SHORT COMMUNICATION

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Accelerated brain ageing in sepsis survivors with cognitive long-term impairment

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Abstract

In the last years, cognitive impairment was emphasized to be a prominent long-term sequelae of sepsis. The level of cognitive impairment is comparable with that in mild cognitive impairment (MCI) patients. Whether sepsis survivors also show a comparable brain atrophy is still unclear. For the analysis of brain atrophy, a novel method named brain age gap estimation (BrainAGE) was used. In this analysis approach, an algorithm identifies age-specific atrophy across the whole brain and calculates a BrainAGE score in years. In case of accelerated brain atrophy, the BrainAGE score is increased in comparison to the healthy age reference group, indicating a difference in estimated chronological age. 20 survivors of severe sepsis (longer than 2 years post sepsis) with persistent cognitive deficits were investigated with a battery of neuropsychological tests. Their MRI images were compared to an age- and sex-matched control group. Sepsis survivors showed a significant higher BrainAGE score of 4.5 years compared to healthy controls. We also found a close relationship between the BrainAGE score and severity of cognitive impairment (a higher BrainAGE score was associated with more severe cognitive impairment). Consequently, sepsis survivors with persistent cognitive impairment showed an accelerated brain ageing, which was closely associated with the severity of cognitive impairment (similar to MCI patients).

KEYWORDS

BrainAGE, cognitive impairment, sepsis

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1 | INTRODUCTION

Survivors of sepsis or septic shock have an increased risk for long-term cognitive impairment which could affect various domains of neuropsychological functioning, for example attention, memory or executive functioning (Girard et al., 2010; Gunther et al., 2012; Hopkins & Jackson, 2006a, 2006b; Iwashyna, Ely, Smith, & Langa, 2010; Jackson & Ely, 2013; Jackson, Mitchell, & Hopkins, 2011; Pandharipande et al., 2013; Semmler et al., 2013). The severity of sepsis-induced cognitive impairment is comparable to patients suffering from mild cognitive impairment (MCI) (Iwashyna et al., 2010; Jackson & Ely, 2013; Jackson et al., 2003). Cognitive decline in MCI patients is associated with brain atrophy (Franke, Luders, May, Wilke, & Gaser, 2012; Leung et al., 2013; Tabatabaei-Jafari, Shaw, & Cherbuin, 2015). Several studies also showed reduced grey matter volumes in sepsis survivors, but in certain regions, for example reduced left hippocampal volume in comparison to healthy controls (Semmler et al., 2013), or precuneus, thalamus and frontal lobe atrophy in a voxel-based morphometry analysis (Orhun et al., 2018).

In this pilot study, we used a new approach for assessing the degree of whole-brain atrophy. The BrainAGE described by Franke, Ziegler, Kloppel, and Gaser (2010) analyses the level of age-specific grey matter atrophy across the whole brain in comparison to a healthy control group. From this analysis, a single value is calculated, named the "BrainAGE score." A higher BrainAGE score indicates accelerated brain atrophy which consequently is associated with higher brain ageing in comparison to the healthy age reference group. The BrainAGE score has already been applied in several studies, including MCI patients and schizophrenia (Franke, Gaser, Manor, & Novak, 2013; Franke, Ristow, & Gaser, 2014; Luders, Cherbuin, & Gaser, 2016; Nenadic, Dietzek, Langbein, Sauer, & Gaser, 2017).

We hypothesize that sepsis survivors suffering from persistent cognitive decline also show brain atrophy similar to MCI patients. Moreover, we assume that the level of brain atrophy measured by the BrainAGE score is associated with severity of cognitive impairment.

2 | MATERIALS AND METHODS

2.1 | Study population

Participants were recruited from the German Sepsis Help National Hotline and from databases of the Jena University Hospital and of the rehabilitation hospital Moritz Klinik between 2011 and 2013. The diagnosis of sepsis was made at that time point according to the sepsis-2 criteria. We retrospectively analysed medical reports of all included patients according to the current criteria of sepsis (Singer et al., 2016) with a history of sepsis one year before recruitment. Sepsis is defined as life-threatening organ dysfunction and for clinical pragmatic aspects, organ dysfunction is represented by an increase in Sequential Organ Failure Assessment (SOFA) Score of 2 and more points. According to quick SOFA and SOFA variables, all included patients were ventilated over more than 48 hr due to the sepsis, suffered from renal failure and needed vasopressors (dobutamine and epinephrine monotherapy or in combination). No one of included patients was described with a delirium. All patients were treated with antimicrobial treatment (for clinical information see Table 1).

Subjects were first requested to fill a modified form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Patients with a value above 3.29 (Ehrensperger, Berres, Taylor, & Monsch, 2010) were included. Exclusion criteria were brain trauma, stroke, symptoms of Parkinson's disease, history of multiple sclerosis, meningitis or other diseases which alter the brain as well as psychiatric symptoms or diseases. A total of 263 patients were announced to have sepsis one year before. 126 patients gave a feedback, from these 61 patients fulfilled the inclusion criteria. From these patients, 37 patients refused their participation. 24 patients were invited for neuropsychological testing and MRI procedure (Figure 1).

The 44 age- and sex-matched healthy individuals (mean age 53.2 ± 0.4 year, 21 males) have also participated in the study.

At enrolment, all participants gave their written informed consent before participating in the study. This study was approved by the local ethics committee (Faculty of Medicine, University of Jena).

2.2 | Neuropsychological assessment

Four basic domains of attention (alertness, divided attention, selective attention and working memory) were measured by the Test of Attentional Performance (TAP—"Testbatterie zur Aufmerksamkeitsprüfung," Zimmermann & Fimm, 2012). TAP distinguishes alertness in tonic alertness, which refers to the intrinsic maintenance of attention in order to provide higher cognitive functions, and phasic attention, which is the rapid change in attention due to a brief warning (i.e. audio event) Posner (2008). For the divided attention task, a simultaneous execution of an auditory and visual task is required. A go/no-go paradigm is used for selective attention and an n-back (2-back) paradigm for working memory, respectively. Furthermore, three domains of verbal memory (learning capacity, delayed retrieval and rate of decay) were tested using the German version of the Auditory Verbal Learning Test (VLMT, Helmstaedter, Lendt und Lux, Beltz Test GmbH, Göttingen, 2001). The test includes 15 aurally presented words with five immediate recall trials, an interference word list, short and long recall trials and a word recognition task.

TABLE 1 Clinical information of patients. The mean age of included patients is 53.8 ± 10.6 years. 9 males and 11 females were included. Days of hospital stay were 24.4 ± 16.9, and the time point of inclusion was 2.6 ± 1.9 years postsepsis. The mean IQCODE was 3.74 ± 0.4

VP	Disease	Multiorgann dysfunction	Renal insufficiency	Dialysis	Mechanical ventilation	Tracheotomy	Vasopressor	Antibiotika	Pathogen in the blood
1	Cholecystitis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Streptococci
2	Sigma diverticulitis	Yes	Yes	No	Yes	Yes	Yes	Yes	
3	Peritonitis after perforation of small intestine	Yes	Yes	No	Yes	Yes	Yes	Yes	
5	Colon dysplasia, operation, anastomosis insufficiency, peritonitis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
6	Pneumonia	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
7	Prostatitis	Yes	Yes	No	Yes	No	Yes	Yes	Pseudomonas, micrococcus species
8	Leptospirosis	Yes	Yes	Yes	Yes	No	Yes	Yes	Clostridium deficile
9	Abscess cleavage	Yes	Yes	No	Yes	No	Yes	Yes	
10	Sigma diverticulitis with perforation and peritonitis	Yes	Yes	No	Yes	No	Yes	Yes	Klebsiella species, pseudomonas, enterococcus faecalis
12	Laparatomy following peritonitis	Yes	Yes	No	Yes	No	Yes	Yes	
13	Pneumonia	Yes	Yes	No	Yes	No	Yes	Yes	Pneumococci
14	Bypass operation	Yes	Yes	Yes	Yes	No	Yes	Yes	*Staphylococcus aureus*
15	Vaginal hysterectomy following phlegmony	Yes	Yes	Yes	Yes	No	Yes	Yes	Escherichia coli; proteus Mirablilis
16	Endocarditis	Yes	Yes	Yes	Yes	No	Yes	Yes	*Staphylococcus aureus*
17	Pneumonia	Yes	Yes	No	Yes	Yes	Yes	Antifungal	Fungal infection
19	Necrotizing fasciitis left upper leg	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Streptococcus, pseudomonas
20	Liver donation and pneumonia	Yes	Yes	Yes	Yes	No	Yes	Antifungal	Candida albicans
21	Sigma diverticulitis and perforation	Yes	Yes	No	Yes	No	Yes	Yes	
23	Enteritis	Yes	Yes	Yes	Yes	No	Yes	Yes	
24	Cut injury right finger	Yes	Yes	No	Yes	No	Yes	Yes	

For all the tests standardized and age-adjusted values in terms of T-values are available.

All neuropsychological standardized tests are interpreted as follows: the average range is calculated from the mean value + one standard deviation. Values below of one standard deviation are interpreted as "below average," and values below than two standard deviations are defined as "far below average" (i.e. Petermann & Macha, 2005). Accordingly,
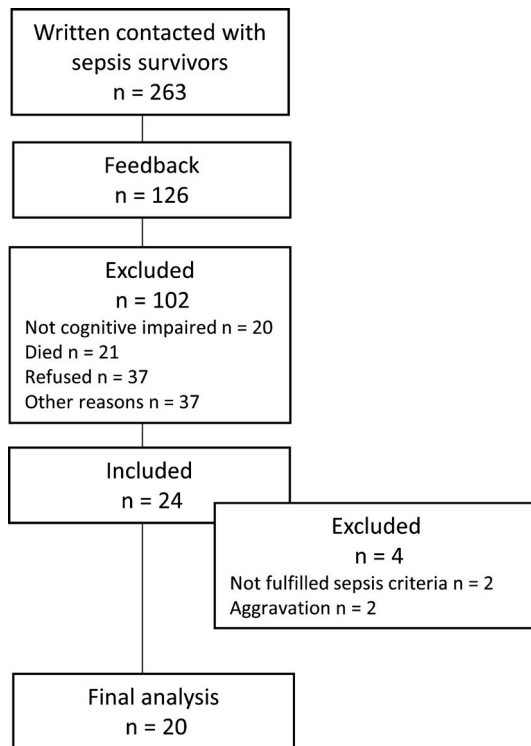
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Written contacted with
sepsis survivors
n = 263
        │
        ▼
     Feedback
     n = 126
        │
        ▼
     Excluded
     n = 102
Not cognitive impaired n = 20
Died n = 21
Refused n = 37
Other reasons n = 37
        │
        ▼
     Included
     n = 24 ────────────►  Excluded
        │                   n = 4
        │          Not fulfilled sepsis criteria n = 2
        │          Aggravation n = 2
        ▼
   Final analysis
     n = 20
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FIGURE 1 The number of patients beginning from enrolment to the final analysis

T-values of 40 are set as mean minus one standard deviation. A value less than 40 is considered to represent "below average."

In order to assess the severity of cognitive impairment, a cognitive sum score was calculated for each sepsis survivor as follows: for each cognitive domain, the *T*-values of test parameters were averaged (i.e. for selective attention errors and reaction time were chosen) in order to obtain one *T*-value for each domain. Then, the averaged *T*-values of the five cognitive domains (alertness, divided attention, selective attention, working memory and verbal memory) were summarized. Consequently, a lower sum score indicates higher degree of cognitive impairment.

2.3 | MRI scanning, processing

For each subject, a T1-weighted MPRAGE sequence (TR 2,300 ms, TE 3.03 ms, TI 900 ms, alpha 9°) was acquired on a 3 Tesla Siemens Tim Trio MRI system (Siemens, Erlangen, Germany) with 192 contiguous slices covering the entire brain, slice thickness 1 mm, field of view: 256 × 256, isotropic voxel resolution of $1 \times 1 \times 1$ mm^3.

Patients would be excluded if they show a macroscopically visible T1-weighted MRI lesion.

As described elsewhere (Luders et al., 2016), the acquired brain images were processed in Matlab (http://www.mathworks.com/products/matlab/), using SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the VBM8 toolbox (http://dbm.neuro.

uni-jena.de/vbm.html), resulting in spatially normalized and smoothed grey matter segments.

2.4 | BrainAGE score

BrainAGE analysis is based on a framework developed for automatically and efficiently estimating the age of healthy subjects from their T1-weighted MRI scans using a kernel method for regression. The BrainAGE framework was applied to a large human sample ($n = 394$) of healthy children and adolescents, whose image data had been acquired during the NIH MRI study of normal brain development. BrainAGE approach considers age-related brain tissue loss and evaluates the complex, multidimensional ageing pattern across the whole brain into one single value. The correlation between predicted brain age and chronological age in healthy subjects is $r = 0.93$, and the mean absolute error was only 1.1 years (Franke & Gaser, 2019; Franke et al., 2010, 2012, 2013, 2014; Gaser, Franke, Kloppel, Koutsouleris, & Sauer, 2013). With BrainAGE, an individual analysis is possible. The grey matter segments were used to calculate the BrainAGE score described previously (Franke et al., 2010, 2012). The difference between estimated age and true chronological age yields the so-called brain [A]ge [G]ap [E]stimate (BrainAGE). For example, if a 65-year-old individual has a BrainAGE score of +5 years, this means that this individual shows the typical structural pattern of a 70-year-old individual. In the current study, individual BrainAGE scores were estimated for 20 sepsis survivors and for age-matched 44 healthy individuals serving as controls.

2.5 | Statistical analysis

The analysis of group differences in the BrainAGE score (sepsis survivors versus healthy controls) was done with a two-tailed Student *t* test. For analysing the relation between brain age and cognitive impairment, a regression analysis (Pearson's correlation coefficient) was performed between BrainAGE and cognitive sum scores.

For all analyses, the assumptions for parametric testing (i.e. normal distribution of the residuals; equal variance between groups) were assessed using Lilliefors' tests for normality and two-sample *F* tests for equal variance. The significance threshold was set at $p \le .05$.

3 | RESULTS

3.1 | Neuropsychological assessment

17 patients had deficits in one or two cognitive domains, and five patients showed impairment in three or more

domains. Tonic alertness was most frequently impaired (in 11 patients), followed by working memory and memory decay rate ($n = 6$) and learning capacity ($n = 5$). The cognitive sum scores ranged from 251 to 394 (mean 323.2 ± 36.3 SD).

3.2 | BrainAGE score

The BrainAGE score (mean $\pm$ SE) of sepsis survivors was 4.6 ± 1.9 years. In contrast, the healthy control group showed a BrainAGE score of 0.1 ± 0.9 years. The BrainAGE score of sepsis survivors was significantly higher (4.5 years) in comparison to healthy controls indicating that sepsis survivors have an accelerated brain age and brain atrophy (at predefined threshold: $T = -2.392$, $p = .02$; Figure 2a).

3.3 | BrainAGE score and cognitive impairment

There was a significant negative correlation between the cognitive sum score and the BrainAGE score indicating that stronger cognitive impairment is associated with higher brain age ($r = 0.63$, $p = .001$ one-tailed; Figure 2b).

4 | DISCUSSION

Sepsis survivors with cognitive impairment even two years after sepsis had a higher brain age of more than 4 years in comparison to age-matched healthy control group.

This emphasizes that sepsis survivors with cognitive impairment show an accelerated brain atrophy. Furthermore, the calculated BrainAGE score was closely correlated with the severity of cognitive impairment.

4.1 | Cognitive impairment

In the present study, a profound battery of neuropsychological tests was used for a comprehensive overview of cognition. We found an individual diversity of cognitive impairment within our patient population, which was also reported by Hopkins & Jackson (Hopkins & Jackson, 2006b). While some patients are only affected in a few parameters of a cognitive domain, others showed deficits in several domains. Recent studies showed that delirium at the early sepsis stage has close influence on the later cognitive outcome and that the duration of delirium is closely associated with brain atrophy (Gunther et al., 2012; Morandi et al., 2012; Pandharipande et al., 2013). In our patients, delirium was not described. Therefore, other conditions can lead to cognitive impairment associated with brain atrophy.

It is noteworthy that the cognitive domain of alertness was mostly affected. Other studies also reported deficits in alertness after sepsis or critical illness (Girard et al., 2010; Hopkins & Jackson, 2006a). Alertness is supposed to be the most basic aspect of attention providing higher attention functions as well as higher cognitive demands (Posner, 2008) (Sturm et al., 1999; Sturm & Willmes, 2001). Consequently, deficits in alertness could also involve some other cognitive domains. This suggestion warrants further studies in larger study populations.

4.2 | Accelerated brain atrophy

Previous imaging studies investigating sepsis-associated structural brain changes showed heterogeneous results in terms of location of brain atrophy. Therefore, we used the BrainAGE approach which aggregates the complex, multidimensional ageing patterns of a whole-brain structural MRI to one single value (Franke et al., 2010).

The brain of sepsis patients with long-term cognitive deficits is four years older than that of a matched control group.
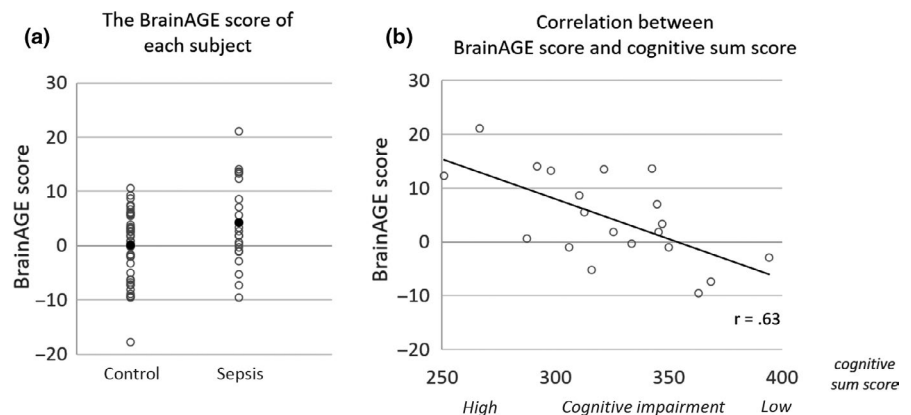

FIGURE 2 (a) Scatterplot of BrainAGE scores of healthy controls and sepsis survivors, filled dots represent the mean value of each group. (b) Relation between cognitive impairment (sum score) and BrainAGE score of sepsis survivors: higher brain age is associated with more severe cognitive impairment

This difference is statistically significant. The brain of sepsis patients therefore shows a faster ageing process. This premature ageing process in the brain is often referred to as an "accelerated brain atrophy" (e.g. Gaser et al., 2013).

This remarkable ageing process of sepsis survivors with long-term cognitive impairment is comparable to the advanced ageing process of patients suffering from mild cognitive impairment (Gaser et al., 2013). The brain atrophy could be triggered by the systemic inflammation process which is considered to play a prominent role in progression of neurodegeneration (Cunningham, 2013; DeLegge & Smoke, 2008; Gunther et al., 2012; Holmes et al., 2009; Pandharipande et al., 2013; Shah et al., 2013). During response to inflammatory signals, the microglia alters their morphology and phenotype, and subsequently it produces pro-inflammatory neurotoxic mediators (Block & Hong, 2005; Cunningham, 2013; Hickman, Izzy, Sen, Morsett, & El Khoury, 2018; Perry, Cunningham, & Holmes, 2007; Perry, Nicoll, & Holmes, 2010). High and long-lasting concentrations of these mediators might lead to brain-damaging effects (Hoogland, Houbolt, van Westerloo, van Gool, & van de Beek, 2015; Perry et al., 2010; Teeling & Perry, 2009). Consequently, it could be argued that the brain atrophy observed in the current patient population two years after sepsis is the long-term consequence of a post-inflammatory reaction during the acute stage with the development of a neurodegeneration and possibly developing a dementia in later life (Widmann & Heneka, 2014).

4.3 | Limitations of the study

The retrospective view is a limited factor of the current study. Therefore, it warrants further investigations. We are not able to evaluate whether a certain clinical value or the combination of different variables are causally responsible for neuropsychological deficits and brain atrophy. However, this study should encourage physicians and scientists to collect clinical variables from early beginning of sepsis and to find out any associations with neuropsychological parameter and brain atrophy. Recently, we have described fatigue as a long-term sequelae after sepsis (Seidel, Götz, & Hamzei, 2019). This underlies that further investigations of long-term consequences after sepsis and their relation to early clinical variables are necessary.

Patients with a history of the central nervous system affection (e.g. stroke, brain trauma or neurodegenerative diseases) prior to sepsis were excluded. Focal neurological deficits in association with sepsis were also exclusion criteria. Patients with a macroscopically visible T1-weighted MRI lesion would also be excluded. We did not analyse the BrainAGE before sepsis; thus, patients with brain atrophy prior to the sepsis without any symptoms (no history of cognitive deficits or focal neurological deficits) could have influence the current results.

At least one year after the sepsis, we asked patients to participate in the current study. However, we only received feedback in about 50% of cases, so we cannot draw any conclusions about the generalization of brain atrophy after sepsis.

We recruited patients who were treated in different centres during the acute stage. Thus, different therapy strategy in each centre could have influence on the long-term sequelae of sepsis. This warrants further studies in future to collect variables from acute stage.

4.4 | Conclusion

Despite many limitations, the results of this pilot study show that sepsis survivors with long-term cognitive impairments underlie an accelerated brain ageing process compared to a healthy control group. The ageing process correlates with the severity of the cognitive deficits.

Sepsis survivors without cognitive deficits should also be considered as control group. Thus, the question can be answered whether accelerated brain ageing is a general consequence of sepsis or only affects sepsis survivors with cognitive deficits.

CONFLICT OF INTEREST
The authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS
GS collected the MRI and neuropsychological data, analysed the neuropsychological data and wrote the manuscript; TG and GS collected the study subjects and managed the study; FH, GS and TG were involved in the design and planning of the study and interpretation of data; CG analysed the MRI data and performed the BrainAGE scores; AG provided neurological consultancy for the patients during the study. All co-authors were involved in editing the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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