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The role of the NADPH oxidase derived brain oxidative stress in the cocaine-related death associated with excited delirium: A literature review

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HIGHLIGHTS

- Excited Delirium Syndrome is commonly associated to cocaine abuse.
- The pathophysiology of this syndrome is complex and not yet fully understood.
- Increased reactive oxygen species production by the NADPH oxidase NOX enzymes might play a crucial role.
- Data from animal models and human evidence are discussed in this review.

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ABSTRACT

Excited delirium syndrome (ExDS) is a term used to describe a clinical condition characterized by bizarre and aggressive behaviour, commonly associated with the use of psychoactive compounds, especially cocaine. The pathophysiology of ExDS is complex and not yet fully understood. In addition to a central dopamine hypothesis, other mechanisms are thought to be involved in cocaine-related ExDS, such as increased reactive oxygen species production by the family of the NADPH oxidase NOX enzymes. In this review, we will summarize current knowledge on the crucial contribution of brain NADPH oxidase derived oxidative stress in the development of cocaine-induced ExDS. Data from animal models as well as human evidence will be discussed.

1. Introduction

Excited delirium syndrome (ExDS) is a term used to describe a clinical condition characterized by bizarre and aggressive behaviour, commonly associated with the use of psychoactive compounds, especially cocaine (Lipsedge, 2015; Gerold et al., 2015). ExDS is still a controversial issue which has provoked heated debate among physicians and pathologists, even concerning its existence (Gill, 2014a; Vilke et al., 2012a; Paquette, 2003; Michaud, 2013; Kodikara et al., 2012; Takeuchi et al., 2011; Grant et al., 2009a; Vilke et al., 2012c). The main clinical characteristics of ExDS are delirium with evidence of psychomotor excitation, hostility, physical violence, bizarreness, ranting, paranoia, panic, public disturbance, surprising physical strength, profuse sweating due to hyperthermia, and respiratory arrest (Beer and Beer, 2013). Deaths from this syndrome are infrequent (Gerold et al., 2015) and currently there is no clear explanation why some subjects progress to death and why some do not (Michaud, 2013). The pathophysiology of ExDS is complex and not yet fully understood. Stimulant drug use, especially cocaine, is associated with ExDS (Bunai et al., 2008; Gruszecki et al., 2005; Escobedo et al., 1991; Ruttenber et al., 1999a; Ho et al., 2009; Mirchandani et al., 1994). In addition to a

Abbreviations: ExDS, Excited delirium syndrome; NADPH, Nicotinamide adenine dinucleotide phosphate; ROS, Reactive Oxygen Species; GABA, Gamma-AminoButyric Acid; HSP, Heat Shock Protein; 17-DMAG, 17-Dimethylaminoethylamino-17-demethoxygeldanamycin; NF-kB, Nuclear factor kappa-light-chain-enhancer of activated B cells; GSH, Glutathione; MDMA, 3,4-methylenedioxy-methamphetamine; MAP kinase, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinases; i-NOS, inducible nitric oxide synthase; Bcl-2, B-cell lymphoma 2; SMAC, Second mitochondria-derived activator of caspases; DIABLO, Diablo homolog.

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central dopamine hypothesis in the pathogenesis of ExDS (Vilke et al., 2012b), other mechanisms are thought to be involved in cocaine-related ExDS (Michaud, 2013). In recent years, alterations of the stress response system, as well as increased reactive oxygen species (ROS) production, have been implicated in the pathogenesis and development of cocaine-induced ExDS (Mirchandani et al., 1994; Pudiak and Bozarth, 1994).

Because of the circumstances surrounding death, and the lack of a definitive cause on autopsy, the validity of the term 'excited delirium' has been considered controversial and is still not universally accepted (O'Sullivan et al., 2014). This argument mainly relates to the fact that most organized medical associations, including the International Classification of Disease, Ninth Revision (ICD-9) do not recognize the exact term 'excited delirium' or 'ExDS'. However, the National Association of Medical Examiners and the American College of Emergency Physicians, the physicians most likely to encounter these patients, do recognize ExDS as a discrete diagnostic entity (Vilke et al., 2012a). From an epidemiological point of view, it is particularly difficult to determine the exact incidence of the ExDS, first of all because there is no current standardized definition of this syndrome but also because excited delirium is described in the forensic literature mainly as a diagnosis of exclusion at autopsy (Plush et al., 2015). An observational study suggests that the incidence of death among patients manifesting signs and symptoms that may be consistent with excited delirium is $<$10% (Barnett et al., 2012). These deaths appear to be caused by several restraint-related factors, such as hyperthermia, hypoxia, positional asphyxia, aspirational pneumonia, use of capsicum spray by police staff and Taser use, which has been shown to increase the risk of fatality, especially when used on a subject with pre-existing cardiac problems or suffering from psychostimulant toxicity and/or psychosis or extreme panic states (Gill, 2014b; Grant et al., 2009b). More than 95% of all published fatal cases involve men at a mean age of 36 years (Bunai et al., 2008; Allam and Noble, 2001). This is probably due to the fact that the highest prevalence rates of cocaine intoxications are observed in male subjects between the age of 25 and 44 years (Vroegop et al., 2009; Pope et al., 2011) and that, in the same class of age, cocaine-induced psychiatric symptoms, such as anxiety, panic disorders, paranoia and psychotic states, which may rapidly convert in an agitated delirium, more frequently occur (Falck et al., 2004; Tang et al., 2007). Concerning the risks related to the physical examination or assessment of subjects with ExDS, one of the most relevant one is undoubtedly represented by suicidal behavior (Vilke et al., 2012c; Otahbachi, 2010; Mohr et al., 2003) which should be constantly considered and carefully evaluated by clinicians.

In the 1980s, there was a dramatic increase in the number of reported cases with behaviour similar to an uncontrolled psychiatric emergency. Most of these cases were found to be associated with the introduction and abuse of cocaine in North America (Fishbain and Wetli, 1981; Wetli, 1987). Since then, the pathogenetic link between excited delirium and cocaine has been taken into consideration (Grant et al., 2009a; Ruttenber et al., 1997; Wetli and Fishbain, 1985; Sztajnkrycer and Baez, 2005; O'Halloran and Lewman, 1993; Otahbachi et al., 2010; Pollanen et al., 1998; Ross, 1998; Wetli and Mittlemann, 1981). Additionally, excited delirium has now been associated with other illicit psychoactive compounds, such as methamphetamine, and phencyclidine, as well as with specific psychiatric conditions and their associated pharmacological treatment (Grant et al., 2009a; Stratton et al., 2001).

This review aims to provide a summary of current toxicological and forensic literature in order to define the role of brain NADPH oxidase-derived oxidative stress in the pathogenesis of cocaine-induced ExDS and to identify factors associated with sudden unexpected death of individuals with symptoms of ExDS, for a better understanding of this complex and debated syndrome. To this purpose, we report data from animal models as well as from human studies. In particular, we reviewed a total number of 133 studies, published in the last 35 years (1981–2015) on PubMed (http://www.ncbi.nlm.nih.gov/pubmed), combining for the searching two or more of the following keywords: excited delirium; oxidative stress; NADPH oxidase; cocaine; reactive oxygen species; brain; neurotransmitters; neurotoxicity.

2. Aetiology and pathophysiology of excited delirium: the role of cocaine

Although current knowledge about the aetiology and pathophysiology of excited delirium appears limited, pre-clinical and clinical studies have provided some new insights. It has been widely demonstrated that psychostimulant drugs and in particular cocaine might be the leading cause of excited delirium (Gruszecki et al., 2005; Ho et al., 2013; Hall et al., 2013; Shields et al., 2015). Thus, *post mortem* toxicological analysis of fatal cocaine-associated deaths in patients with symptoms of excited delirium has shown cocaine concentrations similar to those found in recreational drug users and less than those noted in acute cocaine 'overdose' deaths, clearly suggesting a different death mechanism (Michaud, 2013; Vilke et al., 2012b). The cellular and neurochemical changes induced by cocaine abuse in subjects with symptoms of excited delirium have so far been the subject of lively scientific debate. Using ligand binding and autoradiographic methods, abnormalities in the dopaminergic system and in particular alterations in D1, D2 and D3 dopamine receptors and in the cocaine's ability to block the reuptake pump or 'transporter' by which dopamine is recycled back to the nerve terminal have been identified (Staley et al., 1994; Staley et al., 1995). The appeal of the central dopamine hypothesis lies in the fact that hypothalamic dopamine receptors are responsible for thermoregulation. Disturbances of dopamine neurotransmission may help to explain the profound hyperthermia noted in many patients with symptoms of excited delirium (Ruttenber et al., 1999a). In particular, several reports have suggested that, in case of cocaine-induced ExDS, the abuse of this psychoactive compound leads to alterations of dopamine processing in the mesolimbic pathway in the brain, resulting in hyperactivity and hyperthermia (Ruttenber et al., 1999b; Staley et al., 1997). Furtheron, dopamine processing has been shown to be altered in individuals with ExDS. In these subjects, decreased levels of α-synuclein in the substantia nigra, as well as an increased expression of this protein in the ventral tegmental area, have been reported (Takeuchi et al., 2011). Multiple studies have also documented an elevation of dopamine transporter binding sites in chronic cocaine users with symptoms of ExDS (Little et al., 1998; Wilson et al., 1996). The functional activity of dopamine transporters was also found to be elevated in the limbic system of subjects suffering from cocaine-induced ExDS(Mash and Staley, 1999; Schmauss et al., 1993). The dopamine hypothesis also provides a link to psychiatric aetiologies of excited delirium, such as schizophrenia (Detweiler et al., 2009). Alterations of the stress response system have also been implicated in the pathogenesis and development of cocaine-induced excited delirium (Mirchandani et al., 1994; Pudiak and Bozarth, 1994). In particular, it has been shown that corticosterone and other stress-associated hormones may potentiate cocaine-induced psychomotor stimulant effects. More specifically, cocaine-induced HPA axis functioning alterations may affect catecholamine release, in particular dopamine and adrenaline. This leads to increased blood pressure, with an elevated risk of fatal stroke or heart attack. Further, cocaine-induced alterations of the stress response can lead to rhabdomyolysis, with consequent release of myoglobin into the

bloodstream and deterioration of kidney function (Cador et al., 1993; Piazza et al., 1991).

3. The role of the NADPH oxidase-derived oxidative stress in ExDS pathogenesis

Together with the dopaminergic hypothesis, new pathogenetic mechanisms are emerging for the pathogenesis of excited delirium (Gill, 2014a). Recent literature evidence is in favour of cocaine-induced neurotoxicity via production of a large amount of ROS or reduction of antioxidant systems, with consequent increased oxidative stress in the central nervous system (CNS) (Pedrajas et al., 2015; Uys et al., 2011; Sordi et al., 2014; Muriach et al., 2010).

One of the main source of ROS production in the CNS is represented by the family of the NADPH oxidase NOX enzymes, which are proteins that transfer electrons across biological membranes, producing superoxide. This family includes seven members (i.e., NOX1-5 and DUOX1-2), with distinct tissue distribution and mechanisms of activation (Bedard and Krause, 2007). In the CNS, the NADPH oxidase 2 enzyme (NOX2) is involved in cell fate and modulation of neuronal activity (Infanger et al., 2006). From a pathological point of view, NOX2-derived increase of oxidative stress is thought to play a crucial role in several brain disorders, such as neurodegenerative diseases and psychiatric disorders (Sorce and Krause, 2009).

In particular, some reports on rodent models have shown a pathological association between cocaine-induced ROS production and increased expression of the NADPH oxidase NOX2, as well as its regulatory subunits (Fan et al., 2009; Isabelle et al., 2007). Some evidence points towards the pathogenetic role of NOX2-derived oxidative stress in psychoactive compound-induced neurobehavioural alterations. In this context, we and others have previously demonstrated the crucial role of the NOX2 enzyme in the development of molecular, neurochemical and behavioural alterations induced by mice exposure to sub-anaesthetic doses of ketamine (Behrens et al., 2007; Sorce et al., 2010; Behrens et al., 2008). Other Authors have reported the role of NOX2-derived oxidative stress in neurochemical and neuromorphological changes induced by other psychoactive compounds such as metamphetamine, steroids and opioids. In particular, it has been shown that NOX2-derived ROS might be responsible for methamphetamine-induced dopamine-releasing and locomotor-activating properties, given the evidence that subchronic treatment with apocynin, an antioxidant/NOX inhibitor compound, significantly and dose-dependently decreased methamphetamine's potency and efficacy to evoke [$^{(3)}$H]overflow (Miller et al., 2014). With respect to steroids, Chinaglia and co-workers recently demonstrated that testosterone induces leucocyte migration via NADPH oxidase-derived ROS and that testosterone administration was able to increase, in turn, NADPH oxidase activity and expression. In support of these observations, apocynin treatment suppressed testosterone-induced NADPH oxidase activation (Chignalia et al., 2015). In the same line, it was recently reported that NOX2 or p47phox (one of its catalytic subunit) knock-out mice developed the same antinociceptive tolerance as wild type mice, following continuous morphine administration(Doyle et al., 2013).

Previous evidence supports a crucial role of increased oxidative stress in GABAergic neuronal subpopulation in the pathogenesis of excited delirium induced by cocaine or other psychostimulant drugs, such as ketamine (Takeuchi et al., 2011). Details on this aspect are presented in Table 1.

Together with GABAergic neurons, astrocytes are also known to be potential targets of drug abuse like cocaine, which acts on this cell population by altering their *in vivo* morphology, size and physiological functioning (Araque, 2006; Fattore et al., 2002). Importantly, astrocytes appear to be particularly vulnerable to redox status. Thus, they contain higher levels of GSH compared to other cell type in the brain (Dringen, 2000) and might early respond to detrimental external stimuli, such as abuse of psychoactive compounds, by very high production of ROS (Deigner et al., 2000; LaRowe et al., 2006). Thirdly, very recent findings show that pre-treatment of astroglia-like cells with the clinically available antioxidant N-acetyl cysteine mitigates the acute effects of cocaine-induced toxicity in this cell line (Badisa et al., 2015).

The exact molecular mechanism linking increased NOX2-derived oxidative and cocaine-induced neurotoxicity is not fully understood yet. Increased expression and activation of specific heat shock proteins (HSP), as well as alterations of NF-kB signaling, elevation in protein nitrosylation and iNOS expression and functioning have been reported. Details on these proposed mechanisms are provided in Table 2.

Several studies indicated that cocaine exposure induces apoptosis in different tissues (Cerretani et al., 2012; Blanco-Calvo et al., 2014). Also, cocaine neurotoxicity has been associated with the induction of biochemical features of apoptosis, such as activation of caspases (Dey et al., 2007; Cunha-Oliveira et al., 2006; Imam et al., 2005; Rego and Oliveira, 2003; Mitchell and Snyder-Keller, 2003), loss of mitochondrial potential and cytochrome c release (Cunha-Oliveira et al., 2006; Rego and Oliveira, 2003). Cocaine was also reported to upregulate the content of some pro-apoptotic mitochondrial proteins in cultured cells and brain tissue (Cunha-Oliveira et al., 2008; Cunha-Oliveira et al., 2010). Controversially, other Authors reported the absence of apoptosis after cocaine exposure in brain (Dominguez-Escriba et al., 2006; Alvaro-Bartolome et al., 2011). The aforementioned differences could possibly depend on the tissue, cocaine concentration/duration, animal models used, etc (Lopez-Pedrajas et al., 2015).

In this context, it has been widely demonstrated that oxidative stress induces cellular damage and, eventually, cell death (Calabrese et al., 2007). On the other hand, cell death induced by cocaine in human neuronal progenitor cells seems to be preceded by oxidative stress increase (Poon et al., 2007). Numerous studies indicate that Bcl-2 is involved in opposing cell death induced by oxidative stimuli (Susnow et al., 2009). In an interesting paper by Hochman and co-workers, Authors demonstrated enhanced oxidative stress and susceptibility to oxidants, as well

Table 1
Alterations of GABAergic system induced by increased oxidative stress.

ALTERATIONS INDUCED BY INCREASED OXIDATIVE STRESS	PSYCHOSTIMULANT DRUG	REFERENCES
Changes in gene expression in GABAergic spiny cells	Cocaine	(Nestler, 2001)
Increase in the basal levels of extracellular GABA in the nucleus accumbens	Cocaine	(Xi et al., 2003)
Depression in GABAergic transmission by favoring dopamine release from nigrostriatal nerve terminals	Cocaine	(Centonze et al., 2002)
Loss of phenotype of fast-spiking GABAergic interneurons	Ketamine	(Behrens et al., 2007)

Table 2
Proposed mechanisms linking increased NOX2-derived oxidative and cocaine-induced neurotoxicity.

MECHANISMS	FUNCTIONS	REFERENCES
Increased expression of HSP70 gene in the brain	- Response to hyperthermia (>39 °C) and ischemic stimuli - Cytoprotection and cellular assembly - Rapid response to altered redox state - Redox status dependent regulatory activity on several organs - Biomaker for the identification of excited delirium as cause of death - Biomarker of post-drug survival time and/or interventions by medical and law enforcement personnel - Biomarker of an adaptive response to limit cocaine-induced ischemic neurotoxicity	(Mash et al., 2009; Riezzo et al., 2010; Lind et al., 2005; Johnson et al., 2012; Kubo et al., 1998; Xiao et al., 2002; Chen et al., 2011)
Increased expression of HSP90 gene in the brain	- NADPH oxidase subunits are HSP90 client proteins (interference of 17-DMAG with ROS generation and reduction in pro-oxidative factors)	(Madrigal-Matute et al., 2012)
Increased NF-kB activation in the nucleus accumbens, hippocampus and frontal cortex	- Development of cocaine addiction via increased NADPH oxidase-derived ROS in neurons and microglia	(Ang and Tergaonkar, 2007; Dello Russo et al., 2009; Yao et al., 2010; Block et al., 2007)
Decreased NF-kB activity in the frontal cortex	- Altered behaviour in cocaine-treated rats - Reduced GSH concentration in hippocampus - Reduced glutathione peroxidase activity in hippocampus - Impairement of memory retrieval of experiences acquired prior to cocaine administration	(Muriach et al., 2010)
Increased nitrotyrosine expression	- Role in oxidative myocardial damage in human cocaine-related cardiomyopathy - Role in MDMA-induced neurotoxicity - Protein nitrosylation mediated directly by NADPH oxidase via activation of specific p38 and ERK1/2	(Xiao et al., 2005; Tanabe et al., 2012; Darwish et al., 2007; Frustaci et al., 2015; James et al., 2003; Sautin et al., 2007)
Increased i-NOS expression and functioning	- Development of neuropathological alterations in rodent models of neurological disorders - Development of neuropathological alterations in cocaine-abuse - Role in the cocaine-induced locomotor sensitization and kindling - Synergistic effect with activated microglia NADPH oxidase in inducing neuronal death - Synergistic effect with NADPH oxidase-dependent redox signalling in microvascular endothelial cells	(Chang et al., 2002; Torreilles et al., 1999; Emerit et al., 2004; Hald and Lotharius, 2005; Mendoza-Baumgart et al., 2004; Portugal-Cohen et al., 2010; Park et al., 2001; Mander and Brown, 2005; Wu et al., 2008)

as altered levels of antioxidant enzymes in the brain of Bcl-2-deficient mice, concluding that Bcl-2 affects cellular levels of ROS, which may be due to an effect either on their production or on antioxidant pathways (Hochman et al., 1998). A strong pathogenetic link between cocaine exposure and Bcl-2 up-regulation has been previously reported. Indeed, it has been shown that Bcl-2 upregulation following prenatal cocaine exposure induces apoptosis in fetal rat brain (Xiao and Zhang, 2008) and that cocaine-mediated astrocytes toxicity involves Bcl-2 mediated cell death (Cao et al., 2015). Interestingly, several studies showed that NADPH oxidase activation accelerates apoptosis in different types of human cells, including neurons, via Bcl-2-mediated pathways (Lundqvist-Gustafsson and Bengtsson, 1999; Qin et al., 2006; Jana and Pahan, 2004). Previous observations from our group and others also reported an increased expression of SMAC/DIABLO proapoptotic protein group in psychoactive compounds-induced neurotoxicity (Riezzo et al., 2014; Cadet et al., 2003; Amaral et al., 2013). Importantly, it has also been shown that NADPH oxidase-derived ROS generation is able to induce the release of different proapototic protein group, including Smac/Diablo (Fruehauf and Meyskens,, 2007; Maianski et al., 2004).

A graphical summary of all the proposed NADPH oxidase-induced pathogenetic mechanisms in the development of ExDS is shown in Fig. 1.

4. Conclusion

Cocaine is a widely used substance of abuse; however, the syndrome of cocaine-induced agitated delirium is rare and not yet completely understood. Exact mechanisms behind this syndrome are still poorly defined and why some subjects progress to death and why some do not is not known.

A large body of evidence points towards a role of oxidative stress in cocaine-induced brain alterations, suggesting that a disruption of redox balance in the brain might be considered as a crucial contributor in the pathogenesis of cocaine-related ExDS. However, the involvement of other important pathogenetic mechanisms in the development of cocaine-induced ExDS, occurring both inside and outside the CNS, has to be considered. In particular, among them, neuroinflammation and consequent microglia activation, increased disruption of the blood brain barrier and alterations of peripheral vascular permeability, as well as altered HPA-axis responsivity might represent the most significant ones. Therefore, further investigations will be needed to clarify the neuropathophysiological changes present in ExDS fatal cases and to elucidate ExDS pathophysiology in order to help to determine whether fatal ExDS may be preventable, or whether a point of no return may be detectable.

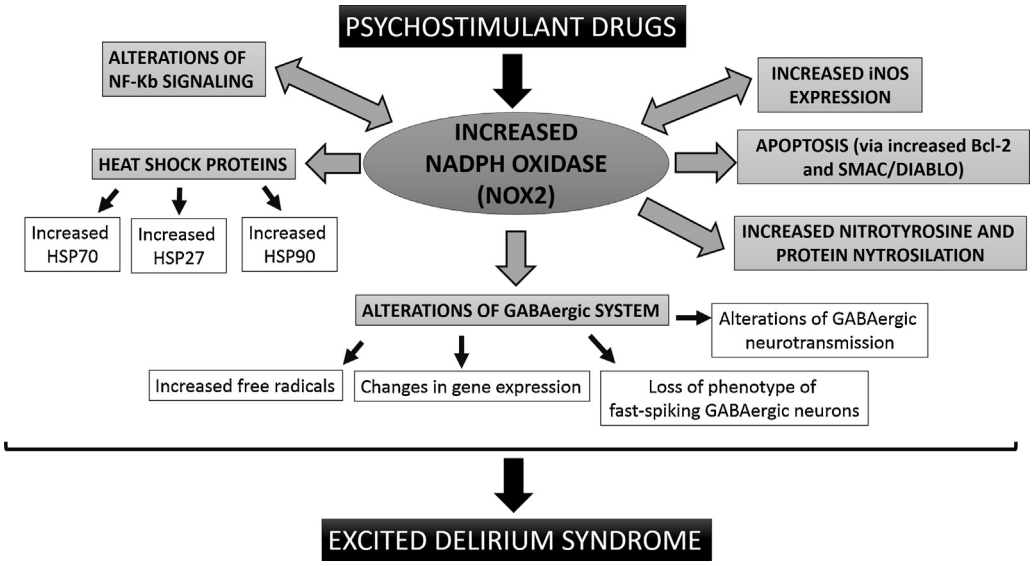

Fig. 1. NADPH oxidase-induced pathogenetic mechanisms involved in the development of cocaine-induced ExDS.
Psychostimulant drugs, such as cocaine, have been shown to induce an increased expression and activation of the NADPH oxidase NOX2. This leads, in turn, to possible alterations of several systems. In particular, the GABAergic one is known to be affected, with consequent increase of free radical production in GABAergic neurons, changes in gene expression, loss of phenotype in fast-spiking interneurons and alterations of GABAergic neurotransmission. Increased expression of HSP70, 27 and 90 has been also observed as a consequence of cocaine-induced NOX2 increase. Other phenomena associated to the elevation of the NADPH oxidase NOX2 include alterations of NF-Kb signaling, increased i-NOS expression, as well as nitrotyrosine and protein nytrosilation. Enhanced apoptotic processes, via increased Bcl-2 and SMAC/DIABLO expression, have been also described, following cocaine-induced NOX2 elevation.

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Appendix A. Supplementary data

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