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DISSERTATION

Die synergistische Aktivierung der Toll-like-Rezeptoren TLR3 und TLR9 beeinträchtigt das Gliomwachstum durch Beeinflussung von Mikroglia

Synergistic Toll-like receptor 3/9 signaling impairs glioma growth via affecting properties of microglia

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I. Abstract

Deutsch

In murinen, experimentellen Modellen von Gliomen hat die Aktivierung von TLR3 oder TLR9 in Mikroglia/Makrophagen nachweislich das Wachstum von Gliomen beeinträchtigt, was jedoch nicht in jüngsten, klinischen Studien verifiziert werden konnte. Deswegen haben wir getestet, ob die kombinierte Aktivierung von TLR3 und TLR9 in Mikroglia/Makrophagen einen synergistischen Effekt hat. Tatsächlich hat die kombinierte TLR3/TLR9-Aktivierung die Suppression des Wachstums von Gliomen in organotypischen Hirnschnitten von männlichen Mäusen in Abhängigkeit von Mikroglia positiv beeinflusst, und diese synergistische Suppression war von der Ausschüttung von Interferon β und der phagozytotischen Beseitigung des Tumors abhängig. Die kombinierte TLR3/9 Stimulation hat ebenfalls mehrere, funktionelle Eigenschaften von Mikroglia erhöht, wie beispielsweise die Ausschüttung von proinflammatorischen Faktoren, Beweglichkeit und phagozytotische Aktivität. Die Stimulation von TLR3/9 in Kombination mit einer CD47-Blockierung hat weiterhin zu einer vermehrten Beseitigung der Gliome geführt. Abschließend haben wir bestätigt, dass die Koaktivierung von TLR3/9 auch die Beeinträchtigung des Wachstums von Gliomen in vivo erhöht. Unsere Ergebnisse zeigen, dass die kombinierte Aktivierung von TLR3/9 in Mikroglia/Makrophagen eine effizientere Unterdrückung von Gliomen zum Ergebnis hat, was eine potenzielle Strategie für die Behandlung von Gliomen bieten könnte.

English

In murine experimental glioma models, TLR3 or TLR9 activation of microglial/macrophages has been shown to impair glioma growth, which could, however, not been verified in recent clinical trials. We therefore tested whether combined TLR3 and TLR9 activation of microglia/macrophages would have a synergistic effect. Indeed, combined TLR3/9 activation augmented the suppression of glioma growth in organotypic brain slices from male mice in a microglia-dependent fashion, and this synergistic suppression depended on interferon β release and phagocytic tumor clearance. Combined TLR3/9 stimulation also augmented several functional features of microglia such as the release of pro-inflammatory factors, motility and phagocytosis activity. TLR3/9 stimulation combined with CD47 blockade further augmented glioma clearance. Finally, we confirmed that the co-activation of TLR3/9 also augments the impairment of glioma growth in vivo. Our results show that combined activation of TLR3/9 in microglia/macrophages results in a more efficient glioma suppression, which may provide a potential strategy for glioma treatment.

II. Manteltext

State of the art – research

Glioblastoma (Glioma) is the most common (comprising approximately 80% of) malignant tumor in the brain, which cause high rate of mortality and disability (Marenco-Hillembrand et al., 2020). Glioma can be most commonly classified by World Health Organization (WHO) according to histologic properties with the spectrum from low grades (I and II) to high grades (III and IV). Current therapeutic strategies including aggressive resection followed by radiotherapy and chemotherapy received improving survival time of patients, while the overall medium survival time of glioma patients is merely 14 months(Marenco-Hillembrand et al., 2020).

Microglia, as the major myeloid cell population in central nerve system (CNS), play crucial role in maintaining brain hemostasis, exerting functions including brain development, synaptic pruning and immune responses (Helmut et al., 2011). Under disease conditions, microglia infiltrate, rapidly activate and polarize into certain phenotypes to react to the pathological signals (Helmut et al., 2011). In glioma, tumor tissue are not only containing tumor cells but also the non-transforming cells, which predominantly are resident microglia from the brain and circulating blood monocytes (macrophages), comprising approximately 30% of the cellular content of these tumors (Hambardzumyan et al., 2015). Over the past decade, these glioma associated microglia/macrophages (GAMs) are revealed that could closely interact with tumor cells to actively affect brain tumor biology (Gutmann and Kettenmann, 2019).

Multiple mechanisms underlying this pro-tumoral effect likely vary from tumor to tumor, while numerous potential etiologies have been identified (Ku et al., 2013; Hu et al., 2015; Dzaye et al., 2016). Toll like receptors (TLRs) are superfamily of pattern recognization receptors that recognize pathogens and mediate responses in innate immune cells by activating inflammatory pathways (Kawai and Akira, 2011). Previous studies illustrated that TLRs (TLR2, TLR4) play important role in glioma progression via regulating MMP9 (Hu et al., 2014), MMP14 (Markovic et al., 2009; Hu et al., 2015) and interleukin-6(Dzaye et al., 2016). On the other hand, some other TLRs (TLR3, TLR7, TLR9) activation on microglia mediate tumor suppression effect (Zhu et al., 2007; Buonfiglioli et al., 2019). Hence, understanding the mechanisms underlying the microglial TLRs regulating glioma progression is important to identify the potential novel therapeutic targets against tumor. In addition, our collaborating group previously reported that co-activating TLRs on microglia result synergistic impact on microglia properties and influence the neuro-inflammation (Rosenberger et al., 2014). Nevertheless, TLR3 ligands, and TLR9 ligands had been utilized in glioma treatment (Hartman et al., 2014; Jordan and Waxman, 2016; Carpentier and Lambert, 2017).

Therefore, we hypothesis that co-stimulation of TLR3 and TLR9 on microglia may synergistically induce microglial property changes which affect tumor growth. This study we focused on the effect of combined activation of TLR3/9 on microglia and the potential synergistic impact on glioma suppression.

Methodology

In this study, to determine the expression pattern of TLR3 and TLR9 on microglia or glioma tissues, we applied immunofluorescence staining to the human glioma tissues. Briefly, after fixation with 4% parformaldehyde solution (PFA), 40 μm free-floating tumor sections were prepared. Subsequently, slices were washed with PBS 3 times for 5 min and blocked with 5% of donkey serum and 0.1% Triton-X. Primary antibodies (1:500 dilution for Iba-1, 1:200 for TLR3 and 1:100 for TLR9) were incubated overnight. After washing with PBS, secondary antibodies Cy3 conjugated anti-rabbit IgG and DyLight 488 conjugated anti-goat were applied to the slices. Nuclei were labeled with 4,6-diamidino-2-phenylindole (DAPI).

We also performed quantitative real time PCR (qPCR) to the Magnetic activated cell sorting (MACS) sorted GAMs from human glioma tissue and normal murine microglia. In brief, tumor tissues were first rinsed with PBS and enzymatically digested into single-cell-suspension using Adult Brain Dissociation Kit. Single cell suspension was incubated with CD11b microbeads™ in MACS buffer and subsequently loaded onto a MACS column. CD11b-positive and CD11b-negative cells were then separated for qPCR. To examine the tumor growth, we generated the organotypic brain slices (OBS) with fluorescence labeled murine GL261mCherry tumor inoculation and singly or combined applied with TLR3 ligand Poly(I:C) and TLR9 ligand CpG Oligodeoxynucleotide (CpG ODN), which clodronate liposome was used to clarify the microglia effect. To detailed, 14-day-old Macgreen (CSF1R-EGFP) mice were decapitated, and brains were cut in coronal plane into 250 μm sections with a vibratome. Brain slices were transferred onto cell culture inserts containing with 0.4 μm pores. Culturing medium (DMEM supplemented with 10% heat inactivated FCS, 0.2 mM glutamine, 100 U/ml penicillin, and 100 mg/ml streptomycin) were added to the inserts. Liposome-encapsulated clodronate or liposome-encapsulated PBS diluted with culture medium (1:10) was added into the well for microglia depletion. Next, GL261mCherry cells were injected into the caudate putamen region of the slice in 150 μm depth of both hemispheres and after 5 days, slices were fixed with 4% PFA. Tumor volumes were assessed by confocal microscopy (LSM710, ZEISS) with Z-stack scanning and were reconstructed by IMARIS software into 3D model for volume evaluation. To evaluate density of tumor infiltrating microglia in the organotypic brain slice, EGFP fluorescence intensity or numbers within the tumor volume were quantified. Using immunofluorescence staining, cell

counting kit (CCK-8), and quantitative real time PCR (qPCR), glioma growth was determined. For CCK-8, briefly, GL261 cells were seeded in the 96-well plate. After treatment, CCK-8 reagent was added (10 ul per well) and incubated for 2 h. Plates were measured with a multi-reader at 450 nm absorbance.

Using qPCR, enzyme-linked immunosorbent assay (ELISA), we verified the phenotype changes of microglia after TLR3/9 activation. Besides, we identified interferon β (IFNβ) as main synergistic target of microglial TLR3/9 activation and the effect of IFNβ on glioma progression were also determined via immunofluorescence staining, CCK-8, qPCR and OBS.

Further, impact of TLR3/9 co-stimulation on microglial phagocytic capability was detected using fluorescence labeled beads and tumor cells using fluorescence-activated cell sorting (FACS) and *ex vivo* OBS. For phagocytosis beads assay, microglia were seeded on coverslips in a 24-well-plate and treated with Poly(I:C) and/or CpG for 24 h followed by adding YF fluorescent beads. Coverslips were then washed 3 times with PBS for 5 min and fixed with 4% PFA. Iba-1 was used to label microglia. Images were taken by a confocal microscope. Phagocytosis index was evalulated as total number of beads in Iba-1 positive cells divided by 100 number of DAPI-positive cells. To assess phagocytosis of glioma cells by microglia, similarly, microglia were seeded on coverslips in a 24-well-plate and treated with Poly(I:C) and/or CpG for 24 h. GL261mCherry cells were applied to coverslips and incubated for 2 h. coverslips were then fixed and stained for Iba-1 as described above. Coverslips were scanned with a confocal microscope (LSM710, Zeiss). Number of mCherry fluorescence within the iba1 volume was determined with IMARIS software as a proxy for glioma phagocytosis.

Furthermore, influence of TLR3/9 on microglial migrating activity was measured via *ex vivo* OBS, agarose spot and Boyden chamber assay. Briefly, low-melting point agarose was dissolved and mixed with or without Poly(I:C), CpG and Poly(I:C) + CpG, using PBS as negative control. Mixed solution was rapidly plated into glass-bottomed dishes. After cooling, microglial cells were plated in the dish in 2 ml DMEM supplemented with 10% fetal calf serum and incubated at 37°C for 3 h. Cells inside the spot were counted at the microscope. For Boyden Chamber, microglial cells in serum-free DMEM medium were added to the upper compartment, while the lower wells contained the TLRs ligands in medium, using polycarbonate filter (8 m pore size). The chamber was incubated for 6 h. Cells remaining on the upper surface of the membrane were removed by wiping, and cells in the lower compartment were fixed in methanol and subjected to Diff-Quik staining.

To verify the tumor inhibition impact induced by TLR3/9 activation, we generated *in vivo* tumor bearing mice and combined administrated with TLR3/9 ligands, which validating the *in vitro* and *ex vivo* tumor growth results. For GL261 *in vivo* model, anaesthetized mice were

mounted onto a stereotactic head holder. 1mm skin incision were made and the skull was drilled with a needle tip. Blunt tip syringe containing glioma cell suspension was slowly injected into the right caudate putamen. After surgery, mice were kept warm, and post-operative condition was monitored daily. For treatment, 14 days after tumor implantation, tumor-bearing mice were intra-peritoneally injected with 200 μg Poly(I:C) every 3 d. For CpG administration, mice were first anaesthetized, and 100 μg CpG in 2 μl volume was administered intratumorally.

In the end, CD47 blockade antibody was applied accompanied with to the TLR3/9 ligands to detect the tumor volume of organotypic brain slice system and tumor clearance in vitro using FACS.

A detailed description of all methods applied for this study can be found in the materials and methods section of Huang *et al*. (2020)

Essential new results

For the first time, Huang *et al.* illustrated that microglial combined activation of TLR3 and TLR9 synergistically suppress tumor growth that could be beneficial for potential therapeutic strategies.

Previous study from our group revealed that microglial TLR activation inhibits tumor growth(Buonfiglioli et al., 2019). Additionally, our collaborating group showed the synergistic effect of increasing pro-inflammatory cytokines induced by TLRs (TLR2 and TLR4) co-stimulation on microglia. Our current study explored the impact of TLR3/9 co-stimulation on microglia functions which affect tumor growth. First, we evaluated the tumor volume change after TLR3/9 combined activation, and observed that TLR3/9 co-stimulation drastically reduce tumor volume with microglia dependent fashion. We verified previous observations that microglia accumulate in the glioma tissue and acquire a defined phenotype. We found that infiltrating microglia expressed significant higher level of Secreted Phosphoprotein 1 (Spp1), Glycoprotein Nmb (Gpnmb), Matrix Metallopeptidase 14 (MMP14) and Matrix Metallopeptidase 9 (MMP9), which represents tumor-supporting phenotype of GAMs as we previously published (Szulzewsky et al., 2015). Next, microglia were singly or combined treated with TLR3/9 ligands, and conditioned medium of microglia (MCM) were collected to treat tumor cells. We revealed that MCM of TLR3/9 co-stimulated microglia synergistically suppressed glioma cell proliferation and induce cell apoptosis, indicating factors released from microglia activated through TLR3/TLR9 impeded glioma growth and promote tumor cell apoptosis. To further measure microglial phenotype affected by TLR3/9 co-activation, we assessed the pro-inflammatory genes and cytokines and we observed that Poly(I:C) alone increased Tumor necrosis factor α (TNFα), Interferon β (IFNβ), Interleukin 1β (IL1β), Nitric oxide synthase (NOS2), and Interleukin

6 (IL6) expression, while CpG increased TNFα, IL1β and IL6 expression. Combined application of Poly(I:C) + CpG augmented TNFα, IFNβ, NOS2 and IL12 expression compared to single stimulation with either Poly(I:C) or CpG, indicating that TLR3/9 combined stimulation synergistically induce pro-inflammatory genes expression and cytokines release.

It has been widely recognized that TLR3 and TLR9 signaling both activate IRF/type I IFN signaling, which IFNβ as crucial member of type I IFN has been identified as a potent anti-tumorogenic factors in multiple cancers (Borden, 2019), we therefore analyzed different time periods of stimulation and different agonist concentrations with respect to IFNβ release. Gene expression of IFNß was most prominently increased after co-stimulation with Poly(I:C) and CpG compared to control. In addition, the combined application of Poly(I:C) and CpG strongly enhanced IFNβ release compared to treatment with Poly(I:C) alone. Further, we testified whether microglia priming with either Poly(I:C) or CpG plays a role in the observed IFNβ release and we observed that CpG needed to be existing in the beginning to reach the synergistic effect of augmented IFNβ release, suggesting the priming effect of TLR9 signaling in TLR3 induced IFNβ release. Next, to verify the potential tumor inhibition effect of IFNβ, recombinant IFNβ was applied to the glioma cells. We found that IFNβ significantly suppressed the proliferation rate of GL261.In addition, we observed tumor volumes significantly decreased after incubation with IFNβ in the organotypic brain slices. We then examined the role of IFNβ in TLR3/9 co-activation induced glioma suppression neutralizing antibodies. We found that when the IFNβ neutralizing antibody was added to the respective supernatant, proliferation rate was no longer reduced. Taken together, TLR3/9 co-stimulation on microglia synergistically increased IFNβ release and IFNβ was the main effective cytokine of microglial TLR3/9 induced tumor proliferation reduction and apoptosis promotion.

To address microglial function influenced by TLR3/9 co-activation, we further found that TLR3/9 combined stimulation synergistically augment microglial phagocytosis activity engulfing fluorescence beads as well as tumor cells, indicating co-stimulation increase direct tumor clearance. In addition, we observed increasing infiltrating microglia in the tumor and higher migration capacity of microglia when stimulated with TLR3/9, and these increasing effect could be attenuated by PI3K/Akt inhibition, suggesting TLR3/9 co-stimulation enhance microglial motility via PI3K/Akt signaling cascade.

To verify the synergistic tumor suppression effect of microglia TLR3/9 activation, GL261 orthotopic murine glioma model was established and administrated with TLR3 and TLR9 ligands. We observed smallest tumor volume in the TLR3/9 ligands co-treatment group, and combined treatment significantly prolong average survival time of tumor bearing mice, indicating efficient tumor suppression compared to single treatment.

Furthermore, since recent studies demonstrated that tumor expressed CD47 is essential to negatively regulate microglia/macrophage phagocytic capacity in tumor clearance (Veillette and Chen, 2018), we also co-administrated CD47 neutralizing antibody along with TLR3/9 ligands and we found further augment of tumor clearance based on phagocytosis, suggesting the potential usage of combined the CD47 blockade and TLR3/9 activation in even more efficient glioma treatment.

In conclusion, combined microglial TLR3 and TLR9 activation triggers an anti-tumor phenotype of microglia, which affects glioma cells via release of cytokines, stimulates their phagocytic activity to directly attack glioma cells, and enhances migratory activity, which may explain increased accumulation of microglia in glioma tissue. Given the fact that single TLR3 and TLR9 stimulation have so far failed in clinical trials, treatment with combined stimulation of TLR3 and TLR9 in concert with CD47 inhibition might provide a novel approach for glioma therapy.

Further scientific questions

The findings of Huang *et al.*(2020) provides the first insight of impact of combined activation of TLR3/9 on microglia function and glioma growth, indicating novel therapeutic method to glioma treatment.

Toll-like receptors (TLRs) are a family of proteins that play a crucial role in the innate immune system, serving as pathogen recognition receptors which leads to comprehensive immune response. TLRs ligands raised plenty of interest in glioma treatment, which have confirmed therapeutic benefits as anti-tumor methods that regulate immune cells of the tumor microenvironment. TLR3/9 ligands were successfully assessed in glioma animal model and utilized in clinical trial against glioma while no satisfying outcome achieved until now (Butowski et al., 2009; Rosenfeld et al., 2010). As we stated above, microglial TLR3/9 activation synergistically impaired tumor growth via releasing IFNβ, phagocytosis enhancement. Previous studies showed that combination of TLRs achieved synergistic impacts on different cells. For example, combined administrated TLR2 with 4 or TLR4 with 7 agonists could form a potent adjuvant system that can be combined with multiple antigens to enhance the innate immunity (ref). Synergistic effect prompted by TLR 2/3 or TLR 2/4 activation has also been observed (ref). Therefore, it is necessary to investigate potential synergistic effect on tumor inhibition of other TLRs combination, using TLR3/7 or TLR7/9 for instance.

The delivery methods of the ligands are essential to the tumor inhibition efficiency. It has been exhibited that nanoparticles containing Poly(I:C) received satisfactory results of tumor

inhibition (Colapicchioni et al., 2015; Alipour Talesh et al., 2016), and the CpG ODN required to be intratumoral administrated (Meng et al., 2005; Alizadeh et al., 2010; Carpentier and Lambert, 2017). Thus, further important investigation could focus on using multiple novel delivery methods to test whether some of the methods improve the treatment efficiency.

In terms of mechanisms, TLRs interaction has been previously revealed (Kawai and Akira, 2011). Adaptor proteins and kinases are essential in the transducing TLRs signal. When triggered by the pathogens or agonists, adapter molecules within the cytoplasm of cells are recruited by TLRs to amplify the signal. There are four identified adapter molecules that involved in signaling. These proteins are known as Myeloid differentiation primary response 88 (MyD88), TIR Domain Containing Adaptor Protein (TIRAP, also called Mal), TIR-domain-containing adapter-inducing interferon-β (TRIF), and TRIF-related adaptor molecule (TRAM). TLR signaling could be divided into two distinct signaling pathways, the MyD88-dependent and TRIF-dependent pathway. The MyD88-dependent response occurs on every TLR including TLR9 except for TLR3. It might be interactions between the MyD88 dependent pathwas and TRIF-dependent pathways. While the mechanism of the synergistic effect remain unknown, especially the signaling cascade involving in the TLR3/9 interaction, which require further investigation to illustrate the cross-talk between TLR3/9 signaling.

In addition, immune checkpoint blockade became promising strategies in multiple cancers, which received exciting clinical outcomes (Ribas and Wolchok, 2018). TLRs ligands have become popular in company with immune checkpoints therapy against tumors (Sato-Kaneko et al., 2017; De Waele et al., 2018; Zhu et al., 2019). In our current study, TLR3/9 activation and CD47 blockade successfully synergistically suppress tumor growth. Further investigation could be performed to determine the impact of TLR3/9 ligands with PD-1 or PD-L1 blockade. Also, it will be interesting to identify whether other TLRs (TLR2, TLR5, or TLR7) amplify the immune-checkpoint inhibition induced tumor suppression. Last, we observed that TLR3 and 9 express redundantly in GAMs of human glioma tissue.

This study is based on murine glioma *in vitro*, *ex vivo* and *in vivo* model, which is difficult to perfectly reflect glioma micro-environment in human. Since our ultimate goal of the study is translating to human glioma treatment. Increasing publications reported the differentiation of human induced pluripotent stem cells (iPSCs) into microglia, provides the new methods for establishing humanized context(Abud et al., 2017). Furthermore, recent studies showed the chimeric model of inoculating human microglia in murine brain (Abud et al., 2017; Hasselmann et al., 2019; Xu et al., 2020), which could be served as a great model to investigate brain microenvironment in diseases. In addition, a novel organoid glioma model using primary human glioma gives us the other chance to verify therapy efficiency in different patients, based on

heterogeneity of glioma(Linkous et al., 2019). It would be extremely interesting to take advantage of these humanized models to further testify the potential therapeutic beneficial of TLRs ligands in glioma treatment.

Overall, Huang *et al.* (2020) provides the very first insights of the effect of microglial combined TLR3/9 activation on microglial properties and affecting tumor growth, which provides multiple further investigation potentiality for microglia based glioma intervention.

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III. Statutory Declaration

“I, Yimin Huang, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “Synergistic Toll-like receptor 3/9 signaling impairs glioma growth via affecting properties of microglia”/ “Die synergistische Aktivierung der Toll-like-Rezeptoren TLR3 und TLR9 beeinträchtigt das Gliomwachstum durch Beeinflussung von Mikroglia”, independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Declaration of your own contribution to the top-journal publication for a MD/PhD degree

Yimin Huang contributed the following to the below listed publication:

Publication : Yimin Huang, Quan Zhang, Malgorzata Lubas, Yang Yuan, Fatih Yalcin, Ibrahim E. Efe, Pengfei Xia, Edyta Motta, Alice Buonfiglioli, Seija Lehnardt, Omar Dzaye, Charlotte Flueh, Michael Synowitz, Feng Hu*, Helmut Kettenmann*
*equally contributed
Title: Synergistic Toll-like receptor 3/9 signaling affects properties and impairs glioma-promoting activity of microglia
Journal: The Journal of Neurosicence
Publication year: 2020
Contribution (in detail): I involved in conception of the study. In addition, data from Figure 1A-1H,Figure 2A, Figure 3A-3H, Figure 4A-4H, Figure 5A-5G, Figure 6A, 6B,6D, Figure 7A-7F, Figure 8A,8D,8G were performed and analysed by me. Also, all the supplementary data were generated by me. All the figures were prepared and composed by me. Besides, I wrote the first and revision version of the draft. Quan Zhang helped to generate data of Figure 6C. Malgorzata Lubas, Yang Yuan, Ibrahim Efe and Pengfei Xia helped to generate data of Figure 2B, Figure 3A and Figure 3B. Fatih Yalcin helped to generate data of Figure 8B and 8E. Edyta Motta offered help in preparation of Figure 3I. Alice Buonfiglioli, Seija Lehnardt and Omar Dzaye involved in conception of the study and experimental materials preparation. Charlotte Flueh, Michael Synowitz helped with experimental materials organization and preparation. Feng Hu and Helmut Kettenmann involved in conception of the study, supervising the project, providing funding and manuscript preparation and revision.

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Signature, date and stamp of first supervising university professor / lecturer

_____
Signature of doctoral candidate

IV. Excerpt of Journal Summary List “Neurosciences”

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI
Selected Categories: **“NEUROSCIENCES”** Selected Category Scheme: WoS
Gesamtanzahl: 267 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	NATURE REVIEWS NEUROSCIENCE	43,107	33.162	0.068480
2	NATURE NEUROSCIENCE	63,390	21.126	0.164700
3	ACTA NEUROPATHOLOGICA	20,206	18.174	0.041660
4	BEHAVIORAL AND BRAIN SCIENCES	9,377	17.194	0.010240
5	TRENDS IN COGNITIVE SCIENCES	27,095	16.173	0.040040
6	JOURNAL OF PINEAL RESEARCH	10,695	15.221	0.010560
7	NEURON	95,348	14.403	0.218680
8	TRENDS IN NEUROSCIENCES	20,163	12.314	0.024480
9	Annual Review of Neuroscience	14,042	12.043	0.015020
10	MOLECULAR PSYCHIATRY	20,353	11.973	0.049290
11	BRAIN	52,970	11.814	0.074030
12	BIOLOGICAL PSYCHIATRY	43,122	11.501	0.053320
13	PROGRESS IN NEUROBIOLOGY	12,929	10.658	0.013230
14	Nature Human Behaviour	1,230	10.575	0.006550
15	SLEEP MEDICINE REVIEWS	6,920	10.517	0.010920
16	ANNALS OF NEUROLOGY	37,336	9.496	0.048630
17	Molecular Neurodegeneration	4,248	8.274	0.011350
18	NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS	26,724	8.002	0.051580
19	FRONTIERS IN NEUROENDOCRINOLOGY	4,196	7.852	0.005490
20	Neurology-Neuroimmunology & Neuroinflammation	1,996	7.353	0.008220
21	NEUROPSYCHOPHARMACOLOGY	25,672	7.160	0.039090

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
22	Brain Stimulation	5,457	6.919	0.014470
23	NEUROPATHOLOGY AND APPLIED NEUROBIOLOGY	3,876	6.878	0.006420
24	NEUROENDOCRINOLOGY	5,046	6.804	0.005690
25	NEUROSCIENTIST	4,986	6.791	0.008520
26	BRAIN BEHAVIOR AND IMMUNITY	14,533	6.170	0.025700
27	BRAIN PATHOLOGY	5,263	6.155	0.007880
28	Alzheimers Research & Therapy	3,160	6.142	0.010700
29	JOURNAL OF NEUROSCIENCE	175,046	6.074	0.233460
30	JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM	19,766	6.040	0.028050
31	PAIN	38,312	6.029	0.039070
32	CURRENT OPINION IN NEUROBIOLOGY	15,090	6.014	0.033650
33	Acta Neuropathologica Communications	3,063	5.883	0.014190
34	Translational Stroke Research	1,955	5.847	0.004330
35	GLIA	14,003	5.829	0.018760
36	NEUROIMAGE	99,720	5.812	0.132720
37	NEURAL NETWORKS	13,063	5.785	0.016060
38	NEUROPSYCHOLOGY REVIEW	2,971	5.739	0.003940
39	Molecular Autism	2,107	5.712	0.008000
40	Journal of Neuroinflammation	11,767	5.700	0.023240
41	Multiple Sclerosis Journal	11,501	5.649	0.022750
42	Annual Review of Vision Science	458	5.622	0.003300
43	Neurotherapeutics	4,475	5.552	0.009060
44	Translational Neurodegeneration	810	5.534	0.002420

Selected JCR Year: 2018; Selected Categories: "NEUROSCIENCES"

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
45	CEREBRAL CORTEX	30,675	5.437	0.059570
46	JOURNAL OF PAIN	10,405	5.424	0.018280
47	NEUROBIOLOGY OF DISEASE	16,363	5.160	0.026710
48	NEUROINFORMATICS	1,277	5.127	0.002920
49	JOURNAL OF PHYSIOLOGY-LONDON	52,037	4.950	0.041100
50	BIPOLAR DISORDERS	5,143	4.936	0.006760
51	Developmental Cognitive Neuroscience	2,470	4.920	0.009240
52	JOURNAL OF PSYCHIATRY & NEUROSCIENCE	3,293	4.899	0.004540
53	JOURNAL OF NEUROCHEMISTRY	35,902	4.870	0.026140
54	Dialogues in Clinical Neuroscience	3,384	4.867	0.004730
55	Annals of Clinical and Translational Neurology	1,858	4.656	0.008750
56	CURRENT OPINION IN NEUROLOGY	5,290	4.647	0.009650
57	MOLECULAR NEUROBIOLOGY	12,806	4.586	0.027560
58	SLEEP	21,434	4.571	0.024240
59	Current Neuropharmacology	3,508	4.568	0.005650
60	EXPERIMENTAL NEUROLOGY	20,500	4.562	0.023440
61	HUMAN BRAIN MAPPING	22,040	4.554	0.043230
62	Journal of Neural Engineering	7,336	4.551	0.012190
63	EUROPEAN NEUROPSYCHOPHARMACOLOGY	7,488	4.468	0.015500
64	CEPHALALGIA	9,983	4.438	0.014480
65	NEUROBIOLOGY OF AGING	22,409	4.398	0.037090
66	EUROPEAN JOURNAL OF NEUROLOGY	10,488	4.387	0.016970

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
67	NEUROPHARMACOLOGY	20,604	4.367	0.034460
68	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	10,674	4.315	0.012400
69	Cognitive Computation	1,578	4.287	0.002230
70	CORTEX	10,302	4.275	0.024590
71	Neuroscience Bulletin	2,027	4.246	0.004070
72	JOURNAL OF PSYCHOPHARMACOLOGY	6,460	4.221	0.010120
73	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	6,551	4.207	0.012320
74	JOURNAL OF NEUROSCIENCE RESEARCH	12,976	4.139	0.010060
75	Molecular Brain	2,467	4.051	0.007180
76	PSYCHONEUROENDOCRINOLOGY	16,809	4.013	0.028150
77	NEUROCHEMISTRY INTERNATIONAL	8,775	3.994	0.009020
78	NUTRITIONAL NEUROSCIENCE	1,778	3.950	0.002260
79	Frontiers in Systems Neuroscience	4,801	3.928	0.015360
80	JOURNAL OF HEADACHE AND PAIN	3,308	3.918	0.007210
81	Frontiers in Cellular Neuroscience	9,711	3.900	0.035870
82	Journal of Neuroimmune Pharmacology	2,486	3.870	0.004750
83	ACS Chemical Neuroscience	5,238	3.861	0.013320
84	CELLULAR AND MOLECULAR NEUROBIOLOGY	4,488	3.811	0.005740
85	NEUROGASTROENTEROLOGY AND MOTILITY	8,314	3.803	0.014510
86	JOURNAL OF NEUROTRAUMA	14,754	3.754	0.019770
87	Fluids and Barriers of the CNS	1,127	3.727	0.002650
88	Frontiers in Molecular Neuroscience	4,752	3.720	0.014230

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
89	Journal of Parkinsons Disease	1,768	3.698	0.006340
90	CLINICAL NEUROPHYSIOLOGY	19,574	3.675	0.021420
91	Social Cognitive and Affective Neuroscience	6,966	3.662	0.020880
92	Frontiers in Neuroscience	13,198	3.648	0.043000
93	Frontiers in Aging Neuroscience	6,791	3.633	0.020910
94	Brain Structure & Function	6,077	3.622	0.019520
95	NEURAL PLASTICITY	3,691	3.591	0.010510
96	Journal of Neurodevelopmental Disorders	1,253	3.590	0.003420
97	Journal of NeuroEngineering and Rehabilitation	4,974	3.582	0.008800
98	Neurophotonics	809	3.581	0.002760
99	JOURNAL OF ALZHEIMERS DISEASE	20,383	3.517	0.041470
100	PSYCHIATRY AND CLINICAL NEUROSCIENCES	3,720	3.489	0.004230
101	JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY	9,205	3.460	0.007510
102	JOURNAL OF SLEEP RESEARCH	5,432	3.432	0.007450
103	PSYCHOPHARMACOLOGY	23,565	3.424	0.022260
104	Current Opinion in Behavioral Sciences	1,763	3.422	0.009020
105	CEREBELLUM	2,785	3.413	0.005970
106	Current Neurology and Neuroscience Reports	3,004	3.400	0.007210
107	CNS Neuroscience & Therapeutics	2,993	3.394	0.005990
108	PSYCHOPHYSIOLOGY	14,275	3.378	0.012150
109	Cognitive Neuroscience	570	3.361	0.001630
110	NEUROTOXICITY RESEARCH	3,067	3.311	0.003750

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
111	HIPPOCAMPUS	8,733	3.267	0.013090
112	NEUROTOXICOLOGY	7,180	3.263	0.007100
113	NEUROSCIENCE	45,939	3.244	0.050820
114	JOURNAL OF COMPARATIVE NEUROLOGY	30,418	3.239	0.017320
115	Current Alzheimer Research	4,026	3.211	0.005930
116	EUROPEAN JOURNAL OF PAIN	7,263	3.188	0.011070
117	GENES BRAIN AND BEHAVIOR	3,670	3.157	0.005300
118	BRAIN TOPOGRAPHY	2,629	3.104	0.004920
119	BRAIN RESEARCH BULLETIN	9,445	3.103	0.006570
120	Frontiers in Neural Circuits	3,107	3.101	0.014190
121	JOURNAL OF THE INTERNATIONAL NEUROPSYCHOLOGICAL SOCIETY	6,773	3.098	0.007380
122	Nature and Science of Sleep	520	3.054	0.001290
123	JOURNAL OF NEUROENDOCRINOLOGY	5,826	3.040	0.005430
124	Purinergic Signalling	1,617	3.038	0.002390
125	JOURNAL OF COGNITIVE NEUROSCIENCE	16,898	3.029	0.017960
126	Cognitive Neurodynamics	914	3.021	0.001650
127	NEUROBIOLOGY OF LEARNING AND MEMORY	6,836	3.010	0.013440
128	Frontiers in Neurorobotics	609	3.000	0.001370
129	Progress in Brain Research	8,018	2.961	0.006860
130	HEARING RESEARCH	9,237	2.952	0.010490
131	BRAIN RESEARCH	53,805	2.929	0.031770
132	Frontiers in Neuroanatomy	2,971	2.923	0.010280

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
133	JOURNAL OF NEURAL TRANSMISSION	6,900	2.903	0.008030
134	NEUROTOXICOLOGY AND TERATOLOGY	3,789	2.902	0.003360
135	NEUROPSYCHOLOGIA	25,503	2.872	0.028230
136	Frontiers in Human Neuroscience	18,310	2.870	0.060330
137	MOLECULAR AND CELLULAR NEUROSCIENCE	6,693	2.855	0.007020
138	JOURNAL OF NEUROIMMUNOLOGY	10,184	2.832	0.009550
139	Frontiers in Integrative Neuroscience	2,134	2.810	0.005670
140	NEUROLOGIC CLINICS	2,233	2.802	0.003290
141	Neurodegenerative Diseases	1,560	2.798	0.002450
142	Brain Sciences	1,190	2.786	0.003460
143	JOURNAL OF NEUROSCIENCE METHODS	17,224	2.785	0.016110
144	EUROPEAN JOURNAL OF NEUROSCIENCE	25,695	2.784	0.021530
145	NEUROCHEMICAL RESEARCH	9,744	2.782	0.012030
146	JOURNAL OF VESTIBULAR RESEARCH-EQUILIBRIUM & ORIENTATION	1,117	2.774	0.001440
147	PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR	12,045	2.773	0.008570
148	BEHAVIOURAL BRAIN RESEARCH	25,833	2.770	0.034190
149	SEIZURE-EUROPEAN JOURNAL OF EPILEPSY	5,557	2.765	0.010290
150	CNS & Neurological Disorders-Drug Targets	2,898	2.761	0.004910
151	IEEE Transactions on Cognitive and Developmental Systems	221	2.755	0.000300
152	Molecular Pain	3,466	2.746	0.005720
153	JARO-JOURNAL OF THE ASSOCIATION FOR RESEARCH IN OTOLARYNGOLOGY	2,145	2.716	0.003400
154	NEUROLOGY INDIA	2,607	2.708	0.001990

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
155	ASN Neuro	936	2.707	0.001890
156	BRAIN AND LANGUAGE	6,613	2.700	0.008080
157	Frontiers in Neuroinformatics	2,213	2.680	0.007300
158	NEUROPSYCHOLOGICAL REHABILITATION	2,173	2.667	0.002360
159	COGNITIVE AFFECTIVE & BEHAVIORAL NEUROSCIENCE	3,775	2.661	0.007460
160	JOURNAL OF THE NEUROLOGICAL SCIENCES	17,679	2.651	0.023320
161	Frontiers in Neurology	6,274	2.635	0.019550
162	Experimental Neurobiology	876	2.630	0.002520
163	Frontiers in Behavioral Neuroscience	6,340	2.622	0.022380
164	BMC NEUROSCIENCE	4,813	2.620	0.005520
165	BRAIN AND COGNITION	6,828	2.619	0.006650
166	JOURNAL OF NEUROPHYSIOLOGY	43,309	2.614	0.037050
167	NEUROMUSCULAR DISORDERS	5,164	2.612	0.008560
168	Developmental Neurobiology	3,083	2.600	0.005580
169	JOURNAL OF MOLECULAR NEUROSCIENCE	5,244	2.577	0.007890
170	NEUROMOLECULAR MEDICINE	1,960	2.576	0.002630
171	International Review of Neurobiology	2,778	2.551	0.003960
172	SYNAPSE	3,956	2.545	0.002550
173	CLINICAL AUTONOMIC RESEARCH	1,761	2.485	0.001950
174	NEUROLOGICAL SCIENCES	5,637	2.484	0.009990
175	NEUROPSYCHOLOGY	5,707	2.477	0.006470
176	Neural Regeneration Research	3,648	2.472	0.008930
177	Clinical Psychopharmacology and Neuroscience	644	2.470	0.001400

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
178	Behavioral and Brain Functions	1,586	2.457	0.001710
179	JOURNAL OF THE PERIPHERAL NERVOUS SYSTEM	1,600	2.441	0.002130
180	GAIT & POSTURE	14,352	2.414	0.017290
181	METABOLIC BRAIN DISEASE	3,070	2.411	0.005510
182	INTERNATIONAL JOURNAL OF PSYCHOPHYSIOLOGY	7,897	2.407	0.009880
182	NEUROPEPTIDES	2,050	2.407	0.002520
184	MUSCLE & NERVE	12,279	2.393	0.014620
185	LEARNING & MEMORY	6,065	2.373	0.007230
186	INTERNATIONAL JOURNAL OF DEVELOPMENTAL NEUROSCIENCE	3,383	2.367	0.004070
187	JOURNAL OF CHEMICAL NEUROANATOMY	2,315	2.357	0.002280
188	CHEMICAL SENSES	4,443	2.336	0.003880
189	Frontiers in Computational Neuroscience	2,458	2.323	0.008650
190	Neural Development	994	2.317	0.001970
191	JOURNAL OF NEUROVIROLOGY	2,577	2.302	0.004270
192	NEURAL COMPUTATION	14,077	2.261	0.006250
193	AUTONOMIC NEUROSCIENCE-BASIC & CLINICAL	2,742	2.247	0.003710
194	VISION RESEARCH	15,884	2.178	0.010650
195	NEUROSCIENCE LETTERS	33,765	2.173	0.027830
196	STRESS-THE INTERNATIONAL JOURNAL ON THE BIOLOGY OF STRESS	2,538	2.168	0.003510
197	NEUROPHYSIOLOGIE CLINIQUE-CLINICAL NEUROPHYSIOLOGY	1,230	2.167	0.001380
198	NEUROPATHOLOGY	1,783	2.161	0.002720
199	REVIEWS IN THE NEUROSCIENCES	2,021	2.157	0.002730

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
200	Computational Intelligence and Neuroscience	2,499	2.154	0.002800
200	Social Neuroscience	1,794	2.154	0.003680
202	DEVELOPMENTAL NEUROSCIENCE	2,145	2.125	0.002460
203	BEHAVIORAL NEUROSCIENCE	6,665	2.102	0.004200
204	Journal of Mathematical Neuroscience	169	2.091	0.000790
205	Brain and Behavior	2,043	2.072	0.006700
206	NEUROSCIENCE RESEARCH	4,944	2.071	0.004920
207	AUDIOLOGY AND NEURO-OTOLOGY	1,825	2.053	0.002500
208	NEUROIMAGING CLINICS OF NORTH AMERICA	1,173	2.046	0.001310
209	Translational Neuroscience	376	2.038	0.001010
210	NEUROLOGICAL RESEARCH	3,894	1.983	0.003940
211	ACTA NEUROPSYCHIATRICA	863	1.978	0.001510
212	JOURNAL OF NEUROPSYCHIATRY AND CLINICAL NEUROSCIENCES	3,615	1.971	0.002540
213	HUMAN MOVEMENT SCIENCE	4,836	1.928	0.006030
214	STEREOTACTIC AND FUNCTIONAL NEUROSURGERY	1,807	1.905	0.002220
215	JOURNAL OF COMPARATIVE PHYSIOLOGY A-NEUROETHOLOGY SENSORY NEURAL AND BEHAVIORAL PHYSIOLOGY	4,992	1.882	0.003930
216	EXPERIMENTAL BRAIN RESEARCH	21,880	1.878	0.014760
217	INTERNATIONAL JOURNAL OF NEUROSCIENCE	3,479	1.852	0.003860
218	RESTORATIVE NEUROLOGY AND NEUROSCIENCE	1,952	1.839	0.002980
219	CLINICAL EEG AND NEUROSCIENCE	1,018	1.822	0.001510
220	CURRENT NEUROVASCULAR RESEARCH	1,044	1.811	0.001370

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
221	BEHAVIOURAL PHARMACOLOGY	2,627	1.788	0.002550
222	JOURNAL OF ELECTROMYOGRAPHY AND KINESIOLOGY	5,533	1.753	0.005230
223	JOURNAL OF NEUROGENETICS	731	1.698	0.001270
224	NEUROPSYCHOBIOLOGY	2,645	1.675	0.001820
225	JOURNAL OF CLINICAL NEUROPHYSIOLOGY	3,076	1.673	0.003540
226	BRAIN INJURY	6,229	1.665	0.007820
227	Journal of Stroke & Cerebrovascular Diseases	5,853	1.646	0.016500
228	VISUAL NEUROSCIENCE	2,222	1.645	0.001510
229	ACTA NEUROLOGICA BELGICA	991	1.612	0.001670
230	Biologically Inspired Cognitive Architectures	256	1.597	0.000360
231	JOURNAL OF CLINICAL NEUROSCIENCE	8,027	1.593	0.013450
232	JOURNAL OF COMPUTATIONAL NEUROSCIENCE	1,928	1.568	0.002210
233	JOURNAL OF MUSCULOSKELETAL & NEURONAL INTERACTIONS	1,564	1.562	0.001780
234	BRAIN BEHAVIOR AND EVOLUTION	2,195	1.542	0.002110
235	ACTA NEUROBIOLOGIAE EXPERIMENTALIS	1,179	1.529	0.001050
236	ACTAS ESPANOLAS DE PSIQUIATRIA	592	1.479	0.000520
237	Cognitive Systems Research	690	1.384	0.000640
238	PSYCHIATRIC GENETICS	920	1.375	0.001180
239	NEUROIMMUNOMODULATION	1,409	1.351	0.001330
240	JOURNAL OF MOTOR BEHAVIOR	2,432	1.313	0.001820
241	BIOLOGICAL CYBERNETICS	4,672	1.305	0.001450
242	MOTOR CONTROL	779	1.302	0.000590
243	JOURNAL OF NEUROLINGUISTICS	1,015	1.247	0.001190

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
244	EUROPEAN NEUROLOGY	3,068	1.235	0.003160
244	SOMATOSENSORY AND MOTOR RESEARCH	780	1.235	0.000630
246	FOLIA NEUROPATHOLOGICA	635	1.160	0.000700
247	NEUROREPORT	13,203	1.146	0.005030
248	Journal of Integrative Neuroscience	419	1.139	0.000450
249	ARQUIVOS DE NEURO-PSIQUIATRIA	2,995	1.048	0.003210
250	JOURNAL OF PSYCHOPHYSIOLOGY	763	1.000	0.000400
250	NETWORK-COMPUTATION IN NEURAL SYSTEMS	755	1.000	0.000110
252	ARCHIVES ITALIENNES DE BIOLOGIE	656	0.974	0.000420
253	Brain Impairment	357	0.958	0.000430
254	ENCEPHALE-REVUE DE PSYCHIATRIE CLINIQUE BIOLOGIQUE ET THERAPEUTIQUE	1,295	0.865	0.001050
255	Chemosensory Perception	373	0.824	0.000590
256	INVERTEBRATE NEUROSCIENCE	323	0.800	0.000190
257	Sleep and Biological Rhythms	600	0.752	0.000830
258	NEUROENDOCRINOLOGY LETTERS	2,082	0.698	0.001720
259	NEUROCIRUGIA	296	0.519	0.000230
260	ACUPUNCTURE & ELECTRO-THERAPEUTICS RESEARCH	194	0.417	0.000030
261	CESKA A SLOVENSKA NEUROLOGIE A NEUROCHIRURGIE	223	0.355	0.000140
262	Neurochemical Journal	163	0.298	0.000150
263	ZHURNAL VYSSHEI NERVNOI DEYATELNOSTI IMENI I P PAVLOVA	290	0.269	0.000170
264	NEUROPHYSIOLOGY	224	0.267	0.000180
265	Journal of the History of the Neurosciences	250	0.244	0.000190

Selected JCR Year: 2018; Selected Categories: “NEUROSCIENCES”

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
266	Ideggyogyaszati Szemle-Clinical Neuroscience	144	0.113	0.000150
267	Journal of Neurological Sciences-Turkish	89	0.075	0.000050

J Neurosci. 2020 Aug 12;40(33):6428-6443. DOI link:
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VI. Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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VII. Publication List

Huang Y, Zhang Q, Lubas M, Yuan Y, Yalcin F, Efe I, Xia P, Motta E, Buonfiglioli A, Lehnardt S, Dzaye O, Flueh C, Synowitz M, Hu F, Kettenmann H. “Synergistic Toll-like receptor 3/9 signaling affects properties and impairs glioma-promoting activity of microglia.” The Journal of Neuroscience. 2020 July 6.(Impact Factor: 6.074)

Buonfiglioli A, Efe IE, Guneykaya D, Ivanov A, Huang Y, Orlowski E, Krüger C, Deisz RA, Markovic D, Flüh C, Newman AG, Schneider UC, Beule D, Wolf SA, Dzaye O, Gutmann DH, Semtner M, Kettenmann H and Lehnardt S. “let-7 microRNAs regulate microglial function and suppress glioma growth through Toll-like receptor 7”. Cell Rep. 2019 Dec 10. (Impact Factor: 7.815)

Triptolide suppresses growth and hormone secretion in murine pituitary corticotroph tumor cells via NF-kappaB signaling pathway Li R, Zhang Z, Wang J, Huang Y, Sun W, Xie R, Hu F, Lei T. Biomed Pharmacother. 2017 Nov;95:771-779 (Impact Factor:3.743)

EPAC mediates cAMP induced proliferation of rat anterior pituitary GH3 cells via the activation of extracellular signal-regulated kinase Sun W, Jiao W, Huang Y, Li R, Zhang Z, Wang J, Lei T. Biochem Biophys Res Commun. 2017 Apr 1;485(2):355-359 (Impact Factor:2.559)

Microscopic Transnasal Transsphenoidal Surgery for Pediatric Pituitary Adenomas Jiao W, Huang Y Sun W, Lei T. J Craniofac Surg. 2017 Jun;28(4):1010-1012 (Impact Factor:0.772)

Hydrogel-coated ventricular catheters for high-risk patients receiving ventricular peritoneum shunt Xu H, Huang Y, Jiao W, Sun W, Li R, Li J, Lei T. Medicine (Baltimore). 2016 Jul;95 (29):e4252 (Impact Factor: 1.956)

High fibrosis indices in cerebrospinal fluid of patients with shunt-dependent post-traumatic chronic hydrocephalus Hao X, Junwen W, Jiaqing L, Ran L, Zhuo Z, Yimin H, Wei J, Wei S, Ting Lei. Transl Neurosci. 2016 Sep 9;7(1):92-97.(Impact Factor: 1.373)

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I would like to close with the following quote from Confucius
“好学近乎知，力行近乎仁，知耻近乎勇”

„ To love learning is akin to knowledge; to study diligently is akin to benevolence, to know shame is akin to courage.”

Thank you all
Yimin Huang