Neuroscience 310 (2015) 742–750

REDUCED CONNECTIVITY AND INTER-HEMISPHERIC SYMMETRY OF THE SENSORY SYSTEM IN A RAT MODEL OF VULNERABILITY TO DEVELOPING DEPRESSION

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Abstract—Defining the markers corresponding to a high risk of developing depression in humans would have major clinical significance; however, few studies have been conducted since they are not only complex but also require homogeneous groups. This study compared congenital learned helpless (cLH) rats, selectively bred for high stress sensitivity and learned helplessness (LH) behavior, to congenital non-learned helpless (cNLH) rats that were bred for resistance to uncontrollable stress. Naïve cLH rats show some depression-like behavior but full LH behavior need additional stress, making this model ideal for studying vulnerability to depression. Resting-state functional connectivity obtained from seed correlation analysis was calculated for multiple regions that were selected by anatomy AND by a data-driven approach, independently. Significance was determined by *t*-statistic AND by permutation analysis, independently. A significant reduction in functional connectivity was observed by both analyses in the cLH rats in the sensory, motor, cingulate, infralimbic, accumbens and the raphe nucleus. These reductions corresponded primarily to reduced inter-hemispheric connectivity. The main reduction however was in the sensory system. It is argued that reduced connectivity and inter-hemispheric connectivity of the sensory system reflects an internal convergence state which may precede other depressive symptomatology and therefore could be used as markers for vulnerability to the development of depression. **© 2015 IBRO. Published by Elsevier Ltd. All rights reserved.**

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Abbreviations: cLH, congenital learned helpless; cNLH, congenital non-learned helpless; DBS, deep brain stimulation; LH, learned helplessness; MDD, major depressive disorder; MRI, magnetic resonance imaging; RCC, Radial Correlation Contrast; ROIs, regions of interest; rs-fcMRI, resting-state functional connectivity MRI; SPM, statistical parametric map.

http://dx.doi.org/10.1016/j.neuroscience.2015.09.057
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Key words: high-risk for depression, resting-state functional connectivity MRI, congenital learned helpless (cLH) rats, congenital non-learned helpless (cNLH) rats, inter- and intra-hemispheric symmetry.

INTRODUCTION

There is a general consensus that the risk of being diagnosed with major depressive disorder (MDD) is high in certain families due to genetic reasons and in certain environmental and developmental conditions such as early postnatal adversities and stressful life events (Nestler, 2014). Depressive symptoms in these groups can appear after many years of normal behavior. It remains unclear, however, whether brain organization and function are different in this high risk population from healthy and/or depressed subjects. In spite of the high clinical value of identifying these patients, very few studies have been conducted in this field, in part due to the difficulty of obtaining homogeneous study groups. In the present study, a unique animal model hypothesized to be associated with vulnerability to depression was used, with the aim of identifying non-invasive biological markers for this vulnerability.

The current view of brain functionality attributes critical importance to the detection of normal and altered connectivity between brain structures, in particular for multiple system disorders such as depression. Non-invasive functional magnetic resonance imaging (MRI) measurements acquired during resting-state make it possible to estimate the functional connectivity between and within brain regions and to infer the existence of functional networks. Resting-state functional connectivity MRI (rs-fcMRI) was used here to identify biological markers that could point to vulnerability to depression.

Estimating alterations in network connectivity that lead to altered functionality is complex. A simpler approach is to search for alterations in regional connectivity which is done by comparing connectivity strength and volume between groups. For example, this type of analysis can show whether a reduction in regional connectivity known to have reduced connectivity in MDD patients (Iwabuchi et al., 2014; Liu et al., 2014; Lord et al., 2012; Peng et al., 2014; Ramasubbu et al., 2014), are related to depressive symptomatology or are present in a high-risk population.

The congenital learned helplessness rat strain is a well-established model for depression. In this model, Sprague–Dawley rats are bred based on their susceptibility to develop learned helplessness (LH) after uncontrollable shock (Schulz et al., 2010; Biedermann et al., 2012). Two strains have been developed by selective breeding: the congenital LH (cLH) strain which is highly susceptible to stress, and the congenital non-LH (cNLH) strain which is resistant to stress. The model has been shown to have excellent face validity, and cLH rats exhibit depressive-like behavior on several different behavioral tests (Vollmayr et al., 2004; Henn and Vollmayr, 2005; Sanchis-Segura et al., 2005; Enkel et al., 2010a). cLH rats show some behavioral abnormalities related to depression even without being subjected to a particularly stressful event (Sanchis-Segura et al., 2005; Richter et al., 2012); however, full LH behavior and other depressive-like behaviors (e.g. anhedonia) require additional stress (Enkel et al., 2010b). In this respect, rats that have not been exposed to any stress (term hereinafter 'naïve cLH' rats) are considered to be at high risk for developing depressive-like behavior, whereas the 'naïve cNLH' strain is stress-resistant. Thus, the unexposed, naïve cLH strain is an ideal model to identify markers for vulnerability to depression.

Here we tested the hypothesis that high risk for depression corresponds to altered functional connectivity of specific brain regions. By comparing functional connectivity of multiple regions obtained from rs-fcMRI data of cNLH and cLH rats, we sought to identify alterations between these strains that have been hypothesized to be associated with vulnerability to depression. We further assumed that the connectivity alterations in rats may correspond to similar alterations in humans.

EXPERIMENTAL PROCEDURES

Animals

All procedures were performed according to the regulations concerning animal experimentation in the European Union (European Communities Council Directive 86/609/EEC) and the German Animal Welfare Act. The experiments were approved by the German animal welfare authorities (Regierungspräsidium Karlsruhe) and conducted at the Central Institute of Mental Health, Mannheim, Germany. Sprague–Dawley rats were bred on the basis of their susceptibility to developing LH, which produces the cLH strain, and the cNLH strain resistant to uncontrollable stress. Twelve male cLH rats (362 ± 25 g) and 10 male cNLH rats (375 ± 31 g) (73rd generation) were used in the experiments. The animals were housed under controlled conditions (19–23 °C, 40–60% humidity) on a 12:12-h light–dark cycle (lights on at 7 am).

MRI measurements

The same data as reported in a previous publication (Gass et al., 2014) were used.

All experiments were conducted in a 94/20 Bruker Biospec MRI scanner (9.4 T; Bruker BioSpec, Ettlingen, Germany). Transmission and reception were achieved with a linear whole-body volume transmitter coil combined with an anatomically shaped 4-channel receive-only coil array for the rat brain. To position rats in the scanner (head first, prone), they were initially anesthetized with 4% isoflurane (Baxter Deutschland GmbH, Unterschleissheim, Germany) in a mixture of N_2 (70%) and O_2 (30%). Afterward isoflurane was supplied at ~2.5% for adjustments. Then a 0.5-ml bolus of medetomidine (Domitor®, Janssen-Cilag, Neuss; 0.07 mg/kg dissolved in saline) was injected subcutaneously. Within the next 10 min isoflurane was slowly discontinued, after which a continuous infusion of medetomidine solution began at a rate of 0.29 mg/kg/h. This anesthetic regime ensured stable conditions for the duration of the experiment (approximately 3 h). The acquisition of the rs-fcMRI dataset started approximately 15–20 min after the beginning of the medetomidine continuous infusion using an echo-planar imaging (EPI) sequence with the following parameters: repetition time/echo time (TR/TE) 1700/17.5 ms, flip angle 60°, one segment, 29 coronal slices (ascending slice order), 96×96 imaging matrix, field of view 35×35 mm^2, in-plane voxel dimension 0.365 mm, slice thickness 0.5 mm with 0.2-mm inter-slice gap, 300 acquisitions over 8.5 min.

MRI data analysis

The functional data were first processed in SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) using standard spatial preprocessing steps. Images were slice-time corrected, realigned and resliced but not spatially smoothed. In the second step, an analysis was performed using custom-made IDL and Matlab software. It included the use of the six rigid body transformation functions produced by the SPM related to motion as regressors and removing their effect, alignment of the MRI images to the rat brain atlas (Paxinos and Watson, 2007), and band-pass filtering ($0.01 < f < 0.1$ Hz).

Functional connectivity was calculated using the seed-correlation map approach which generated seed statistical parametric maps (seed-SPMs). Two methods for seed selection were used. One based on anatomy and the other was a data-driven method. 81 anatomy-based 3D regions of interest (ROIs), 32 cortical and 49 non-cortical were pre-selected in the atlas (Table 1). All ROIs were located between Bregma 4.68 mm and Bregma −7.32 mm (Paxinos and Watson, 1997). Structures that were distributed over more than five slices (3.5 mm) were separated into two or three ROIs. For the data-driven approach, we used the Radial Correlation Contrast (RCC) method (Goelman, 2004). RCC values of each voxel in each set were calculated for a radius of 1 pixel on the processed data after regression and filtering. RCC-SPM was obtained by a two-sample *t*-tests (for the RCC value difference between the cNLH and the cLH rat groups) and a cluster size threshold (yielding < 1% false positives). Clusters from this map were used as seeds to produced RCC-seed-SPMs. The RCC

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