain Canada (MIRI@braincanada.ca) with enquiries about the LOI process.

Before 16.00 EST April 5th, 2013, the team leader must send an email with the subject line “Neurodevelopment MIRI LOI submission” to **neurodev@braincanada.ca**, attaching a Portable Document Format (PDF) file containing the following information:

- **Cover Page:**
 - Title of proposal;
 - Name and contact details of team leader;
 - Amount requested in each of five years;
 - Up to 10 key words;
 - The following statement: “I certify that all members of the team have agreed to their inclusion in this LOI, and allow me to represent them throughout the application process. I also certify that all team members permit Brain Canada to circulate this LOI and subsequent full application to third parties, under a confidentiality agreement, for the purpose of securing matched funding”,
 - Signature of the team leader, date.
- **Pages 1 and 2:** A summary of the research project, emphasizing how its innovative features will accelerate the translation of scientific discovery into novel and effective interventions for neurodegenerative diseases, particularly ASDs and Fragile X syndrome. It is also important to explain how the project is feasible within the time and funding available from a MIRI grant
- **Page 3:** A description of the specific goals and outcomes of the project, its anticipated impact on neurodevelopmental diseases, and an explanation of how the applicants propose to disseminate and further develop their discoveries or interventions and apply them to practice, after the end of this grant.
- **Pages 4a, b, c, etc.:** Provide the name, institution, and disciplinary affiliation of each team member, including those from government, industry, not-for-profit organizations, and other countries. Explain why each member is essential to the project, and end with an overview of how the team will work together at a distance. (Ten lines for each team member, a page for team overview).
- **Pages 5a, b, c, etc.:** For each team member, cite up to five of their recent publications. These should be those that best illustrate the member’s previous experience in innovative systems or translational research, thus providing evidence of the applicant’s technical ability to contribute to the proposed project. Each item should be annotated with a brief reason for the selection. Include the DOI, URL or PMID where applicable so that reviewers can more easily access them (up to one page for each member).
- **Page 6:** Explain the role of any trainees in the project and explain what unique learning opportunities they will have, including those resulting from the international component.
- **Page 7: References** (up to one page).
- **Page 8, voluntary:** Names and contact information for three individuals not in conflict who would be competent to evaluate the LOI and subsequent full application, if invited (up to half a page). The Partners appreciate these suggestions, but do not commit to use them.

Use 12 point Arial or Georgia font, single-spaced, on a letter-size page with 1" minimum margins. It is the sole responsibility of the applicants to ensure their LOI submission is acceptable and received

before the deadline. Those received in any other format, exceeding the page limits, incomplete, or late, will be rejected. Brain Canada will acknowledge receipt of LOIs by email within one working day. If you do not receive acknowledgement please contact neurodev@braincanada.ca to check that your LOI was received.

Brain Canada does *not* require at the LOI stage signatures denoting institutional support, regulatory or ethical approval, CVs, copies of publications, etc. Material extraneous to that requested above will be removed before the LOI is sent to the reviewers.

Full MIRI Applications

Further details of the process will be provided to those invited to submit full applications. These will be up to **11 pages in length** including an outline budget, and will be accompanied by a full CV for team members. The criteria for assessment will be essentially the same as for the LOI, but may be modified or weighted on the basis of experience gained during review of the LOIs.

The Partners recognize that because of the rapid pace of discovery in the brain sciences, there may be changes in the project description or team membership between LOI and full application. Full applications that are judged by Brain Canada to differ substantially from the LOI will be referred to the Chairs of the LOI and full application Selection Committees. If the Chairs agree that the revisions have made the application more responsive to the assessment criteria it will be accepted. Revisions that are consistent with specific advice from Brain Canada will of course be acceptable.

Review and Decision Process

Brain Canada will operate the competition on behalf of both Partners, and both Partners will be involved in the selection of reviewers and will participate in the meetings of the selection committee.

Step 1: Review of Letter of Intent. The Partners will appoint an expert LOI selection committee, which will contain Canadian and international members, to assess all LOIs against the review criteria. The composition of the committee will reflect the topics covered by the LOIs received, and will not contain individuals who have submitted LOIs. The merit scores from the expert LOI committee will determine the outcome of the LOI review.

Team leaders will receive brief comments from the individual reviews of LOI selection committee members, and in the case of LOIs rated highly enough to be discussed in detail, notes taken at the committee meeting, explaining the reasons for the outcome of the LOI. The project titles and names of members of the teams invited to submit a full application will be published on the Brain Canada website. The Partners may advise teams that have submitted similar or complementary LOIs to consider a joint proposal.

Step 2: Review of Full MIRI Applications. The Selection Committee will be composed of experts of international stature, and who are not applicants, from within and outside Canada, recruited according to the range of topics to be reviewed. Full Applications will be reviewed by two expert external reviewers whose assessments will be provided to the Selection Committee, and each application will also be reviewed by two Selection Committee members. To ensure a fair review and minimize the possibility of misunderstandings, the Selection Committee will schedule a 20-30 minute tele- or video-

conference with each team leader, who may be supported by two team members. This permits the Selection Committee to clarify unresolved issues, and the applicants to respond to specific criticism. The Selection Committee will provide a merit score for each application, and recommend to the Partners those application that have received a sufficiently high merit score to be worthy of approval, in descending order of merit. All applicants will receive written comments from the expert reviewers and the Selection Committee.

The Partners will not entertain appeals against the assessment of the Selection Committee.

The Selection Committee membership will be posted on the Brain Canada website after the competition.

Step 3: Allocation of funding. The Partner's funding will be allocated, first and foremost, on merit. Only applications judged to be above the high standard of excellence set by the Selection Committee will be fundable. Such excellent applications will be conditionally approved by the Partners in order of merit until funds are exhausted. Successful applicants will be notified that their proposals have been conditionally approved, and informed of the conditions that must be met before funding can be released.

If full application quality does not meet their high standards, the Partners may fund fewer applications than planned, or none, and re-launch the competition.

Step 4: Due diligence. In order to reduce the burden on applicants, Brain Canada requires certain documentation (e.g. detailed budgets, details of concurrent research funding, regulatory and ethics approval) only from those applicants whose MIRI projects have been conditionally approved, though time-consuming items such as ethics approval should be sought earlier by all applicants. The required documents must be received and other conditions resolved within a reasonable period specified by Brain Canada, before funds can be released to the institution of the team leader. The team leader is responsible for distributing funds to the other team members, through their institutions.

Step 5: Mid-Term Review. In the third year of funding, the progress of MIRI teams will be reviewed, if possible by the original selection committee members who reviewed the full application. Details will be provided to funded teams. The mid-term reviewers may recommend that funding continue for the final two years without conditions; or that it be terminated with six month's notice due to lack of progress; or that it be continued conditional to specific changes in the teams workplan, composition, or funding level.

Confidentiality and Ownership

Brain Canada on behalf of both Partners owns all materials submitted by applicants for both LOI and full MIRI competitions. It will take reasonable steps to keep these materials confidential, and divulge them only to reviewers, committee observers, and representatives of the Azrieli Foundation, who have signed confidentiality agreements. Funded applications will be retained for comparison of intended and actual outcomes, as part of the final evaluation of the Initiative and the Canada Brain Research Fund.

The Partners do not claim ownership of intellectual property arising from research that they fund but encourage teams to disclose and protect intellectual property according to the policies of their institutions in order that it may be fully and rapidly exploited.

Reporting, Communications, and Evaluation

The Partners expect to support truly innovative and therefore inherently unpredictable research. They need to know if the risks in funding such research are acceptable. As a condition of continued annual funding of MIRIs, the Partners require a brief yearly progress report from the team leader, outlining project achievements and impacts realised, as well as difficulties encountered and steps taken to overcome them. Progress reports will be reviewed by members of the Selection Committee, with continued funding based upon a satisfactory review. If the Partners consider that a progress report is questionable, after discussion with the team, they may provide an extension to the period over which the funds are available, or cancel further funding. Details of the reporting process will be provided to funded MIRIs. Annual financial reports will also be required from the institutions employing the researchers, which hold the partner's funds in trust.

In order to demonstrate to Canadians the ongoing value of the Partnership and the Canada Brain Research Fund, MIRI team members will contact Brain Canada, for the Partners, in advance of the publication, release or public presentation of research results obtained with Partner funding, so that a joint press release or other publicity can be prepared. Embargoes will be strictly respected. Acknowledgment of The Azrieli Neurodevelopmental Research Program funding will accompany all publication, release or presentation of such research results.

At the end of the current Brain Canada Research Fund, Brain Canada wants to show that exceptional value was received for the investments of the federal government and the other partners. The Azrieli Foundation similarly needs to understand the impact of every grant and award. Ten percent of the final year's funding will be withheld and released on receipt of a satisfactory end-of-project report that describes the current and estimated future outputs and impacts of the MIRI research project.

For further Information

About the Azrieli Foundation: <http://www.azrielifoundation.org/>

About Brain Canada and the Canada Brain Research Fund: <http://braincanada.ca/>

About this MIRI competition: neurodev@braincanada.ca

Financial contribution from



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About the Canada Brain Research Fund

The Canada Brain Research Fund is a public-private partnership designed to encourage Canadians to increase their support of brain research, and maximize the impact and efficiency of those investments. Brain Canada has committed to raising \$100 million from private donors, which will be matched by government on a 1:1 basis. The Fund was announced in federal budget 2011, which proposed to “allocate up to \$100 million to establish the Canada Brain Research Fund, which will support the very best Canadian neuroscience, fostering collaborative research and accelerating the pace of discovery, in order to improve the health and quality of life of Canadians who suffer from brain disorders.”

The combined investment will fund research in ways that will accelerate the translation of research into new diagnostics, treatments and ultimately cures. Brain Canada will encourage all organizations raising funds for brain research to contribute directly to the fund and have their donor dollars matched, and/or to partner on research programs to further leverage the public-private match. Partnering with the Canadian Association for Neuroscience, Brain Canada has developed a national research program that will support areas of the greatest potential and need. Brain Canada believes that a collaborative approach to research will accelerate the translation of research discoveries into prevention, treatment and cure. Its approach will be to focus on the brain as a single complex system, rather than a collection of distinct diseases. The Multi-Investigator Research Initiative was the first of the Fund’s research programs, followed by Training Awards. Platform Support Grants for development and operating support of national neuroscience research resources will be announced in the coming months.