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REPLY

Response to "A Radical Change in Our Autism Research Strategy is Needed: Back to Prototypes" by Mottron et al. (2021)

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In a "glass-half-empty" appraisal of the status of autism research, Prof. Laurent Mottron (2021) laments the problem of unresolved heterogeneity plaguing the discovery frontier. Although some of the elements of heterogeneity he cites are undoubtedly problematic (e.g., autism with versus without intellectual disability), his proposal for a wholesale redefinition of the condition by decomposing populations of ASD-affected patients into compartments with homogeneous values for DSM 5 specifiers (i.e., groups of phenocopies) is unlikely to succeed because it does not explicitly account for what breeds true in autism.

Let us take stock of the facts: (a) Autism, even when defined according to less-than-perfect parameterizations of the condition, is highly heritable, on the order of 85% in the general population (Sandin et al., 2017), and most affected children are born to unaffected parents; (b) Subclinical variations of the characterizing traits and features of autism aggregate in the unaffected family members of affected individuals (Robinson et al., 2011), and such variations are continuously distributed population wide (Wagner et al., 2019); (c) Within families in which autism recurs, the individual symptom profiles of co-affected family members paradoxically *diverge*—this has been known for two decades (Spiker et al., 2002), but its profound implications forgotten, only to be reinvigorated by "rediscovery" of the low twin-cotwin correlations for careful symptom measurements among affected monozygotic twin pairs (Castelbaum et al., 2020; Mazefsky et al., 2008) which Dr. Mottron appropriately points out; (d) The many disparate *single-gene* conditions that lead to the convergent syndrome of autism are (i) almost never inherited (rather de novo); and (ii) almost always associated with intellectual disability (Myers et al., 2020); (e) What predicts the recurrence of autism in families are joint elevations of heritable early developmental liabilities—*some non-specific to autism*—which can occur in different combinations or permutations in individual patients (Constantino, 2019; Constantino et al., 2017), and which appear independently heritable (Pohl et al., 2019) and, themselves, continuously distributed in the general population.

What to make of these five observations? First, if any "re-compartmentalization" of autism is to occur, it should separate familial autism from non-familial autism (this is not one of Mottron's proposed specifiers for an autism "prototype"), since inheritance is what CAUSES the vast majority of cases in the population. Notwithstanding the value of sporadic monogenic syndromes in elucidating biology, sibling study designs provide the acid test for what accounts for recurrence of an inherited condition. Second, wading through the epiphenomena of symptomatology *after autism develops* is not necessarily the way to identify meaningful markers of heterogeneity, because symptom profiles in affected individuals do not breed true. This would be like compartmentalizing hypertension phenocopies on the basis of blood pressure level and the presence or absence of a history of stroke (see below). The paradox is that autism heterogeneity may most reliably be parsed ("fractionated" as it were) before it occurs, not after, and only in accordance with the inherited liabilities that led to it; traces of which may be partially or completely lost or distorted after the condition itself emerges. The current (and finite!) slate of predictors include variation in social reciprocity, attention, hyperactivity, social visual orientation, motor coordination, tactile sensitivity, and cerebellar-dependent learning (Constantino et al., 2021). If this is where the heterogeneity lies, *these* are promising developmental parameters by which to classify individual cases.

Success in understanding and treating hypertension is instructive here. Because vascular physiology is more

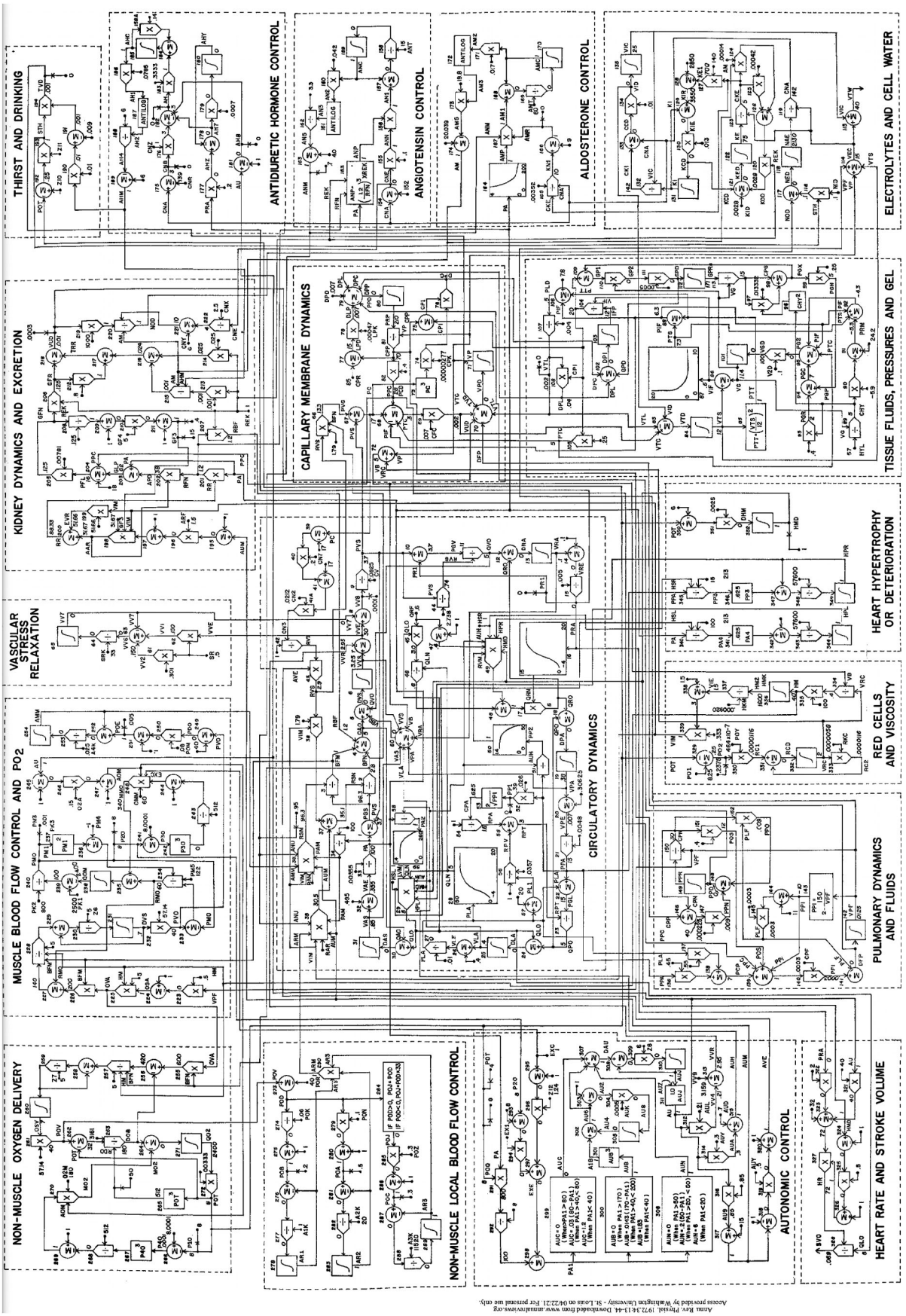

FIGURE 1 Arthur Guyton's computer model of the cardiovascular system. (Reprinted, with permission, from the Annual Review of Physiology, Volume 34 copyright 1972 by Annual Reviews; www.annualreviews.org)

easy to study than brain circuitry, Arthur Guyton was able to summarize (in 1972) that variation in the heritable, continuously distributed trait of blood pressure was resolvable to a *sub structure* of inherited contributors: disparate combinations of variation in vascular resistance, stroke volume, and electrolyte balance could all result in exact phenocopies of elevated blood pressure (Figure 1). A "lucky" feature of hypertension is that those physiologic contributors persist and are measurable in defining different pathways to hypertension, even after hypertension develops, but they are in no way directly reflected by the severity of blood pressure elevation or the comorbidities with which hypertension is associated. In autism, the DSM5 symptoms of the condition—pathognomonic though they may be—are proving themselves to be poor reflections of the combinations and permutations of inherited liability that engender the condition that (secondarily) gives rise to them.

So this is no time to constrain autism to collections of arbitrary-defined or expert-defined phenocopies. We have been through that already. Parse heterogeneity? Yes. Do so by compartmentalization without respect to inheritance? No. Do so on the basis of symptom profiles of affected patients? No, unless consummately aligned with measurement of persistent variation that relates to developmental causes of the condition (eg. ADHD, developmental coordination disorder traits). Study sibling pairs? As often as possible. Identify disparate pathways to the condition? Yes, however I do not believe the hard road ahead is through yet-another novel slicing and dicing of symptom profiles in affected patients. It is more likely to be through developmental research attuned to the indices that predict familial recurrence. And if it is true that those indices are extremes of normally distributed traits in the general population, then the Mottron proposal has missed the point of dimensionality, and a research paradox is that genetic epidemiologic samples will be more informative to new discovery than even the most prototypic of clinical ascertainments. If the common genetic causes of autism are polygenic and incremental, they have been evolutionarily retained in the population for a reason; they are much better understood when studied across the wide range of variation in nature than at the tail of the distribution. In ways that are reminiscent of the Heisenberg Uncertainty Principle, the closer you get to the tail, the more the view gets obscured—for most neuropsychiatric disorders this is likely explained by increased vulnerability to stochastic influences in clinical versus typical populations (Castelbaum et al., 2020; White, 2019), and by the developmental consequences of impairment.

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