Glucose Dynamics of Cortical Spreading Depolarisation in Acute Brain Injury: A Systematic Review

Andrew R. Stevens[1], Isabel H.X. Ng[1], Adel Helmy[2], Peter J.A. Hutchinson[2], David K. Menon[1], Ari Ercole[1].

1. Division of Anaesthesia, University of Cambridge, Box 93, Addenbrooke's Hospital, Hills Road, Cambridge, UK, CB2 0QQ.
2. Division of Neurosurgery, Department of Clinical Neurosciences, Addenbrooke's Hospital, Hills Road, Cambridge, UK, CB2 0QQ.

Correspondence:

Dr Ari Ercole

Division of Anaesthesia, University of Cambridge, Box 93, Addenbrooke's Hospital, Hills Road, Cambridge, UK, CB2 0QQ

Telephone: +44 1223 217889

Running title: Glucose Dynamics of CSD in Acute Brain Injury

Table of contents title: Glucose Dynamics of Cortical Spreading Depolarisation in Acute Brain Injury

Author details:

Andrew R. Stevens, MBChB BMedSc

Division of Anaesthesia

Addenbrooke's Hospital, Cambridge, UK

Email: a.stevens@doctors.org.uk

Telephone: +44 1223 217889

Isabel H.X. Ng, MB BChir MA

Division of Anaesthesia

Addenbrooke's Hospital, Cambridge, UK

Email: ihxn2@cam.ac.uk

Telephone: +44 1223 217889

Adel Helmy, FRCS (SN) PhD

Division of Neurosurgery,

Addenbrooke's Hospital, Cambridge, UK

Email: adelhelmy@doctors.org.uk

Telephone: +44 1223 336946

Peter J.A. Hutchinson, FRCS (SN) PhD

Division of Neurosurgery,

Addenbrooke's Hospital, Cambridge, UK

Email: pjah2@cam.ac.uk

Telephone: +44 1223 336946

David K. Menon FRCP FRCA FFICM FMedSci PhD

Division of Anaesthesia

Addenbrooke's Hospital, Cambridge, UK

Email: dkm13@cam.ac.uk

Telephone: +44 1223 217889

Ari Ercole, FRCA FFICM PhD

Division of Anaesthesia

Addenbrooke's Hospital, Cambridge, UK

Email: ae105@cam.ac.uk

Telephone: +44 1223 217889

Abstract:

Cortical spreading depolarisation (CSD) is an emerging mode of secondary neuronal damage in acute brain injury (ABI). Subsequent repolarisation is a metabolic process requiring glucose. Instances of CSD and glucose derangement are both linked to poor neurological outcome, but their causal inter-relationship is not fully defined. This systematic review seeks to evaluate the available human evidence studying CSD and glucose to further understand their dynamic relationship. We conducted a systematic review of studies examining CSD through electrocorticography and cerebral/systemic glucose concentrations in ABI, excluding animal studies. The search yielded 478 articles, of which 13 were eligible. Across 10 manuscripts, 125 patients received simultaneous monitoring, with 1,987 CSD episodes observed. 8/10 studies observed correlation between CSD and glucose change. 7/8 studies observed possible cumulative effect of recurrent CSD on glucose derangement and two identified correlation between glycopenia and incidence of CSD. These findings confirm a relationship between CSD and glucose, and suggest it may be cyclical, where CSD causes local glycopenia, which may potentiate further CSD. Positive observations were not common to all studies, likely due to differing methodology or heterogeneity in CSD propensity. Further study is required to delineate the

utility of the clinical modulation of serum and cerebral glucose to alter the propensity for CSD following brain injury.

Keywords:

Acute brain injury, brain metabolism, cortical spreading depolarisation, electrocorticography, glucose

Introduction:

Rationale:

Cortical spreading depolarisation (CSD) is a pathophysiology of secondary injury in a variety of cerebral insults, with emerging recognition of its importance.[1] CSD is typically described as a pathological wave of neuronal and glial depolarisation which is self-propagating, and spreads throughout cerebral tissue at a rate of 2-5mm/min, with consequent severe disturbance of local ionic gradients.[2] This can lead to a local energetic-failure mediated abolition of cortical activity known as cortical spreading *depression*. Since the discovery of cortical spreading depression in 1944,[3] the involvement of CSD in the aetiology of migraine has been well described,[4] with its first observed description in human brain injury[5] in 2002.

Since then CSD has been increasingly recognised as a factor in the exacerbation of cellular injury after brain injury. The incidence of CSD has been observed in humans with multiple modalities of acute brain injury (ABI); traumatic brain injury (TBI), subarachnoid haemorrhage (SAH), intracerebral haemorrhage (ICH) and occlusive ischaemic stroke.[6–11] In addition to representing a widespread phenomenon, the incidence of CSD has been linked to unfavourable neurological outcome in TBI.[7]

To re-establish physiological ion gradients after CSD there is supraphysiological tissue metabolic demand and therefore glucose requirement.[12] Animal studies have demonstrated that deranged cerebral glucose can alter the susceptibility of neural tissue for the initiation of CSD.[13,14] As such there are grounds for considering glucose derangement as both a precipitant and consequence of CSD.

It is well established that deranged cerebral and systemic glucose levels correlate with poor neurological outcome and increased mortality.[15–17] As such, glucose control is a prominent component of the clinical management of ABI in the neurocritical care setting. The mechanism by which deranged cerebral glucose metabolism worsens outcomes after brain injury is not fully understood, but appears to be independent of ischaemia.[18] To what extent the relationship between glucose and CSD is involved in this mechanism is also not understood.

CSD has been demonstrated to be a widespread phenomenon in ABI and to correlate with outcome,[6–11] so CSD represents an important potential target for therapeutics in preventing secondary injury. Glucose is a key player in the physiology of CSD, with its derangement also associated with secondary injury. Whilst research into the clinical prevention of the incidence of CSD continues, glucose derangement has established methods for treatment in clinical practice. Therefore defining the relationship between glucose and CSD is a worthy subject

of further understanding, which at present has conflict in its small body of evidence. It is unclear if glucose derangement represents: a factor in initiating CSD, a consequence of CSD, neither, or both - in a self-perpetuating cycle of supply and demand mismatch. As such the aim of this systematic review is to collate and evaluate the evidence examining glucose and CSD in the context of ABI and its composite pathologies, to further understand their complex relationship.

Objectives:

Our objective is to systematically evaluate the available literature examining the correlation between glucose derangement and CSD in humans. Specifically, we seek to summarise the available evidence for: (1) the effects of CSD on extracellular glucose concentration; and (2) the presence of deranged glucose concentrations as a risk factor for CSD.

Materials and methods:

A systematic review of the literature was performed following the methodology of the Cochrane Handbook for Systematic Reviewers,[19] and presented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[20]

The review questions determined by the primary author (AS) in conjunction with the lead researcher (AE) were:

(1) Is electrocorticographic (ECoG) evidence of CSD associated with subsequent changes to cerebral extracellular glucose levels, and does the incidence of CSD correlate with sustained glucose changes?

(2) Is there evidence of a cumulative effect of recurrent CSD as identified by ECoG on cerebral extracellular glucose levels?

(3) Does the incidence of CSD demonstrated on ECoG have an association with preceding or baseline glucose levels (cerebral or systemic)?

Inclusion Criteria:

Population:

The population of interest were human subjects with any of the following conditions: TBI, SAH, ICH or ischaemic occlusive stroke.

Outcome measures:

The outcome measures of interest were: ECoG monitoring evidence of cortical spreading depolarisation; and local (*i.e.* cerebral extracellular fluid) or systemic (*i.e.* serum) glucose concentration measures. Secondary outcomes considered were results of analysis of the relationship between the incidence of CSD and local/systemic glucose concentration.

Setting:

Given the intensive monitoring required to gain the above data such studies would be in the intensive care unit or neurosciences critical care settings.

Methodology:

Any research methodology in humans was considered for inclusion, including observational studies and case series/reports.

Exclusion Criteria:

Studies conducted in animal models or *in vitro* human models were excluded. Studies which recorded the variables of interest, but did not report sufficient data on these variables for our research questions were also excluded.

Information Sources:

We systematically searched the following databases, from their respective inception to December 2017: Medline, Embase, Cochrane Central, NICE Evidence and Web of Science. Reference lists of pertinent narrative review articles on the topic were hand-searched for suitable articles. See appendix 1 for an example of search strategy.

Study Selection:

Studies were independently screened for inclusion by two reviewers, AS and IN, utilising a referential standardised proforma. Eligibility for study inclusion was defined as: a study of human patients with ABI, with the measurement of incidence of cortical spreading depolarisation and local/systemic glucose levels, with subsequent analysis of the relationship.

Data Extraction:

Data were extracted from included reports by two reviewers: AS and IN, conducted independently in duplicate, using piloted forms. Data extracted included; study characteristics, patient demographics, number of patients, ECoG variables (proximity to primary lesion, frequency), microdialysis variables (sampling rate, proximity to ECoG device) and results and conclusions of comparative analysis.

Risk of Bias in Individual Studies:

Two reviewers (AS, IN) assessed the risk of bias of each individual study using the RTI item bank,[21] with discrepancies discussed with a third party (AE).

Synthesis of Results:

The heterogeneous nature of data collection and analysis methods precludes our ability to combine and synthesise results. As such a qualitative narrative summary will be presented.

Results:

Study Selection:

A search for literature pertaining to both CSD and glucose in the context of human ABI yielded 478 articles. After removal of duplicates, 337 titles with abstracts were screened against the inclusion criteria. 31 full text articles were obtained for eligibility assessment, of which 13 studies were included (Figure 1). Of the eligible articles, 10 original articles were included in the full qualitative review (Table 1). The further three eligible articles were short conference proceedings or abstracts, and are considered briefly in (Table 2). All manuscripts screened for inclusion were available in English. [Insert Figure 1]

Study and Patient Demographics:

Of the 13 articles eligible for inclusion,[11,22–33] 10 were published manuscripts[11,22–30] and three were abstract publications from meetings (poster presentations).[31–33] 11 studies were observational,[22,24–33] of which; seven were identifiable as prospective,[22,24–27,29,30] two were mixed prospective/retrospective[28,32] and two reported insufficient methodology for discernible classification.[31,33] Two studies were single-patient case studies.[11,23]

All studies recruited only patients with clinical indication for a neurosurgical procedure (craniotomy, craniectomy or burr hole) for ABI. Four studies recruited only TBI patients,[23,24,31,32] two recruited only SAH patients,[28,29] two recruited only ICH patients[11,26] and one study recruited only patients with ischaemic stroke.[30] The remainder recruited patients with any aetiology of ABI from the above (TBI, SAH, ICH, ischaemic stroke)[25,27,33] with the exception of one study which recruited only patients with TBI, SAH or ICH.[22]

Of the 13 included articles, all identified CSD by a subdural electrocorticography strip. All articles measured local glucose via cerebral microdialysis (CMD), except for one study which examined serum glucose alone.[32]

Of the observational studies published as full articles, six studies recruited only patients with an admission Glasgow Coma Score (GCS) of greater than 4,[22,25–29] and six studies excluded patients with bilaterally fixed and dilated pupils.[22,24,25,27–29] Three studies excluded patients with a history of significant trauma or bleeding less than five days prior to admission.[25,28,29] One study did not describe any exclusion criteria.[30]

Across manuscripts included (Table 1), 125 patients in total were studied, with a mean of 15.6 patients per study, ranging from 10 to 24 (excluding single patient case studies). Mean age was 47.6 years (range 18 to 72). Of studies reporting

patient gender, 56.8% were male: two studies did not report gender distribution of their patients.[25,27] A total of 1,987 episodes of CSD were observed across these studies. Total monitoring time varied between studies, with mean monitoring durations ranging from 67 to 210 hours. Time from injury to recruitment ranged from within 24 hours to within five days.

Monitoring Techniques:

Abstracts from meetings, owing to publication modality, did not report sufficient information on their monitoring techniques for inclusion here. As such the following subsections pertain only to the studies with full manuscripts.

Electrocorticography Monitoring Techniques:

All 10 studies (Table 1) utilised a six or eight electrode electrocorticography device (Wyler/Ad-Tech) inserted during clinically indicated neurosurgical intervention. Positioning of the electrodes was variable: four studies reported the electrode was placed on the cortex alone,[23,26,28,29] and seven studies reported positioning the electrode specifically on the cortex overlying peri-infarct or peri-contusional tissue.[11,22,24,25,27,30] One study utilised intraoperative laser speckle

imaging to identify the infarct rim for placement.[30] Four studies recognised and utilised subclassification of CSD in their interpretation of ECoG data.[25,26,28,30] In identified prospective observational studies, the range of patients with recorded episodes of CSD is between 38% and 90% (72% mean) across all brain injury subtypes.

Glucose Monitoring Techniques:

All 10 studies utilised a CMA cerebral microdialysis device, inserted during clinically indicated neurosurgical intervention. All studies reported insertion of the microdialysis probe with sufficient detail to describe its proximity to the lesion or neural tissue of interest, with one exception.[28] Three studies utilised an online assay through rapid sampling microdialysis (rsMD), with a reported sampling interval of 30 to 60 seconds,[22,26,27] whilst the remaining studies utilised an intermittent offline sampling technique at 60 minute intervals. These were analysed immediately at the bedside with the exception of two studies which either refrigerated[23] or froze[24] samples for later analysis.

Device Proximity:

With one exception,[28] all studies reported proximity between the ECoG and CMD devices. Three studies reported prospective aims of specific distances: within 1cm,[24] 1-1.5cm[22] or 1-2cm[23]. One study utilised two CMD probes, 5mm and 15mm from the infarct rim with the ECoG strip overlying both probes.[30] One study prospectively aimed for the devices to be qualitatively “as near as possible” and recorded proximity on post-operative imaging studies,[27] whilst other studies did not report techniques to confirm position. This imaging approach recognised that in one patient the distance between devices was 8cm. The remaining studies reported proximity of placement as: in corresponding parenchyma,[25] “usually sited on same gyrus”,[26] “regional”[11] or “close”.[29]

Results of Individual Studies:

Given the heterogeneity of the considered studies, particularly when considering their analytical methods, the studies with their key findings are summarised in Tables 1 and 2, with their results further displayed in Table 3.

Qualitative Narrative:

Whilst heterogenous data generated across these studies has rendered quantitative summary of data futile, the studies will here be discussed with relevance to the each of the questions posed by this review. Table 3 gives a brief overview. Given the variety of study size and considered pathologies, brief details of *n* number and pathology/distribution of pathology are included in the narrative for ease of reference. Greater detail is given in Table 1.

Evidence of correlation:

Studies reporting a positive correlation included 70% of the total patients across all studies (88 of 125). Of the 10 manuscripts included, all describe observation of correlation between ECoG findings of depolarisation and deranged glucose concentration, with the exception of two studies.[24,29] Hinzman et al[24] (16 patients with TBI) determined no correlation through their analysis, using a control of daily glucose values from the cohort of patients without CSD, against which daily glucose values of patients with CSD were compared. 83% of glucose values overall were low (<1mmol/L). Also showing no correlation, Sarrafzadeh et al[29] (21 SAH patients) took hourly glucose concentrations and established a control concentration through local regression with locally weighted scatter-plot

smoothing (LOWESS) regression to deal with irregular sampling. Glucose concentrations (median levels 1.48mmol (0.00-8.79 range)) at time points of CSD episodes were then compared with expected levels on the LOWESS interpolations.

Glucose as a metabolic "signature" of spreading depolarisation:

Of three studies utilising rsMD with continuous online assay,[22,26,27] two demonstrated consistent and significant falls in cerebral glucose occurring during or shortly after CSD[22,27] – a phenomenon termed the metabolic "signature". Overall, four studies including 51 patients observed a metabolic "signature", and three studies including 46 patients did not.

Feuerstein et al[22] recruited 10 patients with ABI (TBI n=5, ICH n=3, SAH n=2), and using rsMD compared epochs of glucose values five minutes before CSD with values five and 20 minutes after CSD. They used the area under the curve (AUC) of microdialysis concentration changes and subsequent two-tailed Wilcoxon signed-rank test, finding that 90 glucose AUCs were significantly different from zero (p<0.0001) with no significant difference seen in patients without CSD. This demonstrates a consistent and significant fall in glucose in the five to 20 minutes after episodes of CSD.

A “signature” fall in glucose after CSD was also identified using rsMD by Rogers et al[27]. The study, with a cohort of six patients (TBI *n*=3, ICH *n*=1, SAH *n*=1, ischaemic stroke *n*=1) observed 18 CSD episodes, experiencing technical difficulties with ECoG monitoring, reducing the quantity of data available for interpretation. This study compares peak glucose derangement during or after CSD with a baseline prior to onset, showing by Wilcoxon signed-rank test that glucose fell significantly during or after all observed events ($p<0.01$). O’Phelan et al[31] corroborate these observations in their cohort of four patients with TBI: this study abstract reports 50% of CSD events were associated with a fall in glucose, (exploratory data analysis), as observed using intermittent dialysis techniques.

In contrast, Parkin et al[26] utilised rsMD in 11 patients with ICH. This did not identify a “signature” glucose fall – patterns of dialysate glucose change were classified into transient increase, transient decrease, biphasic change or oscillation. No single pattern was observed as the typical response through exploratory data analysis, though no statistical analysis was performed.

Six further studies examined the glucose response to CSD using intermittent hourly cerebral glucose values. The utility of hourly glucose sampling is significantly limited for investigating the dynamics of a phenomenon occurring over 10 minutes. As such, the results of studies utilising this methodology are not considered in this section.

Prolonged glucose derangement after spreading depolarisation:

Beyond the immediate metabolic “signature”, we examine whether any glucose change in association with an episode of CSD was sustained for a considerable period. To consider this as a distinct finding from the metabolic “signature”, we identified studies commenting on intervals specifically greater than 10 minutes after CSD events, where the CMD collection interval does not include the CSD event itself.

Feuerstein et al[22] (TBI n=5, ICH n=3, SAH n=2) found that at 20 minutes after CSD events there was not recovery in dialysate glucose to the pre-CSD baseline, with sustained glucose changes of -32 μmol/L (Wilcoxon signed-rank test, $p<0.0001$), with longer CSD duration correlating with greater glucose decreases (Pearson product-moment correlation, $r=-0.25$, $p=0.05$).

Parkin et al[26] (ICH $n=11$) used rsMD, analysing glucose values between 60 and 120 minutes after the last CSD episode, against a control value calculated over a 60 minute period in the second hour of the monitoring period. This found glucose change over the monitoring interval strongly correlated with the number of CSD occurrences ($r^2=0.76$, $p=0.0004$), with the suggestion that “each spreading event leads to on average a 0.11mmol/L decrease in glucose”. It is unclear however if this corresponds with a true effect of sustained change in

glucose concentration. Notably, initial glucose levels ranged from 0.19mmol/L to 1.6mmol/L, with the range at the end of the recording period between 0.02mmol/L and 1.4mmol/L.

Rogers et al[27] (TBI *n*=3, ICH *n*=1, SAH *n*=1, ischaemic stroke *n*=1) observed on one occasion that glucose levels 10 minutes post-CSD had not returned to baseline concentration, though this was not reported to be consistent in their exploratory data analysis. As with the consideration of the metabolic "signature", the results of studies utilising intermittent hourly glucose sampling will not be discussed here: this rate of sampling would be of little use in observing the duration of effect of CSD on glucose with sufficient accuracy.

Cumulative effect of recurrent spreading depolarisation on glucose:

Here we report results of studies which examined the effect of multiple CSD episodes on glucose. Of the studies examining this relationship, three studies including a total of 45 patients demonstrated direct evidence of cumulative effect,[22,28,30] whilst across four further studies, 42 patients demonstrated possible evidence.[23,25–27]

Results amongst these studies were divided: three studies reported significant glucose concentration decreases but only in the context of clustered CSD, not in

single non-recurring episodes.[11,28,30] (Schiefeker et al,[11] ICH *n*=1; Sakowitz et al,[28] SAH *n*=17; Pinczolits et al,[30] ischaemic stroke, *n*=18). Fabricius et al[33] also found a correlation between clusters of CSD and decreasing glucose, communicated in their study abstract (*n*=220, pathology distribution not reported, r^2 and *p* value not reported). Three further studies did not identify a glucose fall after CSD, though it is noteworthy that these studies did not report sub-classification of CSD events nor did they distinguish clustered CSD[23,25,29]. (Hartings et al,[23] TBI *n*=1; Krajewski et al,[25] *n*=24 (TBI *n*=3, ICH *n*=1, SAH *n*=17, ischaemic stroke *n*=3); Sarrafzadeh et al,[29] SAH, *n*=21).

Feuerstein et al[22] (TBI *n*=5, ICH *n*=3, SAH *n*=2) observed consistently that where a second CSD episode occurred within 50 minutes, glucose concentrations had not recovered to baseline levels and progressively fell with subsequent episodes. Two studies[28,30] found glucose only decreased significantly in clustered CSD, discussed above, which evidences a cumulative effect eliciting a greater response in glucose derangement.

Further studies found *possible* evidence of this phenomenon: Parkin et al[26] observed strongly significant correlation between ECoG events and a greater decrease in dialysate glucose levels in 11 patients with ICH (r^2=0.76, *p*=0.0004). This study result is unable to draw conclusions on the cause-effect nature of this relationship.

In the TBI case study monitored by Hartings et al,[23] exploratory data analysis demonstrated multiple clustered CSD coinciding with an episode of low cerebral glucose levels. Rogers et al[27] (TBI *n*=3, ICH *n*=1, SAH *n*=1, ischaemic stroke *n*=1) observed a single episode of CSD where baseline dialysate glucose was "low" (100μM), and then fell to "critically low" levels (20μM) after CSD. This low baseline is not reported as being in the context of a shortly preceding CSD and so does not demonstrate "cumulative effect" as such, though it does observe that low cerebral glucose can be lowered further by CSD episodes, in this instance to a critical level of depletion.

Effect of glucose derangement on propensity for spreading depolarisation:

Here we review the evidence of glucose derangement as a causative factor for incidence of CSD. Two studies (35 patients) found a statistically significant correlation between glucose derangement and CSD incidence across the entire recording interval.[25,26] Krajewski et al demonstrate evidence that deranged cerebral glucose may increase the incidence of CSD: cerebral glucose outside the range of 1-3mM was present more frequently 20 minutes prior to CSD, compared with 20 minutes after (p<0.05).

Parkin et al[26] (ICH *n*=11), reported correlation between glucose depletion over the entire study interval and incidence of CSD events (r^2=0.76, *p*=0.0004). However, number of transient glucose derangements did not correlate with CSD events (r^2 and *p* values not given).

Two studies, with a total of 37 patients, did not find evidence of this relationship through their analysis.[24,29] Hinzman et al[24] (TBI *n*=16) found that the subgroup with CSD had no difference in daily glucose dialysate levels to those without (two-way ANOVA with post-hoc Bonferroni, *p*>0.05), in the context of 83% of all dialysate glucose levels in this study being low (<1mmol/l). Sarrafzadeh et al,[29] in their cohort of 21 patients with SAH, found that CSD was not linked to local deviations from their LOWESS curve of cerebral glucose, concluding that this confirms that cerebral glucose derangement does not increase incidence of CSD. The methodological approach resulting in probable data homogenisation of both these studies has been discussed above. Few studies reported results of serum glucose concentration in relation to CSD; these are reported in Appendix 2.

Risk of Bias:

Study bias was assessed by an adapted RTI item bank for observational studies[21], with the results displayed in Table 4. Overall, there were possible

sources of bias identified in statistical methods, inconsistencies or lack of reporting on monitoring techniques, and study design. Despite the potential for bias, the results were deemed to be believable in nine of 10 studies.

Discussion:

Summary of Evidence:

Correlating glucose & spreading depolarisation:

Eight of 10 studies (88 of 125 patients) reported correlation between CSD events and glucose derangement, supporting the existence of a true relationship. The two studies (37 of 125 patients) with negative findings[24,29] have used contrasting analytical methodologies to the other studies, with one[24] reporting a high preponderance of low glucose levels across the cohort (83%), with the possible effect of obfuscating the observation of a relationship.

The metabolic "signature":

High resolution studies analysing short "signature" windows after CSD have yielded consistent observation of the metabolic "signature". Two of three studies[22,27] using high resolution rsMD identified consistent and statistically significant evidence of glucose decrease (~0.2 mM (p=0.01),[27] 43.4 μmol/L (p=0.05)[22]) in the minutes after episodes of CSD. The third rsMD study[26] did not examine the immediate "signature" window, but rather analysed a period 60 to 120 minutes after CSD.

Sampling frequency will affect the ability to detect glucose change; the rate of change of glucose – particularly in the response to CSD – occurs in a time interval considerably less than the 60 minute sampling interval utilised in several included studies. Principles of sampling frequency for continuous functions stipulate that a function with bandwidth B require a sampling frequency of 2B, *i.e.* the Nyquist rate.[34] As such, the results of low resolution studies cannot be considered in observation of the metabolic "signature".

Prolonged effects on glucose:

The true duration of the metabolic effect of CSD seems to be variable, both between and within the considered studies. Given the range of durations within studies, and even within patients, it seems likely that the duration of relative local glycopenia is dependent on a number of factors. For example, findings in included studies have demonstrated continued glycopenia between 10 to 120 minutes post-CSD. This is in contrast to the descriptions of a metabolic "signature" which were relatively homogenous, occurring either during or within minutes of CSD.

If we presume the metabolic *demand* of repolarisation a constant, variability in duration of effect would logically be dependent on *supply* - the physiological variables here would include serum glucose concentrations and CBF. Of course

this is an oversimplification; CSD are not a uniform phenomenon, neither in number, duration nor extent of tissue to which they spread. For example, Feuerstein et al observed overall significantly sustained glucose changes after CSD of -32 μmol/L (p<0.0001), but that longer suppression by CSD led to a greater fall in dialysate glucose, thus increasing the demand with inevitable effects on the recovery interval.[22] Further complicating the phenomenon, the incidence of CSD influences regional CBF (rCBF) which may contribute to the variability of the glucose decrease observed. The normal haemodynamic response is of regional hyperperfusion to match metabolic demand. This is a physiological phenomenon of normal neurovascular coupling, which is followed by a period of regional hypoperfusion termed ‘spreading oligaemia’. However, CSD episodes in the context of disturbed microvascular reactivity have been shown to cause an inverse haemodynamic response, with early vasoconstriction[2,35,36] paradoxically inducing further compromise to metabolically challenged tissue, termed ‘cortical spreading ischaemia’. This concept has been comprehensively reviewed elsewhere.[36,37]

Cumulative CSD and glycopenia:

In support of the cumulative effect model, studies using intermittent CMD sampling techniques *only* identified significance in glucose derangement where clusters of CSD had occurred. Amongst studies using low-resolution CMD techniques, three studies recognised clustered CSD separately finding a glucose fall after these episodes.[11,28,30]

More directly, CSDs recurring within 50 minutes of each other were observed to create a cumulative effect on glucose, whereby the glucose reduction of a second CSD is seen before the metabolic recovery from the first.[22] We have also seen that when glucose is at a low baseline, CSD occurrence can reduce this to critical levels (as low as 20μM), illustrating that CSD can deplete glucose to the point of metabolic crisis, offering a mechanism of neural damage as a direct consequence of CSD. Again this effect has been inconsistently observed, suggesting variation dependent on other factors.

Does glycopenia cause CSD?

The evidence seen in this review in relation to glucose derangement as a precipitant of CSD is minimal. Cerebral glucose derangement correlates with incidence of CSD, but this alone is insufficient to clarify cause-effect. More significant here is the correlation of deranged cerebral glucose (e.c. outside the

range of 1-3 mM) observed as significantly present 20 minutes prior to CSD by Krajewski et al.[25] This is more supportive of glucose derangement also as a precipitant, and not only as a consequence. Similarly, Krajewski et al[25] correlate serum glucose derangement with CSD, though its temporal relationship with cerebral glucose levels was not examined. Previous commentary on the role of insulin therapy to target tight serum glucose control in TBI has outlined the risk of serum glucose modulation on cerebral glucose levels, with the description of a case of absolute cerebral glycopenia in a patient with TBI receiving insulin therapy.[38] As such, serum glucose levels are of clear relevance in the relationship between cerebral glucose and CSD, and further consideration is indicated for future studies. Given the unclear optimal target for glycaemic control, particularly in TBI,[39] further understanding of how this affects CSD incidence would be of benefit to ongoing work examining control of serum glucose concentrations. For comprehensive results reporting and further discussion on serum glucose and CSD, see Appendix 2.

Glucose derangement as a precipitant of CSD would likely have a dose-response relationship, alongside interactions with other physiological variables. Included studies have observed high CSD incidence coinciding with deranged cerebral glucose. This may represent glucose derangement perpetuating CSD. Mild to moderate glycopenia may be well compensated for, where serum

normoglycaemia coupled with normal CBF facilitates adequate glucose provision. Where this does not occur, continuation of this metabolic spiral downward would lead to non-ischaemic cell death. Extracellular metabolite levels can then equilibrate with serum and no longer be subject to the metabolic demands of viable tissue. As such, in the rare circumstances of this phenomenon occurring, the temporal window to observe it is narrow. Experimental animal models[13,40] have illustrated higher incidence of CSD in glucose depletion, though this is more complex to show conclusively in observational human studies.

A cyclical relationship?

From the qualitative accumulation of these studies, we offer a possible sequence of events: (1) episode of CSD; (2) reduction in local tissue glucose, which may be sustained; (3) reduction in local threshold for further CSD; (4) dependent on other factors, further CSD may or may not occur. (5) This sequence then could potentially continue, with contributory influence of other physiological derangement (beyond the scope of this review), until either: (a) physiological factors normalise and CSD threshold rises, or (b) critical glucose depletion

occurs, resulting in neural damage. Once the neural tissue is damaged sufficiently, its ability to de- and re-polarise will cease and the relationship is no longer observed. Possible causative relationships are suggested in Figure 2. [Insert Figure 2]

Study limitations:

Whilst comprehensive in its search, the available evidence for this review is limited. To maximise studies available for consideration, our inclusion criteria includes all ABI. A number of included studies, as does this review, consider ABI as a single disease, whereas the reality is several discrete pathologies, possibly with discrete relationships between CSD and metabolism. As summarised in Table 3, there is no clear relationship between considered pathology and study outcome. However, it remains likely that considering ABI homogeneously will dilute the accuracy of the results, given the distinct possibility of idiosyncratic CSD-metabolism relationships between the differing modalities of cellular injury.

Study groups have employed varying methodology and analytical techniques, which has led to heterogeneous result reporting. As such this review was unable to perform statistical meta-analysis. Each study has collected largely similar data, with the exception of CMD sampling intervals, but the interpretation methods and

statistical models used have differed greatly. This is likely a reflection of the generalised aims of the studies captured, which mostly aimed to “study the metabolic dynamics of CSD” or similar. This lends itself to a broad interpretation of what appropriate statistical methods might be employed to establish the significance of any observed relationship.

The reporting of baseline glucose levels by the included works has been variable. It is likely that if baseline glucose levels are low throughout a study cohort, detecting significant change in concentrations would be less likely, particularly where combined with intermittent sampling methodology. Such “floor effects” have the potential to obfuscate any observable relationship, but we have been unable to account for this given the variability in reporting.

Our study questions are deliberately of limited scope, in order closely examine this important relationship, but in doing so we do not investigate the wider context of other physiological factors.

Other factors:

Besides some consideration of the effect of serum glucose,[25] included studies have not accounted for other variables with the potential to influence either CSD or cerebral glucose. For example, CBF alone is a potential confounder for both

variables of interest; increased probability of CSD has been demonstrated as a function of decreasing cerebral perfusion pressure (CPP),[41] and would also decrease glucose delivery. Lactate has been frequently considered, but cerebral oxygen availability will also have considerable metabolic effects which may obfuscate the observed relationship between glucose and CSD. For further discussion on lactate and CSD, see Appendix 3.

Methodological differences may account for inter-study variability, and patient / monitoring placement differences may account for intra-study variability. However, even intra-patient variability in the CSD-glucose dynamic has been observed here. This suggests physiological variability, where other factors affect the threshold for CSD and glucose derangement. As an example, we have observed the large range of incidence of CSD across cohorts: 38% to 90%, suggesting large individual variation in susceptibility (though it is noteworthy that this may be influenced by injury subtype, not accounted for here).

Broader limitations:

There are wider issues rendering the study of the relationship between glucose and CSD difficult to understand. These relate primarily to the available methods for observing both CSD and glucose concentrations. CSD is a focal phenomenon,

and CMD catheters capture glucose concentration from a focal region; it is likely that for a significant number of CSD events, the point of CSD origin is not at the point of microdialysis monitoring. Global cerebral glycopenia would be detected to coincide with CSD events, resulting in positive findings. However, discrete areas of cerebral glycopenia triggering CSD away from the microdialysis catheter would go undetected. This is an important limitation in the current methodology, which arguably increases the likelihood of negative findings in such studies.

This is further dependent on the location of the probes. Pinczolits et al[30] identified an effect of clustered CSD on glucose only at the CMD probe 5mm from the infarct rim, and not at 15mm. This suggests that glucose fall in response to CSD is highly localised.

Given the transient and localised nature of the glucose fall after CSD, studies utilising intermittent sampling have not detected significant change. This is with one key exception – where recurrent episodes elicit a more profound and lasting effect on glucose, this change becomes amenable to detection through low-resolution sampling. This amenability to observation is also dependent on CMD probes being positioned sufficiently proximate to the area of neural tissue depolarising, evidenced by differing results based on proximity.[30] However, due to insufficient precision in placement and its reporting across the included studies,

it is difficult to draw meaningful conclusions regarding negative findings and subdural grid/microdialysis catheter proximity.

The proximity of CSD and CMD has been discussed, but also of relevance is the proximity of both to the injury. Where located in tissue which is not subject to the same metabolic strains of the injury core, it is probable that the glucose decrease after CSD would be less profound. As such, findings here may not reflect the relationship between CSD and glucose in tissue affected by injury. Further discussion on this as a limitation in the study of CSD has been comprehensively reviewed elsewhere.[2,42]

Future directions:

Whilst we have offered tentative conclusions based on the studies and results included in this review, the evidence offered is inconsistent. As described this is likely in part due to methodological differences. Collaborative efforts could facilitate prospective and homogenous analysis of such data on a larger scale, likely resulting in a greater consistency in evidence. Furthermore, we have discussed the effect of serum glucose on CSD incidence, and two studies associated serum glucose derangement with CSD probability.[25,32] Applying the principle of increasing temporal resolution to improve validity, the investigation of

serum glucose would also benefit from the utilisation of continuous monitoring paradigms. This could elucidate the cause-effect nature of deranged serum glucose and CSD probability by temporally resolving which occurs first. Similarly for CMD: the dynamics clearly occur predominantly in short temporal windows: the high resolution offered by rsMD for its study is far superior to intermittent sampling. Future studies should utilise this technique where available.

The area of most tentative evidence in this review is in the recursive relationship: with both glucose derangement and CSD being both cause and effect. Investigating this will require high resolution studies with close temporal analysis. Furthermore, CSD propensity is more complex than a dependence on glucose alone. High resolution, multimodal monitoring with multivariate logistic regression could elaborate on the spectrum predictor variables of CSD, and their respective significance and interaction.

Considering the above discussion, specifically, we propose the ideal characteristics of future studies:

1. High resolution sampling, with temporally resolved analysis to consider glucose preceding and following CSD.

2. Consistent and close proximity of subdural electrode grid and microdialysis catheter, with confirmation of proximity with post-operative imaging.
3. Consistent relationship between subdural electrode and pathological entity, *i.e.* ischaemic penumbra or peri-contusional tissue.
4. Measurement and reporting of potential confounding factors: systemic glucose, cerebral perfusion pressure (as a surrogate of cerebral blood flow), and brain tissue oxygen.
5. In addition to simple correlation measures observed in these studies, specific analysis based on thresholds of cerebral glucose (*e.g.* <0.2 or <0.5 mmol/L) as potential precipitants, as a more efficient analysis of what would constitute a clinically significant level of extracellular glycopenia.
6. Prospectively defined, or retrospectively categorised, pathology for inclusion, to avoid confounding factors or variability as a result of differing cellular pathology which may result in subtle relational differences affecting validity of results.
7. Recording and nominal analysis of extracellular lactate.
8. Recording of plasma glucose with examination of the inter-relationship with cerebral extracellular glucose in the context of CSD.

Conclusions:

This systematic review has collated the evidence of the dynamics of glucose and its relationship to CSD in brain injury. The identified studies were heterogeneous in their methodology with inconsistent results, though the majority have identified a correlation. There is good evidence that CSD leads to a fall in local cerebral glucose, with evidence that this may be prolonged. There is minimal evidence that deranged glucose may provoke further CSD (likely dependent on other factors), which in turn can lead to progressive glucose depletion. Given the strong correlation between CSD and glucose, a cyclical relationship is possible. Further study, utilising high resolution techniques, would be required to confirm this proposed relationship, specifically examining deranged glucose as a predictor of CSD. Serum glucose, and how this inter-relates with CSD and cerebral glucose, is of clear relevance but to date has received little consideration. With further understanding of these important relationships, the incidence of CSD could be addressed by therapeutic intervention targeted at systemic and cerebral glucose control**.**

Declarations:

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that there is no conflict of interest.

Funding:

None to declare.

Author contributions:

AS was responsible for concept, literature search, data extraction and manuscript composition. IN was responsible for duplicate literature search, and data extraction. AH, PH and DM were responsible for manuscript editing. AE was responsible for concept and manuscript editing. AS, IN, AH, PH, DM and AE approved the final manuscript.

Acknowledgements:

Not applicable.

References:

1. Lauritzen, M., and Strong, A.J. (2017). “Spreading depression of Leao” and its emerging relevance to acute brain injury in humans. J. Cereb. Blood Flow Metab. 37, 1553–1570.

2. Hartings, J.A., Shuttleworth, C.W., Kirov, S.A., Ayata, C., Hinzman, J.M., Foreman, B., Andrew, D., Boutelle, M.G., Brennan, K., Richter, F., Rosenthal, E.S., Sakowitz, O.W., Sánchez-Porras, R., Santos, E., Schö Ll, M., Strong, A.J., Urbach, A., Westover, M.B., and Winkler, M.K. (2017). The continuum of spreading depolarizations in acute cortical lesion development: Examining Leão's legacy. J. Cereb. Blood Flow Metab. 37, 1571–1594.

3. Leao, A. (1944). Spreading depression of activity in the cerebral cortex. J. Neurophysiol. 7, 359–390.

4. Dreier, J.P., and Reiffurth, C. (2015). The Stroke-Migraine Depolarization Continuum. Neuron 86, 902–922.

5. Strong, A.J., Fabricius, M., Boutelle, M.G., Hibbins, S.J., Hopwood, S.E., Jones, R., Parkin, M.C., and Lauritzen, M. (2002). Spreading and synchronous depressions of cortical activity in acutely injured human brain. Stroke 33, 2738–43.

6. Fabricius, M., Fuhr, S., Bhatia, R., Boutelle, M., Hashemi, P., Strong, A.J., and Lauritzen, M. (2006). Cortical spreading depression and peri-infarct depolarization in acutely injured human cerebral cortex. Brain 129, 778–790.

7. Hartings, J.A., Bullock, M.R., Okonkwo, D.O., Murray, L.S., Murray, G.D., Fabricius, M., Maas, A.I., Woitzik, J., Sakowitz, O., Mathern, B., Roozenbeek, B., Lingsma, H., Dreier, J.P., Puccio, A.M., Shutter, L.A., Pahl, C., and Strong, A.J. (2011). Spreading depolarisations and outcome after traumatic brain injury: a prospective observational study. Lancet Neurol. 10, 1058–1064.

8. Dohmen, C., Sakowitz, O.W., Fabricius, M., Bosche, B., Reithmeier, T., Ernestus, R.-I., Brinker, G., Dreier, J.P., Woitzik, J., Strong, A.J., and Graf, R. (2008). Spreading depolarizations occur in human ischemic stroke with high incidence. Ann. Neurol. 63, 720–728.

9. Dreier, J.P., Woitzik, J., Fabricius, M., Bhatia, R., Major, S., Drenckhahn, C., Lehmann, T.-N., Sarrafzadeh, A., Willumsen, L., Hartings, J.A., Sakowitz, O.W., Seemann, J.H., Thieme, A., Lauritzen, M., and Strong, A.J. (2006). Delayed ischaemic neurological deficits after subarachnoid haemorrhage are associated with clusters of spreading depolarizations. Brain 129, 3224–3237.

10. Schiefecker, A., Beer, R., Kofler, M., Pfausler, B., Unterberger, I., Lackner, P., Broessner, G., Rhomberg, P., Sohm, F., Mulino, M., Thome, C., Fabricius, M., Schmutzhard, E., and Helbok, R. (2015). Cortical

spreading depolarizations in patients with intracerebral hemorrhage: preliminary data. Crit. Care 19, P468.

11. Schiefecker, A.J., Beer, R., Pfausler, B., Lackner, P., Broessner, G., Unterberger, I., Sohm, F., Mulino, M., Thome, C., Humpel, C., and Schmutzhard, E. (2015). Clusters of Cortical Spreading Depolarizations in a Patient with Intracerebral Hemorrhage: A Multimodal Neuromonitoring Study. Neurocrit. Care 22, 293–298.

12. Lourenco, C.F., Ledo, A., Gerhardt, G.A., and Laranjinha, J. (2017). Neurometabolic changes during cortical spreading depolarization: High resolution measurements with a lactate-glucose dual microbiosensor array. J. Cereb. Blood Flow Metab. 37, 59.

13. Hoffmann, U., Sukhotinsky, I., Eikermann-Haerter, K., and Ayata, C. (2013). Glucose modulation of spreading depression susceptibility. J. Cereb. Blood Flow Metab. 33, 191–195.

14. Strong, A.J., Smith, S.E., Whittington, D.J., Meldrum, B.S., Parsons, A.A., Krupinski, J., Hunter, A.J., Patel, S., and Robertson, C. (2000). Factors influencing the frequency of fluorescence transients as markers of peri-infarct depolarizations in focal cerebral ischemia. Stroke 31, 214–222.

15. Vespa, P.M., McArthur, D., O'Phelan, K., Glenn, T., Etchepare, M., Kelly,

D., Bergsneider, M., Martin, N.A., and Hovda, D.A. (2003). Persistently Low Extracellular Glucose Correlates with Poor Outcome 6 Months after Human Traumatic Brain Injury despite a Lack of Increased Lactate: A Microdialysis Study. J. Cereb. Blood Flow Metab. 23, 865–877.

16. Zeiler, F.A., Thelin, E.P., Helmy, A., Czosnyka, M., Hutchinson, P.J.A., and Menon, D.K. (2017). A systematic review of cerebral microdialysis and outcomes in TBI: relationships to patient functional outcome, neurophysiologic measures, and tissue outcome. Acta Neurochir. (Wien). 159, 2245–2273.

17. Kramer, A.H., Roberts, D.J., and Zygun, D.A. (2012). Optimal glycemic control in neurocritical care patients: a systematic review and meta-analysis. Crit. Care 16, R203.

18. Hutchinson, P.J., O'Connell, M.T., Seal, A., Nortje, J., Timofeev, I., Al-Rawi, P.G., Coles, J.P., Fryer, T.D., Menon, D.K., Pickard, J.D., and Carpenter, K.L.H. (2009). A combined microdialysis and FDG-PET study of glucose metabolism in head injury. Acta Neurochir. (Wien). 151, 51–61.

19. Higgins, J.P., and Green, S. (2008). Cochrane Handbook for Systematic Reviews of Interventions. Chichester, UK: John Wiley & Sons, Ltd.

20. Panic, N., Leoncini, E., de Belvis, G., Ricciardi, W., and Boccia, S. (2013).

Evaluation of the Endorsement of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement on the Quality of Published Systematic Review and Meta-Analyses. PLoS One 8, e83138.

21. Viswanathan, M., and Berkman, N.D. (2011). Development of the RTI Item Bank on Risk of Bias and Precision of Observational Studies. Agency for Healthcare Research and Quality (US).

22. Feuerstein, D., Manning, A., Hashemi, P., Bhatia, R., Fabricius, M., Tolias, C., Pahl, C., Ervine, M., Strong, A.J., Boutelle, M.G., Feuerstein, D., Manning, A., Hashemi, P., Bhatia, R., Fabricius, M., Tolias, C., Pahl, C., Ervine, M., Strong, A.J., and Boutelle, M.G. (2010). Dynamic metabolic response to multiple spreading depolarizations in patients with acute brain injury: An online microdialysis study. J. Cereb. Blood Flow Metab. 30, 1343–1355.

23. Hartings, J.A., Gugliotta, M., Gilman, C., Strong, A.J., and Tortella, F.C. (2008). Repetitive cortical spreading depolarizations in a case of severe brain trauma. Neurol. Res. 30, 876–882.

24. Hinzman, J.M., Wilson, J.A., Mazzeo, A.T., and Bullock, M.R. (2016). Excitotoxicity and Metabolic Crisis Are Associated with Spreading

Depolarizations in Severe Traumatic Brain Injury Patients. J. Neurotrauma 33, 1775–1783.

25. Krajewski, K.L., Orakcioglu, B., Haux, D., Hertle, D.N., Santos, E., Kiening, K.L., and Unterberg, A.W. (2011). Cerebral microdialysis in acutely brain-injured patients with spreading depolarizations. Early Brain Inj. or Cereb. Vasospasm Vol. 1 Pathophysiol. , 125–130.

26. Parkin, M., Hopwood, S., Jones, D.A., Hashemi, P., Landolt, H., Fabricius, M., Lauritzen, M., Boutelle, M.G., and Strong, A.J. (2005). Dynamic changes in brain glucose and lactate in pericontusional areas of the human cerebral cortex, monitored with rapid sampling on-line microdialysis: relationship with depolarisation-like events. J. Cereb. Blood Flow Metab. 25, 402–413.

27. Rogers, M.L., Leong, C.L., Gowers, S.A., Samper, I.C., Jewell, S.L., Khan, A., McCarthy, L., Pahl, C., Tolias, C.M., Walsh, D.C., Strong, A.J., and Boutelle, M.G. (2017). Simultaneous monitoring of potassium, glucose and lactate during spreading depolarization in the injured human brain - Proof of principle of a novel real-time neurochemical analysis system, continuous online microdialysis. J. Cereb. Blood Flow Metab. 37, 1883–1895.

28. Sakowitz, O.W., Santos, E., Nagel, A., Krajewski, K.L., Hertle, D.N., Vajkoczy, P., Dreier, J.P., Unterberg, A.W., Sakowitz, O.W., Santos, E., Nagel, A., Krajewski, K.L., Hertle, D.N., Vajkoczy, P., Dreier, J.P., Unterberg, A.W., and Sarrafzadeh, A.S. (2013). Clusters of spreading depolarizations are associated with disturbed cerebral metabolism in patients with aneurysmal subarachnoid hemorrhage. Stroke 44, 220–223.

29. Sarrafzadeh, A.S., Santos, E., Wiesenthal, D., Martus, P., Vajkoczy, P., Oehmchen, M., Unterberg, A.W., Dreier, J.P., Sarrafzadeh, A., Santos, E., Wiesenthal, D., Martus, P., Vajkoczy, P., Oehmchen, M., Unterberg, A., Dreier, J.P., and Sakowitz, O. (2013). Cerebral glucose and spreading depolarization in patients with aneurysmal subarachnoid hemorrhage. Cereb. Vasospasm Neurovascular Events After Subarachnoid Hemorrhage 115, 143–147.

30. Pinczolits, A., Zdunczyk, A., Dengler, N.F., Hecht, N., Kowoll, C.M., Dohmen, C., Graf, R., Winkler, M.K., Major, S., Hartings, J.A., Dreier, J.P., Vajkoczy, P., and Woitzik, J. (2017). Standard-sampling microdialysis and spreading depolarizations in patients with malignant hemispheric stroke. J. Cereb. Blood Flow Metab. 37, 1896–1905.

31. O'Phelan, K., Sanchez-Chavez, J.J., Nemeth, Z., Morrison, C., Jaggid, J.,

Hartings, J.A., and Olvey, S. (2011). Evidence of metabolic stress associated with cortical spreading depression. J. Neurotrauma 28, A93–A94.

32. Hocker, S., Learney, R.M., Hartings, J.A., and Fabricius, M. (2012). Paradoxical elevation of serum glucose in TBI associated spreading depressions. Neurocrit. Care 17, S76.

33. Fabricius, M., Dreier, J.P., Graf, R., Hartings, J.A., and Lauritzen, M. (2011). Long-term neuromonitoring of the electrocorticogram in malignant stroke, subarachnoid and intracranial hemorrhage, and traumatic brain injury: Role of cortical spreading depression. Clin. Neurophysiol. 122, S15.

34. Nyquist, H. (1928). Certain Topics in Telegraph Transmission Theory. Trans. A.I.E.E , 617–644.

35. Dreier, J.P., Major, S., Manning, A., Woitzik, J., Drenckhahn, C., Steinbrink, J., Tolias, C., Oliveira-Ferreira, A.I., Fabricius, M., Hartings, J.A., Vajkoczy, P., Lauritzen, M., Dirnagl, U., Bohner, G., and Strong, A.J. (2009). Cortical spreading ischaemia is a novel process involved in ischaemic damage in patients with aneurysmal subarachnoid haemorrhage. Brain 132, 1866–1881.

36. Dreier, J.P. (2011). The role of spreading depression, spreading depolarization and spreading ischemia in neurological disease. Nat. Med. 17, 439–447.

37. Ayata, C., and Lauritzen, M. (2015). Spreading depression, spreading depolarizations, and the cerebral vasculature. Physiol. Rev. 95, 953–993.

38. Strong, A.J., Boutelle, M.G., Vespa, P.M., Bullock, M.R., Bhatia, R., and Hashemi, P. (2005). Treatment of Critical Care Patients with Substantial Acute Ischemic or Traumatic Brain Injury. Crit. Care Med. 33, 2147–2149.

39. Hermanides, J., Plummer, M.P., Finnis, M., Deane, A.M., Coles, J.P., and Menon, D.K. (2018). Glycaemic control targets after traumatic brain injury: a systematic review and meta- analysis. Crit. Care 22.

40. Hopwood, S.E., Parkin, M.C., Bezzina, E.L., Boutelle, M.G., and Strong, A.J. (2005). Transient changes in cortical glucose and lactate levels associated with peri-infarct depolarisations, studied with rapid-sampling microdialysis. J. Cereb. Blood Flow Metab. 25, 391–401.

41. Hartings, J.A., Strong, A.J., Fabricius, M., Manning, A., Bhatia, R., Dreier, J.P., Mazzeo, A.T., Tortella, F.C., and Bullock, M.R. (2009). Spreading Depolarizations and Late Secondary Insults after Traumatic Brain Injury. J. Neurotrauma 26, 1857–1866.

42. Dreier, J.P., Fabricius, M., Ayata, C., Sakowitz, O.W., Shuttleworth, C.W., Dohmen, C., Graf, R., Vajkoczy, P., Helbok, R., Suzuki, M., Schiefecker, A.J., Major, S., Winkler, M.K.L., Kang, E.., Milakar, D., Oliveira-Ferreira, A.I., Reiffurth, C., Revankar, G.S., Sugimoto, K., Dengler, N.F., Hecht, N., Foreman, B., Feyen, B., Kondziella, D., Friberg, C.K., Piilgaard, H., Rosenthal, E.S., Westover, M.B., Maslarova, A., Santos, E., Hertle, D., Sanchez-Porras, R., Jewell, S.L., Balanca, B., Platz, J., Hinzman, J.M., Luckl, J., Schoknecht, K., Scholl, M., Drenckhahn, C., Feuerstein, D., Eriksen, N., Horst, V., Bretz, J.S., Jahnke, P., Scheel, M., Bohner, G., Rostrup, E., Pakkenberg, B., Heinemann, U., Claassen, J., Carlson, A.P., Kowoll, C.M., Lublinsky, S., Chassidim, Y., Shelef, I., Friedman, A., Brinker, G., Reiner, M., Kirov, S.A., Andrew, R.D., Farkas, E., Guresir, E., Vatter, H., Chung, L.S., Brennan, K., Lieutaud, T., Marinesco, S., Maas, A.I., Sahuquillo, J., Dahlem, M.A., Richter, F., Herreras, O., Boutelle, M.G., Okonkwo, D.O., Bullock, M.R., Witte, O.W., Martus, P., Van Den Maagdenberg, A.M.J.M., Ferrari, M.D., Dijkhuizen, R.M., Shutter, L.A., Andaluz, N., Schulte, A.P., Macvicar, B., Watanabe, T., Woitzik, J., Lauritzen, M., and Strong, A.J. (2017). Recording, analysis, and interpretation of spreading depolarizations in neurointensive care: Review and recommendations of the COSBID research group. J. Cereb. Blood

Flow Metab. 37, 1595–1625.

43. Feuerstein, D., Backes, H., Gramer, M., Takagaki, M., Gabel, P., Kumagai, T., and Graf, R. (2016). Regulation of cerebral metabolism during cortical spreading depression. J. Cereb. Blood Flow Metab. 36, 1965–1977.

44. Brooks, G.A., and Martin, N.A. (2014). Cerebral metabolism following traumatic brain injury: new discoveries with implications for treatment. Front. Neurosci. 8, 408.

Appendix 1.

The following example search strategy is taken from our search of Embase:

1. exp spreading cortical depression/
2. cortical spreading depression.mp
3. spreading depolarisation.mp

4. spreading depolarization.mp
5. spreading depression.mp
6. 1 or 2 or 3 or 4 or 5
7. exp glucose/
8. glucose.mp
9. hyperglycaemia.mp
10. exp hyperglycemia/
11. hypoglycaemia.mp
12. exp hypoglycemia/
13. exp brain metabolism/
14. exp energy metabolism/
15. exp glucose metabolism/
16. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. exp traumatic brain injury/
18. traumatic brain injury.mp
19. exp head injury/
20. exp brain injury/
21. exp cerebrovascular accident/
22. stroke.mp
23. exp brain hemorrhage/
24. intracerebral haemorrhage.mp
25. exp subarachnoid hemorrhage/
26. subarachnoid haemorrhage.mp
27. intracranial haemorrhage.mp

27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

27. 6 and 16 and 26

Appendix 2.

Extracellular glucose and plasma glucose in CSD

The relationship between extracellular glucose and plasma glucose in the context of CSD has largely been unexamined in the included studies, despite recording

of both variables. Krajewski et al[25] used both cerebral and plasma glucose in their Spearman's correlation analysis with CSD, though did not examine the inter-relationship between the two. Rogers et al[27] recorded one episode where extracellular glucose was low (100μM), despite plasma glucose being high (11.8mM), but conducted no further analysis regarding this relationship. In the supplementary material for Feuerstein et al[43] – linear regression demonstrated poor correlation between plasma glucose and rsMD glucose through linear regression completed for the six non-diabetic patients with full data available (R^2 values range 0.01-0.40).

Two studies sought to correlate plasma glucose with incidence of CSD. Hocker et al[32] in their abstract observed CSD probability rising as a function of increased serum glucose ($p<8x10^{-6}$), but did not record CMD glucose values. It is noteworthy that this work was not subject to peer review. Krajewski et al[25] showed that periods of deranged serum glucose partially correlated with increased frequency of CSD (hyperglycaemia $r=0.464$, $p<0.05$) (hypoglycaemia $r=0.485$, $p<0.05$). Despite the clinical importance of the relationship between serum glucose, cerebral glucose and CSD, there is a clear paucity of data, with insufficient consideration of all three variables to draw conclusions on the efficacy of modulating serum and cerebral glucose as a means to reduce incidence of CSD.

Considering the interesting observations of inverse plasma-cerebral glucose relationships, and a strong correlation between plasma hyperglycaemia and CSD, this inter-relationship is worthy of further exploration. This is of particular importance when considering clinical intervention to increase plasma glucose with the therapeutic aim of averting cerebral glycopenia. If the relationship is altered or inverted in some instances of CSD, such as observed by Rogers et al,[27] such intervention may be of little value in increasing cerebral glucose. Further, inducing plasma hyperglycaemia in such instances may have a secondary effect of paradoxically increasing CSD propensity as suggested by Hocker et al.[32] Further investigation is required to ascertain the values and risks of these clinical scenarios.

Appendix 3.

Lactate as an alternative metabolic substrate

The metabolic “signature” discussed across included articles is considered as a phenomenon of a transient *decrease* in cerebral glucose accompanied by a

transient *increase* in lactate. However, there is growing recognition of the role of lactate as an alternative substrate for metabolism, particularly post-TBI.[44] Recent microdialysis evidence in the rat model has produced a hypothesised threshold lactate level of >80% above normal, beyond which neurons will utilise lactate as a substrate.[43]

In the included studies, though cerebral lactate has been measured alongside glucose, the analysis has been directed toward recognition of lactate *increase* as a result of classical anaerobic metabolism of glucose during the high metabolic demand subsequent to CSD. There has been little exploration of lactate decrease. Parkin et al[26] have observed transient decreases in lactate around CSD, but have not reported specific evaluation of this phenomenon relative to the baseline lactate level, nor attempts at correlation with low glucose availability at these time points.

Hartings et al[23] recorded an interval of 10 hours with brain glucose <0.1mmol/L. During this time, 11 CSD occurred, with lactate and lactate/pyruvate ratio (LPR) both elevated throughout (3-7mmol/L and >40 respectively), with no indication of utilisation of lactate as a substrate. Concomitantly however, $P_{ti}O_2$ during this interval was 8-10mmHg (a fall from >20mmHg) and CPP was not reported, so it is unclear whether these conditions are entirely dependent on metabolic substrate factors alone, or wider physiological variables such as CBF and oxygen

availability. At a later interval, with cerebral glucose <0.10mmol/L, 20 CSD occurred – during this time LPR rose above 40 (lactate concentration not reported).

Krajewski et al[25] examined lactate values as a dichotomous variable – either "pathological" (>4mM) or normal. Based on this analysis, they observed a "marked improvement" of lactate concentrations for one hour after CSD (*i.e.* decreased incidence of extracellular lactate >4mM). With some conjecture, this could indicate utilisation of lactate as a substrate in the relative absence of glucose, though equally this phenomenon could be explained by, for example, reactive hyperaemia leading to increased lactate extraction from local tissue. Without dynamic, time-resolved, nominal lactate data collection and analysis, these types of studies would be unable to elucidate the role of lactate as a substrate, particularly in the contexts of high lactate or low glucose availability.