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Review

Simplifying study of fever's dramatic relief of autistic behavior

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SUMMARY

Dramatic relief of autistic behavior by infectious fever continues to tantalize parents and practitioners, yet researchers still hesitate to study its physiology/biochemistry, fearing stress and heat of brain imaging, contagion, and fever's complexity. Yet what could be more revealing than a common event that virtually 'normalizes' autistic behavior for a time? This paper proposes study of three simplified scenarios: (1) improvements appearing hours before fever, (2) return of autistic behavior soon after fever, (3) improvements persisting long after fever. Each scenario limits some risk – and some explanation – inviting triangulation of decisive factor(s) in relief and recurrence. Return of autistic behavior after fever may be most revealing. The complex mechanisms that generated fever have all abated; simpler cooling mechanisms prevail – how many plausible explanations can there be? The decisive factor in fever's benefit is concluded to be water drawn/carried from brain myelin and astrocytes by osmolytes glutamine and taurine released from muscles and brain; the decisive factor in return of autistic behavior after fever is return of water.

I think we need to conduct research as if we know this is an emergency.

Martha Herbert 2009 [1]

Introduction: fever's dramatic relief of autistic behavior

Though there is practically no mention of the high fever/improved behavior phenomenon in the entire autism literature, every knowledgeable person – both parent and professional – I approached for information knew of it.

Sullivan 1980 [2]

Ruth Christ Sullivan first published anecdotal reports of fever's benefit in 1980 in *Parents Speak*, her column in the *Journal of Autism and Developmental Disorders* [2]. Campbell reported an outbreak of upper respiratory infection in a Bellevue Hospital nursery. Autistic children with fevers of 102–105 °F [38.8–40.5 °C] socialized with other children and adults; most improvements subsided a few days after temperatures returned to normal. Caparulo and Cohen reported stressful procedures like blood drawing also provoked brief dramatic improvements.

Cotterill described the phenomenon in 1985: "When autistics have a moderate fever, they invariably display dramatically more normal behavioural patterns, including a greater desire or ability to communicate.... The effect appears to reach a maximum for fevers in the range 1.5–2.5 °C [2.7–4.5 °F]." [3] Brown (1999) reported his personal observations: "[T]he changes that occur in these autistic children are… dramatic – more like a metamorphosis in which the autistic child suddenly becomes almost normal. These children experience increased alertness, a decrease in social isolation and self-injurious behavior, an increase in verbal behavior, and an attempt to reach out and communicate with adults." [4].

These reports inspired a prospective study by Curran and colleagues, who compared behavior of children with autistic disorders (ASD) during fevers greater than 100.4 °F (38 °C) against behavior of ASD children with no fever [5]. More than half the parents already knew fever helped. Parents observed less irritability, hyperactivity, repetitive acts, and inappropriate speech during fever, which did not depend on lethargy, height of fever, nor severity of illness.

Publication of this study evoked a spontaneous outpouring of parents' reports of relief by fever in autism and other disorders. Three autistic children improved briefly from a sauna, steam room, or hot tub/bath; some improved hours *before* fever's onset [6]. Zimmerman summarized parents' reports of improvements before

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fever (personal communication 2014): "My impression has been that those children who improve before the appearance of fever are those who also have the most striking improvements overall during fever (and are more likely to have enduring effects after fever subsides), possibly 10% of those who have the 'fever effect.'" Zimmerman suggested low-grade fever might explain early benefits: "It is usually a period of hours [up to 6–8] when benefits are seen before fever is recognized." He noted 80% of parents in Curran et al. [5] reported their child improved during fever on one or more *Autism Behavior Checklist* categories: "In clinical care, approximately 30% of parents report that their children with ASD improved dramatically during fever… their symptoms are so obvious the family recognize them immediately."

Informal parent surveys by the *Simons Foundation* concluded fever helps 30–40% of ASD children [7]. Their workshop on fever in autism considered the effect of temperature to increase *brain blood flow* – consistently low in these children [8] – but the usual lack of benefit of a sauna or hot tub argued against it (J Miles, personal communication 2010). One explanation may be Kiyatkin's observation that fever increases human brain temperature much more than ambient heat, especially in children (personal communication 2010).

Herbert and colleagues have been outspoken advocates of the significance of fever's benefit in papers e.g. [9], chapters e.g. [8], letters e.g. [10], and a book describing a child whose improved speech persisted *weeks* after fever subsided [11]. Herbert concluded the fever phenomenon reveals autism is a "*chronic dynamic encephalopathy*" [8] – ongoing active *reversible* brain pathophysiology.

What happens during fever?

Neurons require several orders of magnitude more metabolic energy than other cells, generating considerable heat [12]. Heat accelerates metabolism about 11% for each °C [13], so the hypothalamus regulates body/brain temperatures closely – normally 98.0–98.8 °F (36.6–37.1 °C) orally [14] – activating and integrating independent heating and cooling mechanisms to stabilize temperature at the most appropriate *set point*. When bacterial or viral infection requires the hypothalamus to raise body temperature to a new set point called *fever*, cooling mechanisms of *vasodilation* and *sweating* are suppressed. When fever *plateaus* at the new set point, skin blood flow returns to balance heat gain and loss, and the child feels neither hot nor cold [15]. When fever *breaks* (*crisis* or *flush*) skin blood vessels dilate abruptly and sweating is profuse.

Fever resembles the body's response to *cold* [16] – skin blood vessels constrict to conserve heat, and heat is generated by muscle contractions (*shivering*) and acceleration of metabolism. *Metabolic* (nonshivering) *thermogenesis* during cold is stimulated by the sympathetic nervous system (SNS) transmitter *norepinephrine* [17]. Fever's thermogenesis is largely due to *epinephrine* from the adrenal medulla, which accelerates metabolism 5–10× more than norepinephrine by stimulating SNS *β-receptors* and mobilizing metabolic fuels [14].

Current views of fever implicate environmental *pyrogens* like bacteria activating the immune system, which orchestrates the response to infection via signaling proteins (*cytokines*, e.g. *interleukins*) and hormone-like fatty acids (*prostaglandins*) that also generate heat [18]. Tang and Kiyatkin found intravenous injection of bacterial tissue in rats caused brain temperature to rise in phases. The first phase was initiated by heat conservation and production in the periphery with sustained vasoconstriction within about 40 min; about an hour later brain temperature rose again, suggesting "metabolic brain activation and subsequent involvement of central mechanisms that increase body metabolism." [18] Presumably SNS release of epinephrine.

These catecholamines also accelerate metabolism during *stress*, generating *stress fever*. Stress fever is genuine fever – body temperature reset to a higher *set point* [19]. Ordinary stress aggravates autistic behavior, but severe stress (e.g. *panic*) often relieves it briefly [2,6,9]. Kiyatkin: "[F]luctuations [in brain temperature] due to stress, environmental warming, etc. are relatively weak (up to 1.0–1.5 °C), but during fever this increase is much larger, especially in children." (personal communication 2010).

What happens hours *before* fever?

Wannemacher and colleagues investigated the response to infection in healthy volunteers inoculated with *sand fly virus* to induce mild illness [20]. Fever appeared 56–70 hr after inoculation. Hours *before* fever's onset, most plasma amino acids (AA) fell: "[S]ignificant depression in the concentration of total amino acids [and most individual amino acids] was evident 9–23 hr before the onset of fever or symptoms of illness ...." Wannemacher [21] concluded amino acids [mostly *glutamine*] released from skeletal muscles by catabolism of their proteins were taken up avidly for anabolic responses to infection by immune cells, liver, and brain.

Muscles release their *free* amino acids, however, long before their proteins break down from fever. Shabert and Wilmore [22] cited evidence adrenal glucocorticoids responding to infection or injury stimulate release of 3–4x usual amounts of glutamine from muscles – "probably all free glutamine" Wilmore observed (personal communication 2014). Shabert and Wilmore: "In the skeletal muscle-free amino acid pool, glutamine and taurine are the most abundant amino acids ...."

Glutamine released by muscles serves as provisional fuel during the loss of appetite (*anorexia*) that accompanies fever. Glutamine is alternative fuel in brain neurons and astrocytes, especially during hypoglycemia [23], primary fuel in rapidly replicating cells – e.g. enterocytes [24] and blood vessel endothelial cells – and precursor (via *citrulline*) of *arginine*, only substrate for primary vasodilator *nitric oxide*.

Glutamine in autistic disorders

Glutamine is normally the most abundant amino acid in blood, but is consistently low in plasma of ASD children, and often low in their brain [25]. Children with high brain glutamine from *urea cycle disorders* rarely show autistic behavior [26]. *Autism Research Institute* (ARI) practitioners commonly give ASD children and adults oral glutamine to heal their intestines – from 250 mg to 8 g/day – but only two of ten reported improved behavior (personal communications 2013). Verzella (MD) gives 5–7 g/day of glutamine after cleansing their intestines of pathogens like *bacteria* and *yeast*: "Multifactorial and multisystemic is the condition, so that the improvement has different aspects in different children. Most common: sedation, less stereotypies, better sleep, more concentration.... A remedy, not a cure." Some practitioners reported increased excitability from glutamine in a few children (one reported *seizures*) – probably because glutamine readily decomposes to glutamate and ammonia in the intestines. Oral glutamine may be more stable as the dipeptide *glutamine/alanine* (e.g. *Sustamine*). Branched-chain AAs are good glutamine precursors.

Taurine in autistic disorders

Pangborn found taurine was the amino acid most wasted or depleted in urine of autistic children [27]. He concluded taurine was the first (and safest) amino acid to supplement in these children, in light of the large amount of taurine in the normal fetal brain, and in breast milk, and taurine's help detoxifying *ammonia* to

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glutamine – but noted researchers recommended no more than 2 g/day of taurine for ASD children. Pangborn suggested natural substances *thyme*, *oregano*, *Goldenseal*, and *S. boulardii* to cleanse intestines before giving these children any other AAs, including glutamine [28].

Taurine is most vulnerable to abbreviated breastfeeding [29], dietary deficiencies of precursors *methionine* and *cysteine* [30], impaired synthesis from lack of bioactive *vitamin B6* [27], and preemptory requirements for *sulfate* and *glutathione*. Mother's milk is rich in taurine; cow's milk is low after calves are weaned [29]. Schultz and colleagues found longer breastfeeding was associated with less likelihood of developing autism [31] – yet many (but not all) infant formulas have been fortified with taurine since the mid-1980s [32].

Unlike glutamine, however, taurine is *never* a fuel – but has other critical functions. For one, β-stimulation by epinephrine moves calcium and taurine into excitable cells (e.g. neurons, muscles, heart) – calcium to activate the cells, taurine to regulate active cytosol calcium [33]. *Intense* β-stimulation by epinephrine [e.g. *fever*, *panic*] *reverses* this shift [34].

Taurine as primary brain osmolyte – and neuroinhibitor

If fever releases free glutamine and taurine from muscles, what do these amino acids have in common? Most obvious – both are *primary organic brain osmolytes*. Taurine is released from brain to cerebrospinal fluid (CSF) to reduce swelling from a variety of provocations [35], notably *ammonia*. Frosini found fever in rabbits released taurine from brain to CSF, perhaps as a cryogen [36]. *Taurine*, *like glutamine*, *carries – and draws – water*.

Boelens and colleagues found supplemental glutamine increased plasma taurine in severely injured patients: "Osmoregulation involves the regulation of changes in the concentrations of solutes over the cellular membrane. The cytosolic concentration must change in parallel with the osmolarity of the extracellular compartment. To maintain the cell's integrity, it is thus important that concentrations do not change drastically and thereby *do not influence the membrane potential*, enzyme activities, or other cellular processes. To meet these requirements… a *metabolically inert* compound is needed that requires a minimum of energy in [maintaining] high concentrations across the cell membrane and in responding adequately to osmotic changes. Taurine… meets these requirements almost ideally." [37] (my emphases).

Huxtable's review of taurine's physiology – and electrophysiology – is monumental [38]: "In animals, taurine concentrations are high in platelets, electrically excitable tissues, and secretory structures.... Concentrations are low in extracellular fluids… and are low or variable in other tissues.... In mammalian heart and brain, taurine can be the organic osmolyte present in highest concentration.... The permeability of the membrane to taurine is a linear function of cell volume.... Ion transport is powered by a Na^+-K^+-ATPase, and amino acid transport is Na^+ dependent. Thus energy consumption, *ion gradients* (*hence cell excitability*) and amino acid accumulation are all linked phenomena...." (my emphasis).

"The osmotic pressure of a cell is determined by the total osmolarity of cytoplasmic solutes. These solutes consist of inorganic ions, low-molecular-weight organic compounds, and macromolecules. Osmoregulation involves alterations… of substances in the first two classes.... K^+ or Cl^- accumulation or release is usually involved.... However, with inorganic ions the requirements for osmoregulation and the regulation of membrane excitability are not coincident, constraining the osmoregulatory role of inorganic ions."

Here Huxtable points out osmoregulation by K^+ and Cl^- is limited because their concentrations are critical to membrane excitability. Taurine too affects membrane excitability directly, as an inhibitor [secondary to GABA]: "The evidence is good both peripherally and centrally that these actions of taurine are the result of a stimulation of Cl^- current. This leads to hyperpolarization of the cell membrane. The degree of hyperpolarization produced by taurine decreases as the membrane potential is made more negative. At sufficiently negative potentials, the effect reverses and taurine produces a depolarization or hypopolarization." Huxtable also noted swelling of astrocytes reduces their membrane potential: "This is an indication that the osmoregulatory and electrical activities of cells are interdependent phenomena. The frequently studied effects of taurine on ion currents may thus be closely connected with its osmotic actions." [38].

Immature overhydrated brain myelin in ASD

Dobbing and Sands studied changes in brain weight, cholesterol and water during the normal growth spurt in human brains from ten weeks gestation to seven years old [39]. The human brain growth spurt begins at midgestation, although five-sixths of the growth is postnatal, they concluded, which may extend beyond the second year. The growth spurt takes place in stages: first, multiplication of *neurons*, then multiplication of *glia* (predominantly *oligodendroglia* to generate myelin sheaths), then deposition of *lipids* in the sheaths. *Decline in water content of the brain reciprocally parallels the increase in lipids*. They described *longitudinal* growth of myelin sheaths as axons lengthen, and *maturational* growth as lipids are deposited, water is displaced, and sheaths thicken around axons: "*[M]yelination as a developmental*, *maturational process will be more reflected by increased lipid concentration*; and the concurrent and later myelination of growth will be reflected by increased total amount." (my emphasis).

Longitudinal growth of myelin sheaths may depend on testosterone becoming *dihydrotestosterone*. *Maturational* growth apparently depends on *estrogens* depositing *lipids* that displace water. Because myelin sheaths compact as water is displaced, *the proportion of lipids to water may be a better measure of maturity than the thickness of sheaths*, Dobbing and Sands concluded. Hendry and colleagues, using *transverse relaxation time imaging*, found brain white matter in autistic boys 6–12 years old contained more water than normal globally and regionally [40]. Decreased *anisotropy* of brain myelin in children and adolescents with ASD [41] also argues water distribution is immature [42].

Deoni and colleagues investigated white matter in adult autistic males using *multi-component relaxation analysis* [43]: "Individuals with autism show evidence of altered structural and functional 'connectivity' across large-scale brain systems.... A recurrent finding… is… increased overall brain volume, which… may be caused by differential effects driving white matter (WM) to be larger.... Specifically, those brain regions exhibiting the greatest volume increases correspond to later and *prolonged* myelinating pathways. Further, these WM volume differences persist into young adulthood.... Myelin plays a critical role in establishing and maintaining congruent brain communication.... Histological evidence for abnormal myelination, myelin content, or myelin structure in the pathogenesis of ASD is derived from *ex vivo* post-mortem studies showing altered myelin composition with *delayed compaction in the sheaths*...." (my emphases).

"Currently, the most robust approach to… estimating myelin content is through multi-component relaxation analysis (MCR). Within brain tissue, MCR aims to decompose the measured MR signal into contributions from two anatomically distinct water compartments: the slow relaxing intra- and extra-axonal water; and the faster relaxing water trapped between the myelin bilayers.... Our results show that individuals with autism have *wide-*

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spread MWF [*myelin water fraction*] *reductions* in brain regions previously implicated in ASD.... *MWF is believed to be more specific to changes in lipid myelin content*.... Altered myelin, therefore, is likely associated with reduced connectivity. Our results are consistent with the current hypothesis that neural disconnectivity underpins ASD, as supported by structural imaging studies; functional imaging studies; and electroencephalography investigations. In each of these prior studies, abnormal connectivity was observed in frontal and temporal regions, consistent with our findings of *lower myelin content* in these areas." [43] (my emphases) Deoni confirmed "decreased MWF is associated with lower myelin content and immaturity." (personal communication 2016).

Salt cravings and hyponatremia in ASD

> *As in other tissues, water is in thermodynamic equilibrium across the plasma membranes of all brain cells. As a result, the osmotic concentration of cytoplasmic and extracellular fluids is equal under steady-state conditions. Because cell membranes are freely permeable to water, changes in the intracellular or extracellular content of solutes establish transmembrane osmotic gradients that result in the flow of water into or out of cells.*
>
> Kahle et al. 2009 [44]

Salt cravings in children with autistic disorders were reported online [45], anecdotally, and in the literature [46]. Primary causes of salt cravings are *salt wasting*, *overhydration*, and *dehydration* [47,48]. Dehydration inducing salt appetite seems counterintuitive, but salt helps dehydrated persons (often 3rd World children with severe diarrhea) expand blood volume by retaining water.

In 2011, emails were sent to 200+ U.S. practitioners formerly listed on the *Autism Research Institute* (ARI) website, inquiring about salt cravings and low blood sodium (*hyponatremia*) in ASD children. Attached was a just-published paper: *Do salt cravings in children with autistic disorders reveal low blood sodium depleting brain taurine and glutamine*? [46]. Two weeks later a similar email + pdf was sent to 100 international practitioners listed on the ARI site.

Of 60 who replied, the great majority reported plasma or serum sodium was normal in their ASD patients, even in those who craved salt. But six practitioners replied hyponatremia was not uncommon. In some ASD children salt cravings signified adrenal insufficiency; in others, magnesium, iodine, or zinc deficiencies.

Because *sodium ions* (Na^+) can't cross cell membranes freely, and sodium is the most abundant ion in plasma and extracellular fluids, abnormal sodium concentrations force water into or out of cells, including brain cells. High blood sodium (*hypernatremia*) draws water out of cells; low blood sodium (*hyponatremia*) drives water into cells. *Hyponatremic encephalopathy* arises when low blood sodium drives water into astrocytes, which swell and exert pressure. Children are more vulnerable to hyponatremic encephalopathy because their brains grow faster than their skulls; a child's brain is adult-sized by six years, his skull not adult-sized till 16 years [49]. Autistic children have enlarged brains within a few months after birth [50].

As Huxtable noted, brain cells respond to excessive water by first releasing electrolytes, then organic osmolytes. Massieu and colleagues: "Among the organic osmolytes involved… free amino acids play a prominent role because of the large intracellular pools often found in nerve cells.... Results favor the role of taurine, glutamine, glutamate, and aspartate as the main amino acid osmolytes involved in the brain adaptive response to hyponatremia...." [51].

Inducing fever in rabbits, Frosini detected a shift of sodium ions from CSF to brain displacing calcium ions [36] – corroborating Myers and Veale's observation that this exchange in the hypothalamus raises the *set point* [52]. The *sodium pump* (Na^+/K^+-ATPase) normally keeps intracellular sodium ions (Na^+) low and potassium ions (K^+) high in neurons, astrocytes, and other cells. An intrinsic membrane protein, the sodium pump transports ions across membranes against their concentration or electrochemical gradient using energy derived from ATP. Na^+/K^+-ATPase exports three intracellular Na^+ ions and imports two extracellular K^+ ions. This maintains and restores the steep Na^+ and K^+ gradients across membranes that polarize neurons and initiate/conduct nerve impulses. The sodium gradient also provides energy for secondary transport processes, including uptake of nutrients and neurotransmitters, and shifts of molecules to regulate cell volume and pH [53].

Impairments of the sodium pump described by Benarroch [53] greatly resemble pathologies detected and suspected in autistic disorders. First, loss of sodium gradients reduces astrocyte uptake of *glutamate*. Wakefield and colleagues suspected brain glutamine was low in autistic children because glutamate transporters were limited [54]. Brain glutamate/glutamine was low in ASD children and adults in three of four studies [25]. Second, impairment of the sodium pump requires the *sodium/calcium exchanger* to remove sodium, accumulating intracellular calcium. Ji and colleagues detected evidence of calcium accumulation in autistic brains [55]. Third, ion gradients maintain cell volume. Astrocytes are swollen in ASD [56], the compensatory osmolyte *myoinositol* is elevated [57], and primary osmolytes taurine and glutamine are depleted [25,46]. Herbert et al. suggested swollen astrocytes and microglia compressing capillaries might explain low brain blood flow in ASD children [8,9].

Discussion – implications of fever's benefit

> *Parent report has confirmed reductions in adverse behaviors with fever. Despite the significance of this observation, it would be even more important if anecdotal reports of increased emotional contact and speech with fevers could be confirmed.*
>
> Helt et al. 2008 [9]

The stress (and heat) of brain imaging and risk of contagion [58] are not the only challenges facing researchers curious about the physiology/biochemistry of fever's dramatic relief of autistic behavior. There's so much going on during fever. Cytokines, prostaglandins, epinephrine, heat, brain metabolism and blood flow, sodium/calcium exchange, free amino acids released, then protein amino acids .... *Where to begin*? But if we *simplify* the scenario – study (1) how improvements begin hours *before* fever, (2) how autistic behavior returns *soon after* fever, and (3) how improvements sometimes persist *long after* fever – not only are risks (and explanations) fewer (Fig. 1), we may 'locate' the decisive factor(s) by *triangulation*.

The most obvious '*weakest links*' in autistic children are *brain blood flow* and *brain myelin* – both consistently abnormal [8,59], both perhaps immature. Immature overhydrated myelin sheaths might readily explain dysconnected brain hemispheres and anomalous asymmetries described by Herbert et al.: "Since the bulk of interhemispheric cortical communication relies on information transfer via the corpus callosum, these larger brains with their disproportionately smaller corpus callosum sizes may experience greater than normal constraints on interhemispheric transfer of information.... This possible disproportionate increase in intrahemispheric connections, along with a bottleneck in interhemispheric linkages, should further increase the likelihood of functional lateralization and anatomical asymmetry." [59].

Yet asymmetric low brain blood flow [60] might also explain these hemispheric anomalies. Fever increases brain blood flow by

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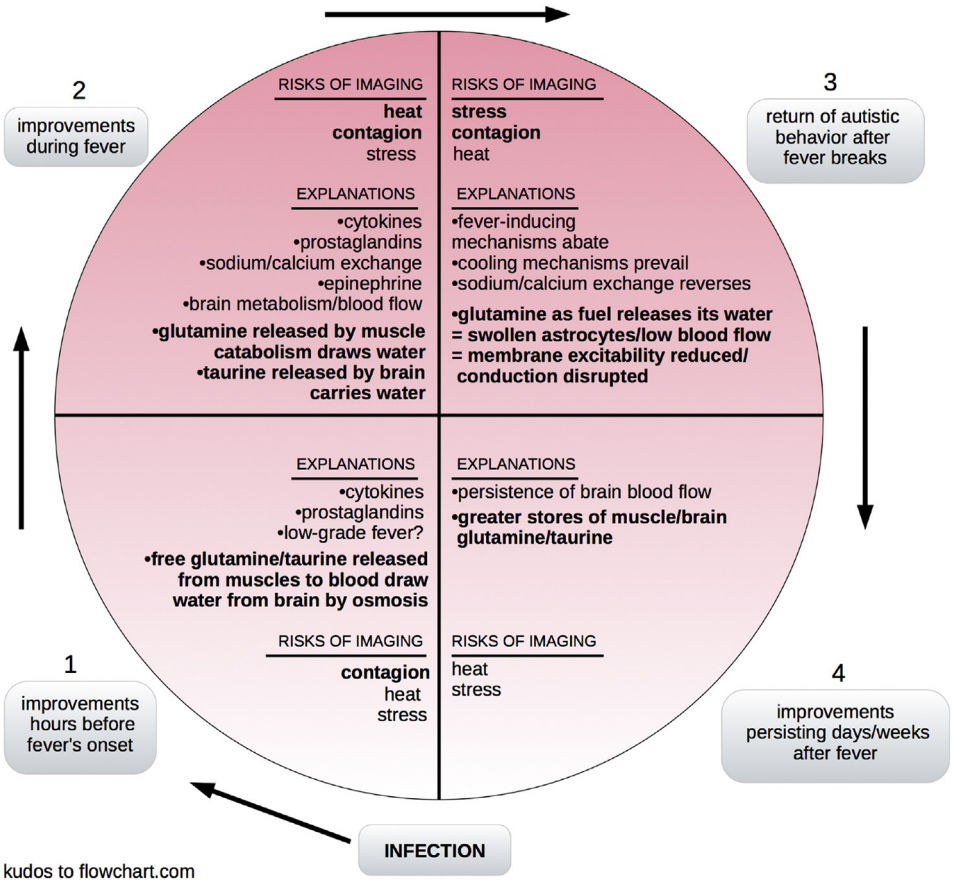

Fig. 1. Phases of fever's dramatic benefit studied by brain imaging: (1) improvements hours before fever's onset, (2) improvements during fever, (3) return of autistic behavior soon after fever breaks, (4) improvements persisting days/weeks after fever. Each phase has more or less heat, stress, contagion – and explanations, allowing triangulation of decisive factors in relief and recurrence. The safest scans (for the child) may be (1) during improvements hours before fever, and (2) during improvements persisting days after fever. Heat at these times will be minimal – and stress as well. A scan as autistic behavior returns will be more stressful – but most revealing – and may serve as baseline.

accelerating brain metabolism – and releasing *nitric oxide* [61] – *but how can fever reverse or compensate too much water in brain myelin*?

The *critical clue* here is improvements hours *before* fever. Cytokines are already active, initiating first responses to infection – constriction of skin vessels to conserve heat, and release of prostaglandins and other pyrogens to generate heat. Epinephrine hasn't yet accelerated metabolism/blood flow. Does low-grade fever induce early improvements? Then why doesn't a sauna or hot bath help more often? *What else happens so early that might improve autistic behavior*? Wannemacher concluded catabolism of skeletal muscle proteins released amino acids (mostly *glutamine*) for anabolic responses to infection. But muscles release their *free* amino acids *hours before* they break down from fever. Is it coincidence the amino acids with the greatest free concentration in muscle – *glutamine* and *taurine* – are *primary organic brain osmolytes*?

Glutamine is also provisional fuel during *anorexia* of fever, especially in brain neurons and astrocytes, and rapidly replicating cells. *But taurine is not a fuel* – arguing another function is more critical to fever's benefit. If taurine helps by drawing/carrying water out of the brain, *does glutamine help likewise*?

If fever relieves autistic behavior by reducing brain water, the obvious inference is that behavior returns after fever because water returns. Frosini reported CSF taurine in rabbits returned to baseline when temperature did (personal communication 2016). When taurine leaves CSF via blood, water leaves with it. Taurine presumably will not return to the brain if that causes swelling. *So how does water return to the brain after fever*?

This dilemma invites speculation that glutamine released by muscles is more critical to fever's benefit than taurine released by brain. Muscles contain many grams of free glutamine (and taurine) [22,62], even in children (NEP Deutz, personal communication 2016); glutamine needed as fuel by so many tissues during fever *must release its water. When free glutamine releases its water, does water (re)enter the brain*?

If so, *where does it go*? If water enters astrocytes when fever breaks, compression of blood vessels [8,9] may explain autistic behavior. Yet high CSF pressure has not been reported in the literature. Water re-entering myelin seems implausible, although ASD myelin *is* more diffusible. *Does brain water disrupt conduction simply by altering membrane excitability* [37,38]?

Return of autistic behavior after fever may be most revealing. Fever has many aspects that develop gradually over many hours. These complex mechanisms all abate or reverse abruptly when fever breaks; simpler cooling mechanisms prevail. *How many plausible explanations can there be for return of autistic behavior after fever*?

The safest scans (for the child) may be (1) during improvements hours *before* fever, and (2) during improvements persisting days *after* fever. Heat at these times will be minimal – and stress as well. A scan as autistic behavior returns will be more stressful – *but most revealing* – and may serve as *baseline*.

In conclusion, free glutamine and taurine released from muscles to blood even before fever appears draw water from the brain by

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osmosis; taurine released by fever from brain to cerebrospinal fluid carries water. Improvements persisting long after fever may depend on individual muscle/brain stores of glutamine and taurine. *Does water return to the brain when fever breaks – disrupting conduction and causing astrocytes to swell*? The implication is obvious. *res ipsa loquitur*

> *[T]he challenge posed by improvement of ASD with fever [is] thinking in terms of measures that can be dynamical. From there it is a short step to thinking about mechanisms amenable to intervention. Measuring taurine in children with autism while following their response to fever is one route of investigation.*
>
> Martha Herbert 2011 [10]

> *Feynman's reinvention of quantum mechanics did not so much explain how the world was, or why it was that way, as tell how to confront the world. It was not knowledge of or knowledge about. It was knowledge how to.... There were other kinds of scientific knowledge, but pragmatic knowledge was Feynman's specialty. For him knowledge did not describe; it acted and accomplished.*
>
> James Gleick *Genius*

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Conflict of interest

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