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The purpose of this form is to collect preliminary information about the planned project and the qualifications, professional training, and relevant experience of the individuals who will be involved in the translation. This information will be used to facilitate subsequent steps in the permission process.

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- Richard Keefe, Ph.D., Duke University School of Medicine
- J. M. Gold, Ph.D.
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Please provide the information requested in each of the sections below. If you do not complete all sections, we will not be able to process your request for permission to translate. Once the form is completed, please send it to the address below with a copy of the curriculum vitae of the lead researcher(s):

MATRICS Assessment, Inc.
914 Westwood Blvd., # 512
Los Angeles, CA 90024-2905
E-mail: matricsassessment@gmail.com

Upon submission of a completed form, the information you provide will be reviewed and shared with MCCB intellectual property owners. We will contact you in within four weeks with information regarding subsequent steps in the permission process.

**Research Organization Information**

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Please specify the language and dialect into which you wish to translate the test battery.
Swedish
Information about Lead Researcher(s)

Who will be the qualified individual or individuals overseeing the translation and use of this instrument?

Prof. Göran Engberg; Ass. prof. Sophie Erhardt; Ann Atlas Med. Dr, M.D.; Helena Fatouros Bergman Ph.D., reg. psychologist; Elisabeth Franzen-Röhl, Med. Dr, M.D.; Prof. Lars Lindquist; Prof. Kristian Borg; Prof. Birgit Sköldenberg, Bibi Johansson, M.D.; Ass. Professor Lena Flyckt, ass. prof. M.D.

Göran Engberg is the main applicant. He investigates interactions between activation of brain immune systems, (i.e. cytokines and KYNA) and dopaminergic/glutamatergic neurotransmission in schizophrenia. Recently, the cytokine IL-1β was found to be markedly elevated in CSF of first-episode schizophrenia patients. Sophie Erhardt develops animal models of schizophrenia and validates these models with regard to brain abnormalities and behavior. They have identified kynurenic acid as an important endogenous modulator of glutamatergic and dopaminergic transmission and demonstrated that this endogenous antagonist is elevated in schizophrenia. Their recent work is now focused on the importance of cytokines for the control of kynurenic acid and its implication for symptoms and cognition in schizophrenia and for CNS infections.

Professor Lars Lindquist has performed experimental as well as studies on clinical prospective material on clinical, genetically, chemical and immunological aspects of infections in the central nervous system. For more than two decades he has devoted much research in defining the cognitive dysfunction seen after viral CNS infections and has been involved in three major follow-up studies on thick borne encephalitis concerning the postencephalitic syndrome associated with this disease. Professor Birgit Sköldenberg is a word leading authority during three decades in the research field of herpes simplex virus encephalitis and meningitis. Professor Kristian Borg research includes immune modulation and analyzes of systemic and peripheral inflammatory and neurodegenerative parameters of patients with post-polio syndrome. His research also includes the effect of immune modulation on cognition and quality of life in patients with post-polio syndrome. He is the chief Head of the Neuro rehabilitation department at the Danderyds University Hospital and the Karolinska Institutet. Bibi Johansson, MD is a specialist of Infectious diseases with an interest in infections in the CNS and will register as a PhD student.

Lena Flyckt’s schizophrenia research ranges from amino acid uptake through cell membranes to studies of neurological aberrations, prediction of course of illness, gender differences and cognitive dysfunction in schizophrenia. An important accomplishment of her group was demonstrating that there is diversity among patients with schizophrenia with regard to the course of the illness that can be predicted by several factors at illness onset. They have also shown the existence of gender differences with regard to prognostic factors. The current focus of her program is to
define a subgroup within the schizophrenia cohort based on biomarkers and clinical characteristics (symptoms and cognition) indicating neuroinflammation.

More information about: Ann Atlas Med. Dr, M.D.; Helena Fatouros Bergman Ph.D., reg. psychologist; and Elisabeth Franzen-Röhl Med. Dr, M.D.; is given under the next headline.

Please describe the professional training in neuropsychological testing of the individual or individuals who will be involved in the translation process. Attach additional pages if necessary.

Professor Göran Engberg, Ann Atlas Med. Dr, M.D, Elisabeth Franzen-Röhl, Med. Dr, M.D. and Helena Fatouros Bergman Ph.D., reg. psychologist are the main persons who will be involved in the translation process.

Dr. Helena Fatouros Bergman is a registered psychologist with many years experience of working with patients with psychosis and schizophrenia, both with neuropsychological testing and with treatment. She has mainly worked with: WAIS-III, WAIS-III NI, Ravens Matrices, Benton Visual Retention Test, Claeson-Dahl verbal memory test, Rey Complex Figure Test, Trail Making Test, Dureman Sälde Battery and Vigilans from Wiener Test system. She has written her Ph.D. thesis on schizophrenia and is now a postdoctoral fellow at the Department of Clinical Neuroscience, Karolinska Institutet. Her post doc focuses on cognition in schizophrenia, she works in a multidisciplinary research consortium that includes expert schizophrenia scientists at Karolinska Institutet covering a wide range in the field of neuroscience, neuropsychiatry and immunology. She is working in the schizophrenia part of the project described in this application and will assist with supervision within the neuropsychological field for the project as a whole. She is a member of The Swedish Neuropsychological Society. She attended the course on MCCB that ass. professor Kathrine Burdick from Feinstein Institute of Medical Research, Long Island, USA, held at Karolinska Institutet in 2009 and has a good knowledge of MCCB and the different tests that are included within this battery.

Dr Ann Atlas (AA) and Dr Elisabeth Franzen-Röhl (EFR) are both specialists in infectious diseases with many years experience of working with patients with infectious diseases, especially infections in the central nervous system. They are head physicians at the Center of Infections in the Central Nervous System at the Department of Infectious Diseases at the Karolinska University Hospital, and are responsible for the part of the research project described in the present application with focus on cognition in patients with infections in the CNS. AA has written her Ph.D. thesis on HIV immunology and EFR has written her Ph.D. thesis on diagnostic methods on aseptic meningitis and herpes simplex virus (HSV) infection in the central nervous system (CNS) and the immune response in HSV. Since 1980 the Department of Infectious Diseases has been world leading on research of infections in the central nervous system. They have a large and unique collection of blood samples, spinal fluid samples
and medical history of patients with infections in the CNS. EFR is a member of the board providing the Swedish national recommendations on investigation and treatment of infections in the CNS. AA and EFR arranged the course on MCCB that ass. professor Kathrine Burdick from Feinstein Institute of Medical Research, Long Island, USA, held at Karolinska Institutet in 2009 and they have a good knowledge of MCCB and the different tests that are included within this battery.

Please describe the prior experience with foreign translations and cultural adaptations of the individual or individuals who will be involved in the translation process. Attach additional pages if necessary.

None.

Research Study Information
Please provide the title of your research project and a brief description (no more than one-half page per study):

Title: Implications of brain immunoactivation for cognition in: psychosis and CNS infections with herpes simplex virus, TBE, HIV, borrelia and pneumococcal infection.

The overall aim of this research project is to study the implication of brain immunoactivation for cognition in several diseases. Researchers at Karolinska Institutet have previously demonstrated that patients with schizophrenia display elevated CSF concentrations of kynurenic acid (KYNA), an endogenous metabolite of tryptophan (Erhardt et al., 2009). Numerous studies suggest that KYNA is a marker of immunoactivation (Dantzer et al., 2008). We have also found elevated levels of KYNA in cognitive impaired patients with HIV-I (Atlas et al., 2006) and in tick-borne encephalitis (TBE) (Schwieler et al., submitted). Our aim is to further study the implication of elevated levels of KYNA and of immunoactivation for cognition in several conditions; psychosis, neuroborreliosis, and CNS infections with herpes simplex virus, TBE, HIV and pneumococcal meningitis. All these diseases are associated with cognitive impairment. We want to evaluate cognition with MATRICS Consensus Cognitive Battery.

KYNA may potentially serve as a link between immunoactivation of the brain and cognitive impairment. Interestingly, elevated levels of KYNA seem to affect cognition in animal models. Pharmacologically elevated levels of brain KYNA induce schizophreni-like behaviour in rats (Erhardt et al., 2009), as well as impaired contextual learning and working memory (Chess et al., 2007), domains that to a large extent are affected in patients with schizophrenia. Elevated levels of brain KYNA in rats reduce prepulse inhibition (PPI) (Erhardt et al. 2004), a phenomena also observed in patients with schizophrenia. Knockout mice lacking the ability to produce KYNA display improved cognitive performance (Bergeron et al. 2007). KYNA is also elevated in Alzheimer's
disease and may be related to impaired memory and learning ability seen in these patients (Baran et al, 1999).

Our main questions are: Do KYNA levels fluctuate over time in the same patient and do brain KYNA levels correspond to a worsening in cognitive outcome. Furthermore, do patients with high levels of CSF KYNA at onset of the disease have a worse prognosis regarding to their cognitive functioning?

If it proves that KYNA is the link between immunoactivation of the brain and cognitive impairment, measuring the levels of KYNA in CSF could potentially help us identifying patients at risk for cognitive impairment. These patients could be offered cognitive training programs, and be treated with medications that lower the levels of KYNA. Clinical trials with Minocycline or selective COX-II inhibitors as adjunctive therapy for schizophrenia have shown positive outcomes on PANSS (Muller et al., 2002; Henry et al, 2008). However, the effect of these treatments on cognition remains to be evaluated.

When do you anticipate that the translation will be completed? Please provide a date of completion:
The goal is that the translation will be completed in September 2010. In September 2010 we will start the data collection for the schizophrenia part of the project that is described within this application. If the translation is not completed in September 2010 we will unfortunately not be able to use MCCB for this part of the project. However, we will still be able to use MCCB for the other parts of the project that involve patients with neuroborreliosis, and CNS infections with herpes simplex virus, TBE, HIV and pneumococcal meningitis, as data collection for these groups is planned to start later on.

Note: Because MAI wants to facilitate the translation of the MAI into multiple languages, and will approve only one translation per language, MAI reserves the right to cancel this agreement if the translation is not completed in a timely fashion. MAI will expect that the translation of the materials will be complete within 8 weeks after the date of completion that you have provided above. For example, if you have stated that the translation will be completed by January 1, then MAI would expect that IP owners will receive copies of the translated materials by February 27th.

When do you anticipate that the research project will be completed? Please provide a date of completion:
The project is planned to be completed in 2016. However, this is only a preliminary date and it is possible that the date of completion will be adjusted.

How many people will you be testing, at how many sites, and how many administrations of the MCCB will you conduct for your research project?
We estimate to include 120 patients with schizophrenia and 120 healthy volunteers. Both these groups will be tested at baseline and after one year. At present it may be difficult to predict the exact number of individuals. This is related to the success of the recruitment, a procedure that may be hampered by the request of undertaking a lumbar puncture which may increase the number of drop-outs. The testing is planned to be performed at two or three psychiatric clinics in the Stockholm area. A preliminary estimation of the specific number of administrations would be 240 for the patients and 240 for the controls. Depending on the success of the recruitment, we estimate to include 280 patients with infections in the CNS and 280 controls. The testing is planned to be conducted at three or four clinics of infectious diseases in the Stockholm area and southern part of Sweden. Both these groups will be tested at baseline, one year and after three years. A preliminary estimation of the specific number of administrations would be 840 for the patients and 840 for the controls.

Note: To review your request, an estimated specific number of administrations is required.