The Basis For A Neurobiological-Associative Model of Personality and Group Cohesion: The Evolutionary And System Biological Origins Of Social Exclusion, Hierarchy, and Structure

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Abstract:

By using a systems biological perspective and available literature on human social interaction, grouping, and cohesiveness, a new coherent model is proposed that integrates existing social integration and neurobiological research into a theoretical neurobiological framework of personality and social interaction. This model allows for the coherent analysis of complex social systems and interactions within them, and proposes a framework for estimating group cohesiveness and evaluating group structures in order to build and organize optimized social groups. This „Neurobiological-Associative“ model proposes two primary feedback loops, with environmental conditioning (learning) being sorted into an associative model that modulates interaction with the social environment, and which impacts the second feedback loop involving the individuals' neurobiological capacity. In this paper, the concept of neurobiological capacity is developed and based upon contemporary research on intelligence, personality, and social behavior with a focus on the oxytocin, serotonin, and dopamine systems. The basis of social exclusion and group structure is thus, expressed in the very most simple terms, neurobiological compatibility and risk assessment modulated by an internal associative model.

I. Introduction

Social interaction is a context-dependent emergent event where two or more individuals interact and exchange information, during which they may collaborate on activities or projects. Exclusion and admission to groups of any and all types is partially dependent on the specific situational context, and is implemented through both subconscious and conscious application of subjective evaluations based on internal probabilistic models and perceived causalities/probabilities (internal Bayesian statistical model). In this paper this will be referred to as the individuals' internal or group's normalized associative model. The application of this associative model on both the individual and group level provides the psychological component of the neurobiological-associative model and works in conjunction with and on top of the biologically derived neurobiological capacity of the individual(s) involved.

It is through these two overarching structures that individuals and, in a similar fashion, groups contextualize information and make decisions with the aim of maximizing group cohesiveness, coherence, and performance. With this understanding, it may be possible to organize groups with the goal of maximizing effectiveness while simultaneously reducing the problems that are typically associated with groupings that do not take neurobiological factors into account.

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To define and answer the question of how much social behavior is genetically influenced, it is possible to measured using twin, family, and adoption studies, which are often used to measure the heritability of a trait, with monozygotic and dizygotic twins serving as measures of genetic similarity. Monozygotic twins share close to 100% of their DNA identity and dizygotic share roughly 50% (Mayhew & Meyre, 2017), with the further inclusion of GWAS (Genome-Wide-Association-Studies) data giving a realistic approximation of the influence of genetic markers and effects of SNPs (single-nucleotide polymorphisms) on behavior, personality, and social phenotype. Because dynamic social interactions are difficult to quantify, it should be noted that the effects of lifestyle and genetics are historically measured indirectly with tests designed to capture singular dimensions of social behavior or personality.

Genetic predisposition regarding personality and social behavior has been well researched, with monozygotic twins showing approximately 70% consistency and dizygotic twins showing approximately 30% consistency regarding prosocial behavior, with the genetic component calculated to be more than 55% (Ebstein et al., 2010). That said, the specific expressions of prosocial behavior are modulated by life experience (associative model), such that an individual's general impulse to be prosocial is genetically rooted, with the form it takes being modulated by experience. An example of this can be found in Ebstein et al's 2010 analysis, where trust in the Trust Game demonstrated less than a 20% consistency between monozygotic twins.

Within this paper, the approximately 55% of prosocial behavior represented by genetic predisposition will be called “neurobiological capacity” and the remainder will be described as belonging to the “associative model,” which will be explained in depth later in this paper.

Neurobiological capacity relates to both the connectivity between brain cells and the DNA sequence of relevant proteins (like receptors and regulators) within, including mutations in introns which lead to differential splicing, as well as potentially changing their relative expression and localization. Although the DNA sequence is entirely genetically determined, the relative expression, translation, and localization of proteins interact with lifestyle to form an intersection between the mostly “learned” associative model and the mostly “predetermined” neurobiological capacity.

Although genetic predisposition determines protein sequence, and thus 3d structure and specific activity, the factors of the localization and expression rate can be influenced through epigenetic regulation and the specific ontogenesis. The base expression rates will be determined by the activity of the promoter elements (how well the sequence is bound by transcriptional regulators and the polymerase) in the specific cell type, which is determined by the sequence and affected by modifications to the DNA or histones on which it sits, which can occur, for example, via methylation. It is also important to note that the same receptor can have a different function depending on its tissue localization, the metabolic flux and efflux of the neurotransmitter, its availability in the neurons, and the specific context (Carhart-harris & Nutt, 2017).

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Due to the fact that activation of chemical neurons increases the odds of neurogenesis and helps determine cell fate (Berg et al., 2013), it is clear that both the architecture/interconnection and expression rates of relevant neurobiological components are impacted by events and factors in the ontogenesis with cumulative effects over time.

Neuroepigenetics is a subfield of epigenetics which deals with neural cells based on the experience-dependent epigenome regulation, which contributes to gene expression in non-dividing neural cells as well as contributing to cell fate determination and differentiation. Further, it has been shown that early life stress can change both gene expression and brain structure in both animals and human models (Lux, 2018).

The question of how permanent epigenetic changes are is unclear. For example the methylation status of the MAO-A (Monoamine oxidase A) gene is increased in those suffering from PTSD (post-traumatic stress disorder), with sufferers seeing significantly higher methylation at several relevant CpG sites, which are not seen in healthy controls or those remitted. This may indicate that psychological state and experience can affect gene expression through DNA modification, and successful therapy may correlate with the reversal of epigenetic changes (Ziegler et al., 2019). This theory is supported by lower levels of 5-HIAA (5-Hydroxyindoleacetic acid, resulting from the degradation of serotonin by the MAO) following trauma, along with higher levels of norepinephrine and adrenaline (which draw their pool from dopamine and the latter norepinephrine, both of which are subject to MAO degradation) (Kawa et al., 2015). This process may normally serve the purpose of helping cope initially with trauma by increasing monoamine availability, which would have less benefit and/or effect for individuals carrying the low-expression MAO allele, since such individuals more frequently go on to develop aggression problems (Caspi et al., 2002), potentially due to increased flux into adrenaline via an unclear regulatory mechanism and the lower relative increase in monoamine levels.

Neurobiological capacity is thus itself a combination of genetic potential interacting with the ontological context. The capacity of a receptor to bind a neurotransmitter is central in its signal transduction, but doesn't alone decide how this particular signal will be interpreted/carried downstream with regulatory effects, or how well represented the receptor or neuron type is in a particular individual or brain region. For these reasons, often no single polymorphism will be able to alone explain the full nature of a complex personality condition. It is likely, however, that a thorough analysis of the metabolic and sensing infrastructure can be more reliably used with regard to predispositions: an individual having both mutations in the flux and sensing/signal transduction modules for a particular neurotransmitter will be more likely to display defects or abnormalities than an individual with no mutations or mutations in only one of the relevant modules or components. It is also relevant to mention that the full sequence helps determine both the expression and activity, so SNPs can have additive effects and intronic SNPs can still be relevant as a result of changes in expression and differential splicing.

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Thus the potential variability represented within human neurobiological capacity is massive, since there are a myriad of components in each signal transduction system that vary genetically and which can potentially be affected in their relative expression by ontogenetic and epigenetic factors. For this reason, the associative model is able to supply a contextual "script" that helps homogenize output among individuals despite the wide range of different genetic and effective neurobiological differences affecting specific neural activity.

II. Neurobiological capacity in focus: oxytocin, serotonin, dopamine

Neurobiological capacity is dependent upon the functionality and expression of the receptor and signalling network, as well as the availability of the neurotransmitter itself, and this is modulated in each specific context based on existing network architecture (connectome) developed during ontogenesis. The neurobiological capacity expresses the "associative model," displayed physically as the connectome and in social reality displayed as the effective personality. To demonstrate what is meant regarding how some of these factors impact the neurobiological capacity, context will be given here through the examination of two of the central monoamine neurotransmitters (serotonin and dopamine) and the neuromodulating nonapeptide hormone oxytocin.

Further, a new signal-transduction-efficacy model of intellectual capacity/intelligence will be proposed and used to explain differences in information processing and learning, along with an examination of the interplay between neuromodulatory subsystems and their contribution to social style and personality. However, these are by no means all the relevant signal transduction pathways, nor are they exhaustively covered here. Additionally, the role of these subsystems in non-cognitive/emotional biological dimensions will not be covered here in order to allow for a clearer and more detailed focus on the neurobiological system dynamics.

2.1 Oxytocin

The hormone and neurotransmitter oxytocin plays a complex role in the human body, affecting social attachment (King et al., 2016), as well as playing an important role in emotional empathy in repeated experiments (Geng et al., 2018). Furthermore, it induces childbirth and influences motherly behavior (Bell et al., 2014), and has also been shown to affect social style by positively modulating generosity and to a lesser degree altruism (Zak et al., 2007).

The oxytocin receptor functions via G-protein coupled phosphorylation signal transduction, with the specific downstream activity of oxytocin receptor activation dependent on type of neuron (or cell) and the specific G-protein involved (Stoop, 2012). Oxytocin receptors are expressed on inhibitory GABA neurons in human tissue, modulating downstream activity depending on localization and connectivity (Bakos et al., 2018). Based on human PET (Positron Emission Tomography) imaging experiments and mouse models, the oxytocin receptor is also expressed on serotonin neurons and helps modulate the effects of serotonin (5-HT1A) signalling (Parks et

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al., 2014). The oxytocin nonapeptide is slightly promiscuous, binding to the oxytocin receptor with only ten times more affinity than to the vasopressin receptor, with vasopressin binding comparably well to both oxytocin and vasopressin receptors (Kimura et al., 1994).

Brain mRNA distribution has been mapped via voxel-based (3d pixels) expression for the oxytocin and oxytocin receptor genes, showing shared co-expression of dopaminergic and muscarinic acetylcholine receptor genes (Quintana et al., 2019). While the nonapeptide showed high expression in almost every section of the cerebrum and olfactory center, the oxytocin receptor shared high expression in the hypothalamus and caudate with oxytocin, but, unlike the nonapeptide, the receptor also had high expression in the amygdala and nucleus accumbens (Quintana et al., 2019). Thus although the oxytocin receptor and the nonapeptide are co-expressed, this is not a universal quality and oxytocin expression cannot be taken as equivalent to that of oxytocin receptor expression or vice versa.

The oxytocin system is in some ways more simple than the monoamines discussed here due to only having one receptor, no reuptake mechanism, and being degraded independently of the MAO proteins into oligopeptides and eventual dimers by peptidase activity (Wiśniewski et al., 2013). Thus the potentially limiting factors in oxytocin signal transduction are the expression and biosynthesis of the nonapeptide (depending on a final mono-oxygenase for activation), the secretion involving calcium and the co-expressed CD38 (Riebold et al., 2011), as well as the functionality of the oxytocin receptor and downstream signalling components, the expression of any involved components, and its degradation.

The impact of synthesis/secretion on capacity can be demonstrated with the finding that lower serum levels of oxytocin have been associated with autism (Modhal et al., 1998), alongside callous unemotional traits and psychopathy when combined with a methylated receptor (Dadds et al., 2014). For autistic individuals who have problems in oxytocin secretion, nasal application of oxytocin can help rescue social sharing behavior by overcoming the bottle-neck (Andari et al., 2010). Mutations in the CD38 gene, required for oxytocin secretion, have been shown to lead to significant deficits in maternal care and social interaction in a mouse model (Jin et al., 2007), which also applies to a human model and modulates serum oxytocin concentrations (Feldman et al., 2012). Further, it is worth mentioning here, that the genomic deletion of the oxytocin receptor has also been linked to autism, indicating that oxytocin limitation, both in serum (limitations in synthesis and secretion) and lacking the receptor (removal of the trigger for the entire signal transduction pathway) can lead to a significant reduction in the capacity for social bonding (Gregory et al., 2009).

In addition, it is known that SNPs in the oxytocin receptor can alter social abilities (Baribo et al., 2017) and social network tendencies (Creswel et al., 2015), although explaining the exact mechanism for most SNPs remains largely elusive. There are no known SNPs in the coding

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regions of the oxytocin receptor, but it is known that SNPs in the initial RNA product and mRNA can affect expression, localization, and methylation levels..

The undertaking of structural and functional imaging studies have provided data that shows associations between oxytocin receptor SNPs and morphological alterations, as well as differences in the activity of neural circuitry involved in the processing of social information and negative affect. These imaging studies suggest that genetic variation of the oxytocin receptor influences limbic circuitry and connectivity involving the amygdala (Inoue et al., 2010), the hypothalamus (Tost et al., 2010), right supramarginal gyrus (Ozefovsky et al., 2019), and the cingulate gyrus (Tost et al., 2011).

An investigation of 23 SNPs across the oxytocin receptor gene region found that the combination of six loci able to significantly predict emotional recognition following oxytocin administration (Chen et al., 2015). They found some SNPs increased oxytocin sensitivity (quantified by emotional recognition) under oxytocin conditions while others significantly delayed the recognition time. The T-T-C-G-G-G haplotype comprising intronic SNPs rs237917 – rs2268498 – rs4564970 – rs237897 – rs2268495 – rs53576 is associated with increased emotional recognition performance under the influence of oxytocin compared to placebo, and the C-C-G-A-G-A haplotype displayed the opposite pattern. The effects associated with the A allele of rs53576, which has previously been associated with phenotypes including reduced dispositional empathy and increased stress reactivity (Rodrigues et al., 2009), increased jealousy (Tanaka et al., 2019), less sensitive parenting (Bakermans-Kranenburg & van IJzendoorn, 2008), lower self-reported empathic concern (Bachmann et al., 2016), and lower prosocial temperament (Tost et al., 2010) seem to fall almost exclusively on the common C-C-G-A-G-A haplotype.

Another intronic SNP, T-rs2268494, was shown to significantly speed-up the reactivity to oxytocin in Chen et al's 2015 haplotype study, has been associated in previous studies with faster and increased aggression after betrayal (Tabak et al., 2014) (Chen et al., 2015). If the person, however, has A-rs2268494, then this would instead be associated with problems in romantic communication (Schneidermann et al., 2014).

Additionally, the rs1042778 SNP is in the 3' UTR within the oxytocin receptor mRNA, and has a significant effect on mothering style, despite self-reporting suggesting the opposite: mothers with the T-allele homozygotes demonstrated higher intrusiveness, lower behavioral sensitivity, lower engagement, and more frequent frightened/frightening behavior than mothers carrying the T/G or G/G genotypes (Julian et al., 2019). The T-rs1042778 allele is also associated with significantly reduced sharing in Social Values Orientation and Dictator Game scenarios (Israel et al., 2009).

Considering that all the aforementioned SNPs are intronic means that their relative impact is exerted either in differential splicing or differences in expression rates, with the clearest results being generated by studies examining multiple loci for each subject.

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Since none of the aforementioned mutations actually affect the coding of the receptor, it would be very useful to conduct haplotype studies that look at whole-brain activity to correlate with the other tests, and using genotype combined with receptor immunohistology from deceased individuals to study expression and localization. This could give a much clearer impression as to how SNPs specifically influence the expression of what, where. Fortunately, volumetric and activity data can provide clues, and are useful in informing hypotheses regarding the downstream effects of non-coding mutations.

A meta-analysis of literature concerning the SNPs G-rs2254298 and A-rs53676 (Bakermans-Kranenburg & van IJzendoorn, 2014) showed the former to have a significant correlation to autism, but no significant interactions within the meta-analysis parameters for A-rs53676. Interestingly, G-rs2254298 is also part of a four SNP haplotype correlating to psychopathy (Dadds et al., 2014), with fMRI also showing significantly increased functional coupling in the anterior cingulate gyrus to the amygdala relative to A-rs2254298 (Tost et al., 2011), with the former region showing higher activity in psychopathic individuals in a salient lying fMRI experiment (Glenn et al., 2017). However, G-rs2254298 still showed significantly reduced activity in the rSMG in egocentricity bias testing where it clustered with autism (Uzefovsky et al., 2019). As previously discussed, psychopathy is also correlated with reduced serum oxytocin and implied receptor expression via increased methylation, which together give clues as to why meta-analytical significance could be achieved for rs2254298 but not rs53676 in these dimensions.

One likely explanation is that although A-rs53676 clusters with increased neutral amygdala activity (Luo et al., 2017), while also displaying significantly higher jealousy-related amygdala activity (Tanaka et al., 2019), but nonetheless being associated with significantly increased emotional recognition (Chen et al., 2015), and thus doesn't cluster fully with autism despite significantly reduced right supramarginal gyrus activity similar to what is seen with autism in regard to egocentricity bias (Uzefovsky et al., 2019). However, because A-rs53676 does correlate with increased jealousy (Tanaka et al., 2019), lower empathic concern (Bachmann et al., 2016), less sensitive parenting (Bakermans-Kranenburg & van IJzendoorn, 2008), and lower prosocial temperament (Tost et al., 2010), the SNP clearly leads to differential activity, expression, and/or localization.

It is possible that the A-rs53676 polymorphism showing "no effect" in the meta-analysis (Bakermans-Kranenburg & van IJzendoorn, 2014), while showing so many individual differences in social bonding interaction in individual studies, may be due to A-rs53676 displaying increased activity in the amygdala and thus increasing fear, which involves oxytocin in both fearful memory formation/salience and fear attenuation (Hasan et al., 2019). Furthermore, this may explain somewhat the increased jealousy (Tanaka et al., 2019) if combined with a reduced capacity to overcome egocentricity bias (Uzefovsky et al., 2019) and thus leads to differential social perception and b#onding. It is clear that the A allele can cause

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differential downstream activation and potentially alters the relative activity of downstream receptor signalling, potentially altering expression in certain types of neurons. This intronic SNP may cause differential expression, localization, and/or translation, leading to altered downstream oxytocin effects relating to receptors such as 5-HT1A, but also 5-HT2C, 5-HT4, and 5-HT1B (Jørgsen et al., 2003). This may lead to an imbalance between relative connectivity, for instance to 5-HT1A and 5-HT1B neurons, with high 5-HT1B activity, for instance, being associated with aggression and psychopathy (Cunha-Bang et al., 2017). The paradoxical A-rs53763 SNP has also been associated with reduced hypothalamus volume (Tost et al., 2010), and was shown to significantly reduce activity in the right supramarginal gyrus (rSMG) relative to G-rs53763, with the A-allele showing activity similar to that of autists, in an egocentricity bias in the emotional domain fMRI study (Uzefovsky et al., 2019).

Regarding rSMG activity, has been established that it is required for overcoming emotional egocentricity, and thus an effective theory of mind for others and avoidance of bias projection (Silani et al., 2013). A differentiation between autistic individuals and psychopaths can be made here with regard to activity in the rSMG: all four facets of psychopathy (interpersonal, affective, lifestyle, and antisocial behavior) correlated with increased rSMG activity during salient lying when compared to controls (Glenn et al., 2017). Still, that G-rs2254298 shows an association with both autism (Bakermans-Kranenburg & van IJzendoorn, 2014) and psychopathy (Dadds et al., 2014), it is clear that a single SNP can affect the same subsystem in different ways depending on the total genomic and ontological context.

It is thus clear that A-rs53763 has some reduced downstream oxytocinergic signalling capacity, which is not significantly autistic or psychopathic in nature, although exactly how this functions is not fully clear. So although the molecular biological mechanism of how this intronic SNP leads to differential brain activity is thus far unknown, the differences in social processing are significant, and measurable in brain activity, although not explicitly autistic in nature. The locus appears to also modulate sensitivity of childhood attachment security, with the A-allele conferring resistance when compared to the GG-allele subjects (Schneider-Hassloff et al., 2016). Interestingly, the A-allele carriers for rs53763 also displayed borderline personality disorder traits depending on the family environment, whereas G-carriers had middle scores regardless of their family environment (Hammen et al., 2015). This implies that the A-rs53763 allele doesn't necessarily confer resistance to negative relationships, but seems to change the nature of bonding in some way relative to the G-allele, and may be related to the downstream reduction in rSMG activity.

It is clear that the downstream effects of this SNP, in a whole-brain (with and without oxytocin) fMRI experimental setup, optimally also utilizing a not-yet developed PET-detectable oxytocin receptor ligand to show receptor localization, must be conducted and thoroughly evaluated. Having full-sequence data for the gene, in this case the oxytocin receptor, would also minimize noise generated by only focusing on one locus, and allow even clearer interpretation of the

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proximate effects of genetic predisposition on personality in order to avoid contradictory results and noise that may be generated by secondary and unmeasured allele-frequencies in the subject populations.

As mentioned above, it has been shown that low serum oxytocin levels and receptor methylation have correlated significantly with psychopathy (Dadds et al., 2014).The increased methylation, seen more often in psychopathic individuals, is likely modulated via epigenetic regulation during ontogenesis (Kumsta et al., 2013), potentially occurring even before their birth based on the lives of their parents (Yehuda & Lehrner, 2018). Methylation within the oxytocin receptor has also been shown to modulate brain activity after oxytocin application, and thus epigenetic modulation of the oxytocin receptor clearly has downstream perceptual and social/bonding effects (Chen et al., 2020).

Still, the interaction of a SNP with experience or abuse doesn't have to be mediated by methylation, for instance the major allele C-rs237889 which gives significantly more utilitarian/individualistic answers relative to T-rs237889 (Bernhard et al., 2016), and is associated with psychopathy (Dadds, Moul et al., 2014). However, the difference is unlikely to be based on differential methylation, since abuse-related interactions at this locus are not mediated by methylation (Smearman et al., 2016). Thus there are surely multiple mechanisms with which genotypes can interact with epigenetic factors and connectome development, or modulate independently based on transcription or translational efficiency. More research will elucidate the diverse mechanisms that affect how genotype interacts with ontological context and influences complex personality, to affect gene expression alongside the resulting connectome, giving altered social and relational perception.

There are many more SNPs, certainly not all of which have been identified, and here several were chosen to illustrate the point that significant differences can arise from mutations not even affecting the amino acid sequence. It is difficult to accurately express the differences created by a single intronic polymorphism, although expression studies can help, and normally the effect size may be minimal unless the trait quantification is either clean or takes the contribution of all SNPs in the gene into account. It is also important that other subsystems, biosynthesis machinery, epigenetic regulation, secretion, or degradation are not ignored. The method would otherwise reduce all carriers of other relevant SNPs and epigenetic modifications to the control group and add noise to the results, thereby reducing test group validity.

This single-locus, non-systemic perspective makes most abstract correlations regarding any specific oxytocin SNP difficult to use and interpret, especially for any intronic SNP in a meta-analysis, which in this context often gives no information about epigenetic effects. This is why the comparison of 23 SNPs combined with fMRI data in Chen et al., 2015 offers a coherent design and allows haplotype groups to be compared in the context of quantifiable data

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acquisition functionally implicating oxytocin signal transduction efficacy and downstream effects as the basis for differential brain activity.

One issue is also that symptomatic profiles of behavior or social interaction can sometimes lump non-homogenous activity profiles together, for instance with regard to oxytocin and borderline personality disorder where oxytocin has been found to both reduce trust (Bartz et al., 2011) while also improving social cognition and approach (Domes et al., 2019), or in regard to antisocial personality disorder where oxytocin application can result in both ameloriated and intensified aggressive urges against a partner (Gedeon et al., 2019), implying a mixed bag of genotypes. Clearly, future studies would benefit from larger sample sizes and clearer genotyping.

Clear genotyping could also limit experimental noise in the investigation of pharmacological manipulations and thus allow therapies to better fit the capacity of patients. This same issue regarding the oxytocin receptor and function is seen with autism, with oxytocin application leading high functioning autistic individuals to increase sharing and trust with a reciprocating virtual partner versus non-preference in the placebo condition (Andari et al., 2010). The condition can also apparently be caused by a genomic deletion of the oxytocin receptor, which would likely not benefit from oxytocin application (Gregory et al., 2009). This implies that problems with oxytocin secretion likely significantly contribute to some forms of autism, since the nasal application of oxytocin would otherwise not elicit an effect as shown in some studies. This implies that some individuals on the autism spectrum retain functional receptor binding and signal transduction.

Clearly, correlations involving a complex behavioral phenotype and a single intronic SNP are often tenuous, implicating the correct system but including diverse predispositions which display similar symptoms or characteristics. This can be due to their associative models and epistatic or interactive effects, making them potentially susceptible to different interventions. A clear investigation of receptor-modulated activity relative to genetic predisposition, taking the whole sequence and if possible complex genotype and brain activity into account, would enable a much clearer analysis of a genotype’s effects on brain function and cognition. This argues for a systemic, data-driven approach that avoids analysis of a singular criterion in a binary fashion.

To elucidate what oxytocin signalling efficacy as a single trait means in social context: in one study, participants showing a high negative bias towards foreigners were shown to be comparably withholding with regard to theoretical local people in need. However, when oxytocin was applied the negative-bias group demonstrated no significant effect (unlike the control group), indicating low oxytocin signal transduction (potentially non-responder status) as quantified through the complex behavior/sharing. The expression of the oxytocin non-responder impulse was perceived via the subject's associative model to be towards foreigners, but it is reasonable to infer that the actual impulse was to be withholding towards those in need

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regardless of the origin of the theoretical person in need since there were no differences in their generosity between their generosity to the groups (Marsh et al., 2017).

Interestingly, the introduction of social reinforcement for the participants with a high negative bias towards foreigners led to increased generosity, despite their lack of a response towards the oxytocin intervention (Marsh et al., 2017). This could potentially be explained with the assumption that some forms of social support and interaction are likely more dependent on other subsystems, for instance serotonin signal transduction (Kiser et al 2012), than oxytocin's. These two subsystems work side-by-side, along with other subsystems, to help generate emergent personality and social caring/prosocial behavior. Each subsystem is potentially able to somewhat compensate for weaknesses in another subsystem when presenting complex social behaviors, depending on the context.

2.2 Serotonin

It is extremely likely that every receptor and associated signal transduction pathways play integral roles in systemic function, resilience, and coherence. The goal here is not to be comprehensive or exhaustive, but to provide sufficient information to make clear the basis and dynamics of a neurobiological-associative model of personality in an applied capacity. In this context, serotonin signaling capacity can be viewed as a multifaceted complex trait, representing a major subsystem in the neurobiological capacity as well as participating in the formation of the associative model.

The monoamine neurotransmitter serotonin (5-Hydroxytryptamine) has a diverse number of receptors, with seven major families with only one subtype demonstrating a mechanism of action that doesn’t involve G-protein coupled signal transduction. Whereas the 5-HT3 receptor activates an ion-channel, all the remaining 5-HT receptors convey their downstream action via G-protein coupled phosphorylation and secondary messengers (Fraser & Hensler, 1999). In total, there are 14 serotonin receptor subtypes, with only the 5-HT3 activating an ion-channel (Palacios, 2016).

For explaining the model, the focus will be primarily on the G-protein coupled signal transduction due to its greater number of regulatory actions and dependence on a greater number of biological components. These signal transduction mode including all serotonin receptors except the 5-HT3 receptor, which instead functions via an ion channel and thus depolarization effect that can be clustered more cleanly with the Hebbian learning effects beyond their relative capacity for substrate binding.

Thus the serotonin system, and its relationship to the dopaminergic and oxytonergic systems, will here be examined primarily through the 5-HT1 and 5-HT2 families. On the other hand, the last G-protein coupled families containing 5-HT4, 5-HT5, 5-HT6, and 5-HT7 receptors will be largely neglected due to comparably limited biological systems research regarding them and because no clear relation to social interaction or personality has been defined, although ongoing

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research continues to further define the role of these receptor subtypes. The receptors differ in the specific G-protein coupled interaction partners, downstream effects, localisation, specific affinity for serotonin, and the number of splicing isoforms, and modulate the effects of different medications and drugs (Howell & Cunningham, 2015).

Regardless of a serotonin receptor's mechanism of action, the activity of the neurons is affected by neurotransmitter availability, biosynthesis, and degradation rates.

Acute tryptophan depletion (ATD) is a method for examining the consequences of a dietary lack in tryptophan to cause a decrease in serotonin biosynthesis and thus brain serotonin. This depletion occurs because normal protein biosynthesis is ongoing and requires tryptophan as well, and the resulting reduced biosynthesis has been shown using marked tryptophan and thus serotonin via α-[11C]methyl-l-tryptophan and PET scanning combined with fMRI (Nishizawa et al., 1997). This experimental paradigm has been widely tested in both rats and humans, causing increased anxiety and decreased mood in more susceptible individuals when tryptophan was removed from the diet (Young, 2013). It serves the same purpose as limitations in the flux pathway caused by mutations in metabolic infrastructure. This is a logical result since the synthesis rate and capacity is limited by precursor availability and translates into lower serum tryptophan levels and thus reduced expression of the infrastructure (enzymes) for serotonin biosynthesis, with dysfunction in any component potentially limiting flux (Nishizawa et al., 1997).

The advantage of measuring marked tryptophan versus measuring 5-HIAA is that the latter will skew availability relative to MAO activity, such that low 5-HIAA levels can be interpreted to represent either low serotonin levels or weak MAO activity.

The depletion of the precursor, tryptophan, allows the serotonin system to be considered as a single trait, mimicking limitations in the flux pathway and limiting receptor activity. It should be noted that a more refined analysis of the functions and interactions of the different receptor subtypes and the cells expressing them grants a better view of how specific mutations can individually affect aspects of the serotonin module without necessarily affecting the other serotonin neuron types.

G-protein coupled signal transduction is diverse in its specific applications, targets, and termination (Luttrell, 2008). Dysfunction in G-protein coupled signal transduction, for example by increasing GTPase accelerating protein (GAP) activity via regulator G-protein signalling proteins leads to reduced signal transduction and cAMP production (Ghavami et al., 2004), and such mutations would thus affect numerous cellular processes. For instance, a brain-specific GAP protein (SynGap1), found primarily in excitatory synapses and having differential splicing isoforms, has heterozygous mutations that, although survivable, are the major cause of NSID (non-syndromic intellectual disability) (Jeyabalan & Clement, 2016) in humans. Such mutations thus cause serious developmental and functional problems even heterozygously, and their

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phenotypic severity is an indication of how many downstream processes and genes depend on the correct expression, coding, localization, function, and translation of a protein.

As a "serotonin trait," 5-HT functionality has been negatively associated with aggression, while the depletion of the precursor, tryptophan, also leads to less cooperative play in the prisoner's dilemma (Crockett, 2009), increasing several types of impulsivity (Dougherty et al., 2010), and increased aggression (Alia-Klein et al., 2008), potentially due to depleted activity of the inhibitory 5-HT1A receptor. The 5-HT1A receptor is inhibitory, while the 5-HT2A receptor is excitatory, with the former associated with "passive coping" and the latter with "active coping" (Carhart-harris & Nutt, 2017). Interestingly, decreased transporter functionality correlates to lower receptor binding, shown via PET in humans with 5-HT1A (David et al., 2005) and knockout SERT mice showing a 42% reduction in 5-HT2A receptor binding (Rioux et al., 1999). It has also been shown that the efficacy of the transporter is regulated via phosphorylation to more quickly adapt to intersynaptic concentrations and modulate uptake (Baudry et al., 2019). Individuals with the short (low transcription) form of SERT are more impulsive, despite higher average serotonin levels, with this effect enhanced in an ATD experiment (Walderhaug et al., 2010).

Thus higher levels of intersynaptic serotonin do not translate to increased receptor activity, and in fact seem to reduce effective serotonergic signal transduction if persistent. This may explain why individuals with the low-expression version of the transporter have increased aggression: less transporter, but only leading to increased transporter efficacy due to phosphorylation if the subsystem is functional, with a dysregulation in the serotonergic system and insensitive receptors translating to reduced signal transduction efficacy and increasing the effect of chronic stress on aggression (Conway et al., 2012).

There also appears to be a co-regulation where decreases in 5-HT2A receptor binding can predict SERT binding as shown using two agonists, displaying a slightly inverted U-Shape curve of receptor to transporter binding potentials, meaning low serotonin binding generates the lowest binding for both transporter and receptor, and the highest transporter binding seen with middle receptor binding and the highest receptor binding displaying mid-range to low transporter binding (Erritzoe et al., 2010).

Since antidepressants based on the serotonin reuptake inhibition mechanism of action are also shown to reduce SERT expression (Baudry et al., 2010), and reduce binding akin to a low-expression transporter, the implied co-regulation can be taken as an implication that increased intersynaptic serotonin reduces both transporter expression and receptor binding. This reduces sensitivity to serotonin over time, and reduces reactivity of the system to context due to reuptake inhibition, making this a paradoxical primary target for therapeutic modulation.

These effects can help explain why individuals with low-activity MAO genotypes tend towards higher trait aggression since reduced receptor binding makes higher brain serotonin levels less

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"effective" when compared to an equivalent conspecific with a high-activity MAO in a mouse model (Evrard et al., 2002; Owesson et al., 2002; Lanoir et al., 2006) and in a human model via PET (Mickey et al., 2008).

Still, in spite of higher trait aggression, when the MAO is expressed at lower levels, it increases harm avoidance and reduces impulsivity (Passamonti et al., 2006), although it leads to amygdala dysregulation (Buckholz et al., 2008). In humans, lower MAO-A was also associated with significantly slower response time but significantly better response sensitivity (Ross et al., 2018).

Fittingly, knocking out the Rines E3 Ubiquitin Ligase responsible for the degradation of MAO-A leads to significantly different social behavior in mice with more intense but shorter contact, and much faster conditioning in light-dark test and significantly reduced immobility during the second encounter with the forced swim test (Kabayama et al., 2013). This further evidences processing differences depending on the MAO genotype.

Together this supports a model of the MAO genotype modulating the effects of stimuli, with adaptation occurring faster and with increased salience associated with the stronger/more highly expressed MAO having likely higher receptor sensitivity, with the weaker MAO, however, increasing response sensitivity while decreasing impulsivity. Taken together, it shows epigenetic regulation of the MAO-A gene may serve a purpose in adaptation to trauma by reducing downstream risky and impulsive behavior, and lowering serotonin turnover. This decreases the chances of tryptophan depletion, which has a more pronounced effect on those with low-expressing MAOs (Klasen et al., 2019), as well as potentially reducing psychological projection (based on the increased response sensitivity (Ross et al., 2018)).

For these reasons, the MAO-A protein thus presents a potentially useful target for treating PTSD, and indeed the inhibition of SIRT1 (which upregulates the MAO-A) in mice ameliorated the effects of PTSD-induced fear conditioning and anxiety, and , further, improved neural plasticity (Li et al., 2019). Short-term increase of MAO-A expression via SIRT1 expression, which is triggered by social defeat stress (Kim et al., 2016), may be regulated in the near-future by methylation and downregulation of the MAO-A to better allow reprogramming following acute or chronic stress-induced restructuring (McEwen, 2017).

Provided serotonin availability is not a limiting factor (e.g. no dietary or metabolic limitations), and having looked at how the MAO and SERT activity contribute to the function of the serotonergic system, an analysis of receptor function can be undertaken via a closer look at the 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, and 5-HT2C receptors in the brain. Each of these receptor subtypes partakes in providing the "serotonin trait," with their function, localization, expression, and translation together providing the capacity for neural network structure in the context of ontogenesis.

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The 5-HT1A receptor is expressed early in embryogenesis and functions via G-protein coupled phosphorylation based signal transduction, with the downstream excitatory action having an inhibitory effect on 5-HT release from serotonergic neurons, while also supporting neurite growth and synapse formation (Rojas et al., 2016). The 5-HT1A receptor is also expressed in brain regions receiving serotonergic expression as heteroreceptors, thus modulating the downstream effects of 5-HT release as well (Garcia-Garcia et al., 2014). If the receptor is knocked out in a mouse model, it leads to chronic anxiety, likely due to overstimulation through a lack of the inhibitory action (Toth, 2003). The 5-HT1A receptor is probably best understood as the target of CBD (cannabidol), which through serotonergic modulation can lead to reduced pain and anxiety (De Gregio et al., 2019).

The 5-HT1 receptors are all inhibitory autoreceptors negatively coupled to adenylate cyclase activity , but their downstream targets vary (Alex & Pehek, 2007). While 5-HT1A agonists reduced attacks in a mouse provocation model, 5-HT1B agonists instead increased violent attacks (Centenaro et al., 2008). The 5-HT1B receptor inhibits glutaminergic, GABAminergic, (Lemos et al., 2006), and 5-HT signalling (Groot et al., 2003), and can lead to downstream dopaminergic release (Yan et al., 2004), in a mouse model. Indeed this inhibition of glutamatergic signalling is likely the reason that receptor agonism inhibits learning in a rat model (Corbit et al., 2019). If the 5-HT1B is knocked out in a rat model, it leads to increased aggression and impulsivity (Nautiyal et al., 2015).

In humans, higher 5-HT1B receptor activity correlates to psychopathy and trait anger (Cunha-Bang et al., 2017), and lower methylation correlates to callous unemotional traits, whereas lower activity via higher methylation correlates to Attention-Deficit-Hyperactivity (ADHD) (Moul et al., 2015). Thus the 5-HT1A receptor appears to serve a purely beneficial role, with lower expression levels correlating to depression and borderline personality disorder but no apparent fitness cost at higher expression levels, whereas the 5-HT1B receptor carries social costs at higher levels of expression and correlating to borderline personality disorder and schizophrenia (López-Figueroa et al., 2004), with lower 5-HT1B expression leading to other difficulties which often accompany ADHD.

Thus although the 5-HT1 receptors share an inhibitory effect and a G-protein coupled phosphorylation signal transduction mechanism of action, their specific action and downstream effects are completely different, and the balance between relative receptor subtype expression and sensitivity contributes to overall system functionality.

Further, although the 5-HT2 receptors are excitatory in nature, they nonetheless function via G-protein coupled signalling with different downstream effects. The 5-HT2A receptor is found on dopaminergic (Nocjar et al., 2002), glutaminergic (Carhart-harris & Nutt, 2017), and also GABA neurons (Santana et al., 2004), in a rat model. In humans, low expression of the 5-HT2A receptor was associated with borderline personality disorder (López-Figueroa et al., 2004), thus

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demonstrating the role of 5-HT2A in social processing. Further, its role in working memory implies that it is important in overall information processing, since following antagonist application there is a loss of spatial task-related tuning in putative prefrontal pyramidal cells (Williams et al., 2002).

The 5-HT2A receptor appears to be relevant to mood states, with a functional polymorphism (Histidine in His452Tyr) within the 5-HT2A gene being associated (although not significantly) with suicidal depression, with the SNP C-rs6313 showing no significance in that study, and with only the long-type transporter showing a significantly associated with suicidal depression (Du et al., 1999). The SNP C-rs6313 was also associated with reduced 5-HT2A receptor density (significantly higher Bmax but same Kd) with the rank order of TT>TC>CC, although no significant interaction of any SNPs in 5-HT1A, or 5-HT2A was found with suicide (Khait et al., 2005).

Another more recent study also found no significant association of His452Tyr with suicidal depression, but did find the SNP C-rs6313 (T102C) to be significantly associated with suicidal depression alongside stressful life events and loss (Ghasemi et al., 2018). Epigenetic imprinting can make matters even more complicated, where epigenetic modifications can lead to the expression of one inherited version of an allele, but not another. For instance there are indications that the 5-HT2A receptor gene is only expressed from the allele inherited from the mother, while the father's allele is silenced (Ohara et al., 1998), and, given this, familial data regarding allele origin for heterozygotes would be helpful in better interpreting results. As a result, it is very likely that extreme behaviors like suicide and mood disorders like clinical depression are multifactorial and modulated by ontological development and context, given tht a single SNP is frequently not sufficiently causative to attain statistical significance.

Activation of the5-HT2A receptor by agonists like LSD (lysergic acid diethylamide) leads to enhanced emotional empathy and reduced fear recognition (Dolder et al., 2016), and it is worth noting that LSD also increases serum oxytocin levels, further implicating the relevance of serotonin receptors on oxytocin neurons and subsystem interactivity (Liechti, 2017). Connectome remodeling following LSD application argues for acute and regulatory effects of receptor activation, likely due to neural and glial activity (Atasoy et al., 2017). Further, in a meta-analysis of LSD and another 5-HT2A agonist, psilocybin, they were shown to have consistently produced immediate and significant antidepressant and anxiolytic effects that persisted for several months (Muttoni et al., 2019). Some of these effects may also be modulated by agonism to 5-HT1A, as well, since both LSD and psilocybin bind both receptors well (Reissig et al., 2005). Evidence suggests, however, that selective agonism of 5-HT2A may be sufficient for these effects, with selective 5-HT2A agonist DOI (2,5-dimethoxy-4-iodoamphetamine) also increasing synapto- and neurogenesis alongside neuroplasticity (Ly et al., 2018), suggesting that direct agonist modulation could be a promising strategy for therapeutic intervention with a clear mechanism of action.

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All this shows that the 5-HT1A and 5-HT2A receptors clearly play roles in social, affective, and cognitive processes, although the latter's formation of heteroreceptor complexes with 5-HT2C may be implicated in functions derived from agonism or antagonism of either one of the receptors (Felsing et al., 2018).

Evidence shows that the 5-HT2B receptor has a molecular mechanism and structure similar to the other 5-HT2 receptors, and is also capable of being efficiently bound by LSD, although its downstream effects differ from 5-HT2A activity and involve ß-arrestin signaling (McCorvy et al., 2018). Although seemingly little is known about this receptor's impact on personality beyond its significant contribution to SSRI (selective serotonin reuptake inhibitor) efficacy (Diaz et al., 2012), itclearly plays an important role in subsystem function and systemic resiliency.

The 5-HT2C is expressed as several mRNA isoforms in dopaminergic, GABAminergic, glutaminergic, and serotonergic neurons, with the neurons and brain regions on which it is localized being interconnected (Wold et al., 2019) The complex self-limiting interactions of these are, however still being elucidated, with its heteroreceptor formation with 5-HT2A making it more difficult to elucidate the individual activities of this receptor. However, it is included here in order to provide a glimpse into the complex interrelation of the 5-HT system, and to emphasize the utility of examining more than a single SNP when exploring the genetic contributions to personality.

Serotonin neurons and receptors do not just trigger the downstream activation or inhibition of other neuron types, but can also be activated by other neurotransmitters, with the mouse model indicating serotonin neurons can express oxytocin receptors, based on a mouse model (Yoshia et al., 2009) and confirmed via PET for a human model (Mottolese et al., 2014).

Thus serotonin levels, based on the availability of precursors, alongside the genotype, epigenetic regulation, and the ontologically determined connectome, determine specific activity of the serotonergic signalling network prior to interacting with the other signal transduction systems and neurons. This, and other, signal transduction systems help modulate mood, processing, and perception, which have effects on interaction and behavior, thus contributing to the neurobiological part of the neurobiological model.

2.3 Dopamine

Dopamine, like serotonin, is a monoamine which is degraded by the MAO. Unlike serotonin, however, it has a smaller number of receptors and is metabolically derived from tyrosine/phenylalanine. Further, unlike serotonin, dopamine is also degraded by COMT (catechol O-methyltransferase) via O-methylation, producing less oxidative stress than via the MAO-A degradation route to homovanillic acid (Meiser et al., 2013). This also impacts dopamine availability, with the Met functional variant of Val158Met in COMT protein decreasing enzyme efficacy and thereby increasing intracellular availability and thus intersynaptic concentration,

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with a positive impact on fluid intelligence and the agency subdomain of extraversion (Wacker et al., 2012)

The basic signal transduction infrastructure differs from the serotonin system in its specific components but not in its system dynamics. As with serotonin, precursor depletion leads to a simulated deficiency in the flux pathway and allows the examination of the system as a whole by reducing affiliated neural activity and capacity. Dopamine precursor depletion leads to lower DA levels and negatively affects receptor activity, as quantified by reduced signal and spatial reasoning capacity (Harmer et al., 2001; Bjork et al., 2014).

Post-translational modifications to the dopamine transporter (DAT) are variable and reactive to cellular context, including ubiquitinylation, glycosylation, and palmitoylation. Similarly to SERT, the phosphorylation of residues on DAT can modulate its efficacy and thus the uptake rate (German et al., 2015). The dopamine transporter is regulated by the serine and threonine phosphorylation, with increased stimulation via amphetamine, which is shown to increase transporter phosphorylation (Foster & Vaughan, 2017).

There are five dopamine receptor in two families, the D1-like dopamine receptors (DRD1 and DRD5) and D2-like dopamine receptors (D2,D3, and D4), all of which are connected to 7-transmembrane G-protein coupled signalling systems, and they play a role in both motor and non-motor systems including motivation, cognition, emotion, and neuroendocrine transmission (Carlsson, 2001). Parkinsons' disease, causing both motoric and mood dysfunction, displays as a reduction in dopamine-receptor density and in amelioration of symptoms using L-Dopa to stimulate dopamine neurons and downstream neural stem cell activation, further implicating the complex role of dopaminergic neurons in neural functionality (Mishra et al., 2018)

Dopaminergic activity in the ventral striatum (VS), a target area for dopaminergic midbrain neurons (O'Doherty,2004), is involved with, and actively correlates with, error prediction (Pessiglione et al., 2006). A PET/fMRI imaging analysis using marked 6-[18F]fluoro-L-DOPA, showed that both BOLD (Blood Oxygen Level Dependent, also measured as the hemodynamic response function) VS PE (prediction-error) activity and a decrease in local dopaminergic synthesis in the target neurons after disappointment/error which is associated positively with fluid intelligence (Schlagenhauf et al., 2013). These results imply that error prediction involves local modulation of synthesis rates and neural activity in order to continually adapt to new input. This is consistent with work in a rat model showing that dopaminergic activity is heavily involved in reward prediction, and thus learning (Doll & Daw, 2016).

Although dopamine and dopaminergic signalling is important in intelligence, there appears to be no significant association between DRD2 receptor SNPs and intelligence (Moises et al., 2001), although a higher number of methylation modifications in DRD2 significantly correlated to general IQ, implying epigenetic regulatory differences contribute significantly to intellectual capacity (Kaminski et al., 2018).

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Dopamine is also involved in emotional responses, with dopamine modulating amygdala activity during the processing of negatively salient pictures as shown via PET and BOLD imaging (Kienast et al., 2008). This result is congruent with hypodopaminergic Parkinson's patients showing blunted amygdala response to negative facial expressions relative to a repleted dopaminergic state (Tessitore et al., 2002). Indeed, reduced dopamine availability due to the Val/Val genotype for the Val158Met functional polymorphism, with functional CD38 in the placebo, leads to an amygdala reaction similar the repleted state for Parkinson's patients (Kienast et al., 2008). This depleted state is most similar to Val/Val genotype with dysfunctional CD38 (Sauer et al., 2013). This indicates that systemic dopaminergic depletion for Parkinson's patients may allow their brain responses to cluster more towards a low-dopamine state with functional oxytocin secretion when repleted, with depletion allowing for extremely limited signal transduction (similar to Val/Val with dysfunctional CD38).

Predictably, there is a correlation between negative emotionality and high-expressing DAT1, and a significant association also found with the Met-configuration of COMT, potentially mediated by dopamine availability and sensitivity, with the low-expressing DAT1 potentially leading to a desensitization of the receptors and Val/Val leading to lower dopamine levels (Felten et al., 2011). Although dopamine receptor binding relative to transporter expression has not yet been investigated for dopamine, the hypothesis of lower transporter activity relating to lower receptor sensitivity is suggested based on evidence from the serotonin system, as evidenced for the 5-HT1A (David et al., 2005) and 5-HT2A (Rioux et al., 1999) serotonin receptors relative to SERT expression. Further, the contribution of dopamine to interpersonal aggression is similar to that of serotonin, with an increased prevalence of low DAT1 (Qadeer et al., 2017) and SERT (Toshchakova et al., 2018) expression in violent criminals relative to the general population and other criminals.

And although predisposition helps modulate probabilities by mediating the effects of environmental interactions and experience, it nonetheless doesn't determine someone's future. When looking at the qualities of a highly sensitive personality, the main facets are ease of excitation (EOE), aesthetic sensitivity (AES), and low sensory threshold (LST), making these individuals more susceptible to the impact of their immediate sensory context (Grimen et al., 2016). Although this has a genetic component, shown for instance when examining the impact of SNPs in dopamine synthesis, receptor, degradation, and reuptake systems for and highly sensitive personality (HSP), only mutations in the dopamine receptor and reuptake systems were significant alongside the severity correlating to the number of stressful life events (Chen et al., 2011). Capacity is thus modulated by ontological development to determine the effective personality and the reaction to specific stimulus.

The consolidation of memories strongly implicates the interdependence of the dopamine system with the serotonin system, together helping produce long-term potentiation and effective learning(González-Burgos & Feria-Velasco, 2008). In a rat model, agonists of the DRD1, DRD2,

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and DRD3 receptors have been shown to significantly increase novel object recognition in a dose dependent manner (Papp et al., 2017). In fact, increasing dopaminergic activity via acute reuptake inhibition significantly increased novelty seeking behavior in monkeys (Costa et al., 2014),. This result has also been shown with heterozygous DAT-KO (knock-out) rats which displayed significantly higher novelty seeking/curiosity behavior relative to the wild type, and with the homozygous DAT-KO mice exhibiting indifference to novel stimuli, likely due to receptor insensitivity (Adinolfi et al., 2018). Dopaminergic signalling is thus responsible not just for the cognitive processing of novel stimuli, but also the impulse to seek it out.

The dopamine system thus contributes to cognitive, sensory, and social perception, as well as cognitive/emotional processing. Dopaminergic contribution is dependent on the specific process, and as with HSP, environment modulates the effects of predisposition, with SNPs in dopamine receptors and transporter significantly increasing extraversion and neuroticism in demanding, but not temperate, climates (Fisher et al., 2018).

2.4 A signal-transduction-efficacy based model of intelligence: agonists, regulation, and glia cells

Intelligence relates to the capacity to perceive, assimilate, infer from, and process stimuli in a coherent fashion, as measured by a myriad of intelligence tests containing different subtests. An analysis in 2013 included all literature containing results of the Wechsler Intelligence Test or revisions thereof for children and adults and was correlated with 23 twin studies to generate a heritability index. This Wechsler analysis also looked at the proportion of shared variance between the heritability of the results of different IQ subtest categories and the cultural loading (defined by modifications in the questions when translated for use in 13 other countries) in relationship to general intelligence. This found that the subtests with the highest genetic contribution and having the highest shared variance with general intelligence were also the most culturally loaded, with vocabulary taking the top spot (Kan et al., 2013). The verbal IQ and vocabulary test were also the most stable and consistent of intelligence measures over a 40-year period in a Canadian longitudinal study (Schwarzman et al., 1987).

Thus intelligence is dynamic, with the higher cultural loading for subtests requiring a higher number of changes to the questions within the test in order to confer the information relevant to the questions, thus showing higher shared covariance with general intelligence and genetic heritability translating to a higher specific complexity. Increased abstract complexity, with its increasing divergence from concrete reality, requires more linguistic maneuvering to be clear. In other words: the questions which require the most rewriting are those containing higher levels of abstraction, thus requiring more efficient neural networks to solve and the most changes in order to formulate the question successfully in another language.

As discussed in the dopamine section, error prediction within dopaminergic neurons leads to a reduction in synthesis following a reward that was lower than anticipated (due to an incorrect

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choice), while an accurate prediction causes no change in biosynthesis and thus translates to higher average levels with higher accuracy (Schulz, 2013).

To get a clearer picture, it is important to note that neural activity increases the strengthening of connections and that errors lead to decreased dopamine synthesis. Since dopaminergic neuron functionality depends on the availability of dopamine, local downregulation of synthesis is effectively akin to tyrosine/phenylalanine depletion for these neurons, and thus we see higher activity and capacity for "accurate" connections. The relative signal of downregulated neurons is weaker following error-modulation thus providing an advantage for the "correct neurons" in the "competition" for resources since synthesis remains higher and neurons can regulate the intake of precursor molecules depending on substrate concentrations. This can be seen, for instance, in serotonin transporter efficacy which is regulated by transporter phosphorylation (increasing SERT activity) and which is dependent on extracellular concentrations, and this post-translational modification also affecting reuptake inhibitor binding (Baudry et al., 2019).

The model herein described is still incomplete, as the neurons do not stand alone and it is not only the activity and growth of the neurons that matters. Which is to say that the function of the populous glia cells (astrocytes, Schwann cells, oligodendrocytes, and microglia) that regulate homeostasis, growth, synaptic formation and remodeling, as well as removal of dysfunctional connections, also contribute to the activity and inhibition of neurons. Specifically, the astrocytes, oligodendrocytes, and Schwann cells can directly foster synapse formation and function, while the microglia also fulfill the role of degrading synapses and neurons (Allen & Barres, 2009). Thus while the astrocytes, oligodendrocytes, and Schwann cells fit into the traditional Hebbian model of neural activity, the microglia represent a factor which is more relevant to the neural remodeling processes and the dynamic connectome.

The microglia thus have the most diverse role, so not only can microglia and astrocytes excrete some of the same factors like ATP, D-Serine, glutamate, and NO (nitric oxide) to encourage neural growth and function, the microglia can also secrete TNF-α and free radicals (Archer & Pascual, 2010). Interestingly, the microglia can have diverse impacts with its effectors. For instance, microglial TNF-α is seemingly required for effective long-term potentiation´(Ikeda et al., 2007), but ca,n however, similarly to free-radical formation, also cause microglial-induced cortical cell death, and thus can also function to "clear" dysfunctional neurons (Parvathenani et al., 2003), although this requires phagocytosis (Neniskyte et al., 2014).

The microglia are therefore highly dynamic. They are responsible for supporting growth, reformation, as well as the death of neurons, which makes correct microglial functionality highly relevant to neurofunctionality, since the balance of cell proliferation and death needs to be correctly regulated to meet the evolving and changing needs of the brain. The microglia have receptors for several neurotransmitters, namely glutamate (kainate, NMDA, mGlu5, mGlu2/mGlu3, AMPA), norepinephrine, GABA, acetylcholine, (Liu et al., 2016) as well as

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dopamine (DRD1, DRD2, DRD3, DRD4, DRD5) (Huck et al., 2015) and serotonin (5-HT2A/B and 5-HT4) (Glebov et al., 2015). It should be noted that although microglial activity is modulated by the activity of various neurotransmitter receptors (Liu et al., 2016), in order to remain within the specific confines of this limited application of the neurobiological-associative model, this paper will primarily focus on examining the effects of dopamine and serotonin on microglia via substrate concentration (motility) and the downstream effects of receptor binding.

Microglia demonstrate two functionally different activation states known as classic (pro-inflammatory, M1) neurotoxic activity and alternative activation (anti-inflammatory, M2), the lattery previously being described as the resting state before its constant cell-monitoring was evidenced (Fan et al., 2017). Microglia appear to have distinct “territory” where the neurons within them are continually scanned, with diverse bidirectional signalling taking place (Szepesi et al., 2018).

Although not shown for the other neurotransmitters, higher serotonin concentrations induce microglial movement towards the substrate while also attenuating phagocytic activity (Krabbe et al., 2012). Phagocytic activity is the mediator of whether TNA-α signalling leads to neural cell death, and the attenuation of phagocytic activity is therefore a likely indicator of long-term potentiation (Neniskyte et al., 2014). Indeed, the activation of 5-HT2A/B and 5-HT4 serotonin receptors on microglia lead to secretion of exosomes containing significantly more (but not limited to, due to thus far insufficient research) flotillin-1 -which is an integral membrane protein of unknown function-, actin -structural protein-, and IDE -which when downregulated causes Alzheimers- , which together strongly argue for support rather than cytotoxicity (Glebov et al., 2015). In the context of long-term potentiation, astrocytes are also mobilized, with their own serotonin (5-HT1A) (Miyazaki & Asanuma, 2016) and dopamine receptors (DRD1, DRD2, DRD3, DRD4, and DRD5) (Kuric et al., 2013; Huck et al., 2015), and interact with microglia as well as support synaptogenesis, thus showing that neuro- and synaptogenesis are not unilateral processes (Schiweck et al., 2018)(Pascual et al., 2012).

Although dopamine does not mobilize microglia, dopaminergic activation of microglia leads to ERK downregulation in activated microglia, but not in resting ones, implicating a neuroprotective quality for neurons successfully involved in learning (Fan et al., 2018). Thus the reaction of microglia to serotonin and dopamine are likely to be primarily neuroprotective given the studies in existing literature.

Due to the diverse roles microglia can play, along with their relative mobility, the functional microglial regulation is integral to neurofunctionality, with microglial dysregulation strongly implicated in depression. This is the case, for instance, with mitogen-associated protein kinase (MAPK) and extracellular signal-related kinase (ERK), which are upregulated in activated microglia (e.g. via upregulation of MiR221 and MiR222 in microglia) (Kaminska et al., 2009 ;

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Brites et al., 2015). This shows that correct microglial function is integral to functional neural activity, affect, and connectome remodeling.

Regarding the processing of conflicting (inconsistent with the existing associative model) or dissonant information, there is an initial reaction to the discrepancy that has arisen, followed by a cognitive regulation to reduce the perceived inconsistency via, for instance, self-affirmation (Steele and Liu, 1983), trivialization (Simon et al., 1995), denial of responsibility (Gosling et al., 2006), , value affirmations (Randles et al., 2015), or another form of motivated explanation (Patterson et al., 2015).

In a wider sense this regulation frequently entails ignoring the central content of the discrepancy, but can, however, also proceed with processing of the dissonant information, with the latter then falling into two main strategies of dissonance reduction: either applying an argument in favor of the current belief or minimization of the point to “balance” the information, or critically evaluating the topic to determine what is correct. Intelligence, based on signal transduction and remodeling capacity, is thus based on the total neurobiological capacity ranging from substrate availability, receptor binding, and downstream signal transduction, to glial cell behavior interacting in the specific context and ontological development.

It is well known that the presentation of stimulus or information conflicting with existing internal cognitive models creates cognitive dissonance. Which is to say that people will tend to avoid contact with individuals whose assumed neurobiological functionality doesn't sufficiently conform to their own minimal/free-energy internal model. Thus the relative intelligence of an individual -or a group- will determine their capacity to differentiate and correct themselves in areas where they find conflicting evidence, thus requiring the display of more efficient associative network/functional connective reconfiguration (Schultz & Cole, 2016).

Continuing on this line of thought; those of higher intelligence are able to expend lower relative energy in order to more efficiently rewrite neural connections within their internal associative model, thus achieving more efficient remodeling of the connectome. This means that more intelligent individuals incur a lower relative energy deficit and are more capable of efficient reprogramming with the goal of improving long term efficiency and effectiveness (Schultz & Cole, 2016). In this context and within the single dimension of intelligence, measuring the capacity to internally integrate, rewrite or expand on associations and analytical structures, makes it possible to predict the efficacy and cohesiveness of discrete groups. This method can allow for selection of those who are cognitively capable of expending energy to rewrite and optimize their internal associative model relative to those who are more predisposed to reduce dissonance by avoiding or ignoring information in order to consistently minimize cognitive energy use and need for remodeling.

Both strategies are aimed at improving the “predictive error rate” relative to energy expenditure as expressed by Friston (see Kaaronen, 2018 for an elaborate explanation). This indicates that

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individuals of higher intelligence are able to make more energy efficient and effective improvements than those of lower intelligence, thus leading to two distinctly different strategies for dealing with novel information that appear to contradict the existing associative model: the one involving an evaluatory/update process and the other an ignore/deny/compensate process.

Taken together with the fact that activated (M1) microglia downregulate their oxygen consumption (Ghosh et al., 2018), the increased BOLD signal seen with regard to the prediction-error rate after an error that correlates with fluid intelligence (Schlagenhauf et al., 2013) may include neural activity as well as microglial remodeling and neurogenesis (Hooker et al., 2013). The system thus adapts as the affected neurons downregulate their dopamine biosynthesis, effectively cooperating in efficient remodeling of future connections to better predict a correct answer. Thus fluid intelligence, and general intelligence, are not just based on signal transduction following agonist binding, but are also part of the entire network which is responsible for neural and synaptic growth and remodeling, achieving a regulatory answer following unexpected feedback, and the functionality of an existing network within the specific subtest parameters.

2.5 Interplay between serotonin, dopamine, and oxytocin systems

In determination of intelligence, it is not only the interaction of the signal transduction networks which helps determine intelligence and connectome structure, but also the contribution of each subsystem to overall social style and perception. Were a cooking metaphor to be applied: a soup will, depending on the ingredients added, have different flavors, given that some ingredients play a more significant or noticeable role than others. This is dependent not only how one measures such things as individual perceptions, but also on the influence of dietary and cultural factors. Therefore, one could say that not every version of the “soup” will please everyone, will suit every occasion, nor leave everyone feeling sufficiently satisfied in every context. This is a function of many factors, obviously, which come into play including individual, family, community, and cultural values. Further extending the metaphor, people associate certain “ingredients” with certain “flavors” based on their past experiences and cultural biases, and the “nutritional” value of these factors are not linearly related to how people may or may not have enjoyed the “meal.”

Going yet further with the metaphor: perception of the functionality and value of the various factors at play depends on the goals and context of the group at hand, and the success that the interplay of the various factors/subsystems will depend upon when the context and values are applied.

Returning to specifics, some emergent capacities require more than one subsystem to function, for instance the inhibition of either 5-HT1A or the oxytocin receptor leads to abolishment of the prosocial effects generated by MDMA in mice, with equivalent effects from blocking either receptor (Thompson et al., 2007 ; Kuteykin-Teplyakov & Maldonado, 2014). This shows that the function of oxytocin for prosocial effects was modulated by 5-HT1A and the prosocial

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effects of 5-HT1A were also modulated by oxytocin signal transduction. This is congruent with the increased empathic capacity and serum oxytocin levels which resulted following LSD application (Liechti, 2017), further evidencing the interplay between serotonin and oxytocin systems.

The interplay between serotonin, dopamine, and oxytocin systems is complex, with the activity and expression of the MAO genes affecting both serotonin and dopamine levels, but having no effect on oxytocin levels. The oxytocin, dopamine, and serotonin systems are intertwined, with the full functionality of the system depending on the functionality of the subsystems. Further, the individual subsystems interact even before the specific connectome is formed, with oxytocin neurons not just expressing oxytocin receptors, but also dopamine (Baskerville & Douglas, 2010) and serotonin receptors (Mottolese et al., 2014).

Thus, unsurprisingly, a function of these dopamine receptors on the oxytocin neurons is to help modulate social perception. A study measuring amygdala-induced reaction to negative social stimuli for mutations in COMT and CD38 genotypes found that those with higher levels of DA via the Met/Met polymorphism in rs4860 Val158Met had reduced amygdala signal (higher oxytocin activity) with functional CD38, but displayed high signal with dysfunction CD38 (C/C genotype in rs3796863) in the placebo condition which, after oxytocin application, was significantly reduced. The high signal intensity seen for higher DA combined dysfunction CD38 was comparable to that signal seen for lower DA (Val/Val) with functional CD38, with both situations showing reduced signal after oxytocin application. Individuals with lower DA levels (Val/Val) showed no reactivity to oxytocin application if the CD38 genotype was dysfunctional (C/C) with insignificantly higher signal averages after oxytocin application. In this situation, however, the functional A/A or A/C genotypes showed functional reactivity regardless of DA levels. This implies a dopaminergic compensation for a genetic predisposition for low oxytocin secretion, while retaining functional transduction capacity as shown with reduced amygdala activity following oxytocin application (Sauer et al., 2013).

Thus the lowest signal change was seen, for different reasons, in those with either the most and least effective signal transduction combinations, and either a higher DA level and/or high CD38 were required for oxytocin signal transduction to function if the nonapeptide was applied. This shows that higher dopamine levels with low levels of serum oxytocin lead to higher amygdala activation (low initial oxytocin signal transduction) with the placebo, but potent signal reduction (oxytocin signal transduction efficacy) when the agonist is supplied. Higher function in either one of the systems led to functional reactivity (oxytocin application reduced amygdala signal), whereas only sufficient dopaminergic capacity (at least heterozygous Val/Met) was able to likely prevent the CD38 oxytocin secretion deficit from causing functional systemic deficits (Sauer et al., 2013). This demonstrates that in some contexts, system components can compensate for the lack of reactivity or functionality of another, and, further, that there is more than one combination that can lead to functional reactivity (even though absolute reactivity or activity

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differs). This also shows that maximal signalling capacity is attained through the full functionality of the subsystems involved, with each contributing to the complex personality and brain activity.

In humans, lower cerebrospinal fluid levels of homovanillic acid, a DA metabolite after MAO and COMT action, have been detected in impulsively violent antisocial personality disordered subjects as compared with non-impulsively violent offenders (Linnoila et al., 1983). This is analogous to impulsive violent offenders also having lower levels of 5-HIAA (degradation product of serotonin) (Virkkunen et al., 1995; Higley et al., 1996). The potential effects of precursor depletion and/or receptor desensitization on systemic function and coherence are thus clear, and although the specific goal-oriented function and the use of the serotonin and dopamine systems differ, they both interact with oxytocin to contribute to improved social style and perception, and are regulated via similar mechanisms.

Both serotonin and dopamine systems work synergistically in helping to determine "loving style," with 5-HT2A and DRD2 polymorphisms modulating "eros," and 5-HT2A mania (Emanuele et al., 2007), and 5-HT1A genotype having a moderating impact on relationship status (Liu et al., 2014).

An issue in understanding the interaction of the different subsystems which contribute to social functioning is that social interaction and its associated domains have to be effectively defined and operationalized. However, too often, the interconnected subsystems are frequently examined separately. A study by Pearce et al 2017 described the three domains disposition, dyadic/romantic relationships, and social network by examined variation in 33 SNPs for significant effects on the receptor genes for serotonin (2 SNPs), dopamine (4 SNPs), oxytocin (10), endorphins (5), vasopressin (2), and testosterone (1) on the three domains via several tests per domain. The analysis found that disposition was significantly determined by SNPs in testosterone (25%), endorphins (30%), vasopressin (12.5%), dopamine (12.5%), and oxytocin (4%), that dyadic relationships were determined by oxytocin (45%), dopamine (37.5%), and endorphins (20%), and that the wider network was determined by dopamine (50%), serotonin (25%), and endorphins (10%) (Pearce et al., 2017).

Although this is a great reference offering a correct systemic perspective, the complex interaction between subsystems is hard to quantify given the limited number of SNPs (for instance including only 5-HT1A and 5-HT2A for serotonin despite 14 receptors and many possibilities, and only finding a 5-HT1A SNP significant with regard to network size, while ignoring 5-HT1B). Still, Pearce et al 2017 demonstrated that the emergent capacity of social style (especially beyond dyadic relationships) is determined via the complex interaction of different subsystems which are influenced by the context. Further, studies which consider complete genotypes and the sequence of all genes of interest can enable much more accurate mapping as to how various social and personality domains are affected by the specific subsystems and their various components. If the

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tests were applied in the context of fMRI scanning, then the results could greatly inform the more intricate workings of brain activity dependent on genotype in a replicable context. With a large enough sample and sufficient geographic distribution, it would also be possible to better measure the influence of culture and genotype, thus contributing to a better quantification of the individual subsystem and metasystem functionality in a myriad of testing domains.

Emergent capacity allows system components to synergistically create novel output as derived from increased systemic complexity and functionality. There is no doubt that the brain is a dynamic and complex system, with genetically determined capacity modulating the interaction and the ability for self-regulation with regard to the environment. It is not just the function of a receptor on a neuron, and the connected signal transduction network which determines outcome, but also the interplay of the entire and different signalling systems and their regulation. Although high function in one subsystem can, in some ways, compensate for dysfunction in others, either through functional connectivity or for vasopressin being able to compensate for oxytocin deficiency by binding to the oxytocin receptor (Kimura et al., 1994), it is unlikely that a deficiency in a subsystem can be fully compensated for in every context. Unfortunately, a reduction in function, even if effectively compensated in most contexts by another subsystem, will reduce emergent capacity by reducing flexibility and absolute capacity.

III. Associative model in focus: bias and homophily

Finding the optimal, or correct, solution to an evaluative or procedural problem is frequently difficult for humans. We rely on experience, preconceived notions, synthesized understanding, and our feelings, all of which frequently leads to reduced sampling accuracy and a suboptimal perception of the full situation and the theoretical solution/action space (Bang & Frith, 2017).

Despite the fact that humans show great variations in neurofunctionality, individuals in a group must find ways to negotiate, understand, agree, and work together with one another. The associative model is built upon the mechanism with which the connectome and regulome, based on genetic capacity and ontological development, process and interact directly with objective reality (see Figure 1). It is through navigation of this dynamic that humans adapt to their social surroundings, and find agreement on a shared subjective “infrastructure” of perception and beliefs which is expressed on top of their specific genetic potential. Thus, in order to function, members of the groups attempt to develop a mutually agreed-upon model of the solution space, in which the global optimum is often forgotten.

Decisions reached by a group are the result of the emergent interactions of the individuals within the group. The choices are not based on the evaluation of information in a purely factual sense, but rather are achieved through complex interactions of the relevant social and neurobiological systems within the given context (Miller et al., 2013). Thus how effectively information is processed by the individuals within the group is dependent on and influenced by the composition of the group itself.

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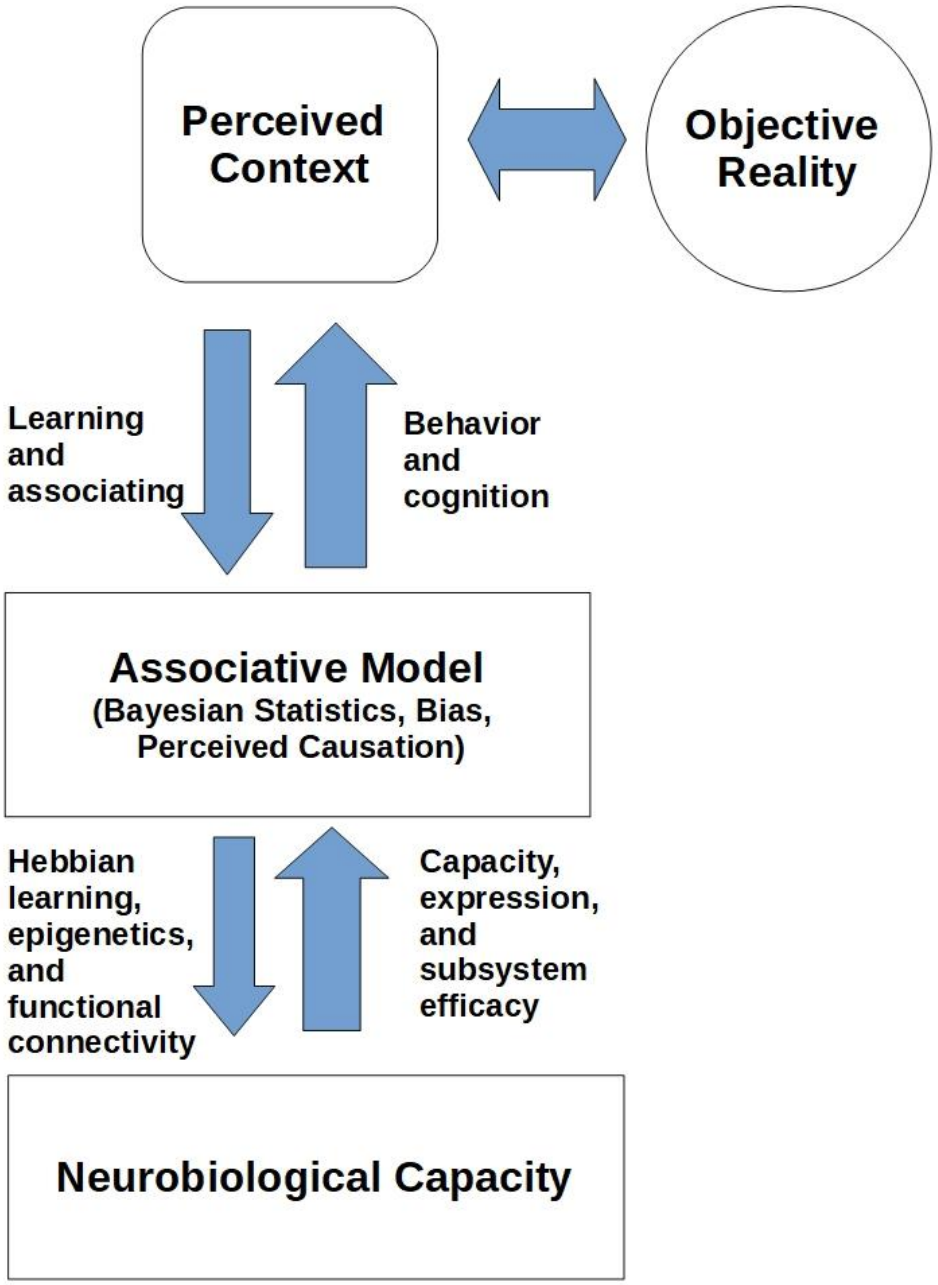

Figure 1: The neurobiological-associative model is portrayed in a simplified form, with internal systems represented with squares and external systems with the circle, and the perceived context is the border and builds the specific context for an individual's effective personality. The thickness of the arrows indicates the relative impact of the factors: neurobiological capacity determines the basis on which the associative model is developed but is still itself impacted through functional connectivity, epigenetics, and Hebbian learning with potential effects on future capacity. There is more projected into the context from the individual's associative model

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than is directly taken from the context and applied to the existing associative model, and therefor there is a certain resilience of the existing associative model towards change, modulated by perceived contradictions or congruence relative to new information, as discussed in the section 2.4.

Taken together this constitutes the emergent group conception, which we can refer to as the "normalized associative model". In use, this normalized associative model functions to further the group's productive interactions by boosting group cohesiveness through homophily (McPherson et al., 2001). Within a group context there is a level of selection and emphasis that occurs which results from the combination and interaction of the individuals' associative models as existing within the specific group's context and as defined by the boundaries and limits of their genetic predisposition and capacities.

The nature of the specific conditioning and its interplay with genetic potential leads to the development of cognitive/emotional networks that are developed in order to compose a coherent subjective reality which provides a context for the group's interactions. To increase efficiency and reduce friction within the group the normalized associative model (consensus group model) can be utilized to ease the group's dependence on neurobiological similarities in order to function effectively and it thus facilitates functional cohesiveness based on peripheral information, cues, and biases. This structural homophily furthers group coherence and functionality and, further, reduces neural energetic costs despite the diverse neurofunctionality that existent in the group.

IV. Group processes explained through the neurobiological-associative model: cohesiveness, subgroup formation as a function of increasing cohesiveness, and hierarchy

One social application of the associative model is to use observable criteria to deduce neurobiological predispositions of individuals in a group with the aim of stabilizing group cohesion, interaction, and efficacy. The back-end of this process is based on the application of a (minimal) free-energy model (as expressed by Karl Friston in his Free-Energy Model paper, 2010) in order to infer the specific brain activity and contextual attribution of meaning.

The application of this associative model provides a measure of subjective perception, which can be seen as a contextually activated associative model built out of (sub)conscious associative networks based on interconnection/functional connectivity and Hebbian learning within an individual's specific neurobiological capacity. This neurobiological-associative model seeks to use a minimum of energy in analyzing novel input while remaining internally coherent and efficiently functional. This means that the resulting output (thoughts, expressions, behavior) is a dynamic representation of the individual's processing capacity within their ontological and social context. The effectiveness of constituent subsystems (neurobiological predisposition) and specific neural network construction (associative model) are the result of multifactorial

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interactions, and function collectively to influence a human's personality and interactions with others in the shaping of group norms and decision-making.

Since the basis of the associative model is predisposed, it makes sense that individuals cluster, or otherwise surround themselves with people who are more genetically similar to themselves than the „average" person. This is to say that people "stay friends" with those who are more similar to themselves, however this is not true for every gene, for example there is a significant correlation seen for genes related to academic attainment but not seen with genes related to height (Domingue et al., 2018). It is probable that shared neurobiological predispositions based on genetic similarity results in similarity in the function of constituent signal transduction pathways between social connections, with modulating factors facilitating a shared normalized associative model and higher cohesion.

The specific social contexts an individual finds themselves in over time is thus a major contributing factor in determining the expression of the effective personality. Behavioral and personality traits are sufficiently flexible in humans such that most can effectively adapt and function within their societies. Niche diversity is thus proportional to the size of the society and is able to explain differences in personality structure between large and small societies since the niche diversity correlates with trait variance and thus social ecology will impact upon the expression of the effective personality (Smaldino et al., 2019).

Cognitive positions/associative models give each individual or group a set of conscious and subconscious criteria with which they can filter and evaluate whether to seek out or avoid interaction with specific concepts, individuals, or groups. Since an individual's effective personality is composed of that person's associative model and neurobiological capacity existing within a specific context, there are reasonably high requirements in overall similarity in order for a group to attain high and stable cohesiveness. Further, certain personality markers may be socially stigmatized or serve as signals of potential danger, and thus work as a learned bias within the associative model (Kurzban & Leary, 2001).

Therefore the requirements for a truly cohesive and dynamic (non explicitly goal-oriented) group are high, although the pressure of neurobiological similarity is reduced through goal-oriented activity and/or homogenization of the individuals' associative models.

Thus, in a goal-oriented context, assuming a normal distribution of constituent neurobiological systems and a sufficiently shared associative model, there will inevitably be some individuals possessing high efficacy in constituent neurobiological subsystems, which will therefore lead the group to develop a natural preference for pyramid-shaped hierarchies. Also, given the higher levels of complexity within functional hierarchies, higher neurofunctionality would be desired in addition to the possession of capabilities beyond what would be considered neurotypical. Lower job complexity typically requires a lower level of neurofunctionality, and it follows that the

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lower the neurobiological requirement, the more people available who can fulfill the requirements, thus typically leading to pyramid shaped hierarchies.

Pyramid shaped hierarchies define themselves by having multiple individuals on each hierarchical level, thereby creating subgroups, which differs significantly from a ladder hierarchy where each individual is directly below and above another (except at the extreme ends of the ladder). The pyramid hierarchy thus provides subgroup and whole-group perspectives, whereas the ladder hierarchy only provides an individual and whole-group perspective, with the former thus taking advantage of the cohesiveness effects derived from more homogenous small groups. Further, a recent study of intra-organizational cohesiveness supports this idea, having shown that hierarchical groups (pyramid structure) display significantly better performance and satisfaction than ladder-shaped hierarchies (Yu et al., 2019).

V. Neuro Compatibility: a paradigm for optimizing groups

Although the basis for impulses is genetically predisposed, the specific expression -- the behavior and cognitive constructs -- is not, and there may exist a wide variety of predispositions which, however different, end at the same phenotypic point. An individual's actual neurobiological efficacy and effective personality includes not only complex hereditary traits, but also emergent capacity. This is why a trait like grit, viz.perseverance and resilience, is only predicted to be 37% genetically predisposed (Rimfeld et al., 2016), while intelligence -- estimated using a Dutch cross-sectional twin study -- is approximately 80% genetically predisposed between the ages of 26 to 50 (Bouchard, 2004). However, since actual success relies upon a variety of factors, some of which are predisposed and others based on experience and the associative model, intelligence is shown to explain only 31% of the variance in academic performance and to explain only 1.6% of the variance in adult employment (Duckworth et al., 2011).

Thus the emergent capacity of a person, their ability to successfully process and produce novel content can be described as the result of their total coherent signal transduction. This emergent capacity results from the interplay between the neurobiological capacity and the associative model interacting with external reality.

Since intelligence only explains 1.6% of the variance for adult exployment (Duckworth et al., 2011), many jobs likely only require sufficient specific neuromodulatory signal transduction pathways to function at a specified level, as required in order to fulfill the requirements of a particular job. Thus the relevance of fluid intelligence may be minimized by a reliance on protocols (normalizing of the associative model) and redundancies in goal-directed behavior.

In a non-goal-oriented context people tend to group based on the dynamic presentation of constituent neurobiological systems within the given context. Individuals may share high similarities in several networks, but through the presentation of output that places a low priority

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on shared signalling capacity, differences can be accentuated and lead to friction despite the above-average similarity between the individuals involved.

Tolerances for differences in constituent neurobiological signaling systems are based on the relative hierarchical position of the evaluator in the normal distribution of the relevant neurobiological subsystem efficacy. If we assume a 30% tolerance (within relative signal transduction efficacy of the constituent system), then someone at 98% efficacy cannot be tolerated by anyone below 68% efficacy, but someone at 68% efficacy can be tolerated by all those between 98% and 38% efficacy.

By forming pyramidal hierarchies, it should be possible to create subgroups that cohesively function and fulfill their responsibilities, while providing significantly less social conflict and hierarchical stress to the group compared to those closer to ladder-based hierarchies (Yu et al., 2019). The neurobiological-associative model thus provides a framework for understanding not only neurobiological, but also socio-psychological phenomena, and can inspire further innovation and inform choices within groups, by allowing more coherent hierarchical level design and more efficient grouping.

When individuals' internal models indicate that coherent and cohesive interaction between the group's individuals is very unlikely, social exclusion occurs. For those at the lower end of the spectrum, exclusion is the result of the group attempting to normalize efficacy and increase the average productivity and efficacy of the group. At the other end of the spectrum, those with higher neurobiological efficacy may be excluded in an attempt by the group to normalize efficacy and increase hierarchical stability and functional group homeostasis. Thus individuals are on the one end are excluded for being a weight on society, and those at the other end for potentially undermining existing power structures or systemic coherence .

In some cases, the exclusion of those at the higher end of the neurobiological efficacy spectrum may be seen as a social strategy used by those of lower efficacy to increase their competitive ability and overall odds of survival. . In all cases there is the application of risk/use probability models based on learned/predisposed markers of potential danger or group incompatibility. Recognition of this can help prevent the exclusion and encourage better integration of individuals in the group whose capabilities and functionality could significantly contribute to group functionality.

As group performance is strongly correlated to group cohesiveness (Mullen & Copper, 1994), it is clear that dysfunctional groups will have low performance and cohesiveness. Because in-group bias works in the favor of similar in-group members (Mullen et al., 1992), it thus serves the group to exclude individuals who would weaken group cohesiveness/performance, as not doing

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so would carry a double cost. Thus although social exclusion and inclusion serve different purposes, they share the common factor of being an attempt to maintain group homeostasis.

High group cohesiveness, which also translates to high group performance, means the members of the group show a greater capacity to predict, support, and correctly contextualize the behavior, actions, and decisions of the others within the group. This provides a greater feeling of coherency and a lower requirement for dissonance reduction, as well as allowing a greater allocation of cognitive resources to the tasks and goals at hand. And, finally, this allows the group to minimize neural/cognitive energy use and maximize effectiveness, in line with Karl Friston's free-energy theory (Friston, 2010).

Thus, it should theoretically be possible to create larger groups with extremely high context-independent cohesiveness by profiling a constituent neurobiological subsystem's functionality using this to facilitate and improve the in-group normalizing of associative models.. Similarly, it should also be possible to predict group cohesiveness based on the relative efficacy of the constituent neurobiological subsystems in a general context, and of those subsystems relevant to goal-oriented behavior in a strategic context.

VI. Final Thoughts

On many levels and in many fields, the neurobiological-associative model of personality and behavior provides a theoretical framework for understanding and modelling the intersections of brain activity, plasticity, intelligence, perception, and group processes. It aims to build a bridge between social-, neuro-, and biological sciences which may be used to further interdisciplinary research and cooperation. Application of the model may also be useful on several levels in regard to the creation and organization of more functional groups. Further, it could be very useful for illuminating and explaining differences in interpersonal perspective and behavior, both at the individual and group levels. And, finally, it provides possible avenues for exploration and research in many fields, including education, culture, system analysis, and the construction of behavior modelling paradigms.

The neurobiological-associative model is applicable at many levels, for individuals and organizations as well as their subsystems. It provides tools for analysis, modeling and the development of systems for modulation and accomodation. The use and further development of the neurobiological-associative model can be useful for measuring and increasing awareness of the existence of personal bias, developing individual efficacy as related to the tasks at hand, and the capability to modulate the effects of predisposition. The model could find application and usefulness within organizations across a wide variety of fields and disciplines, thus contributing to a significant improvement of organization and group dynamics, functionality and efficacy at all levels.

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Not to plunge too deeply into specifics, but the neurobiological- associative model touches upon and may have applications in a variety of disciplines and fields. For example, in clinical psychology diagnoses are made based on similarity to archetypal criteria, as defined by the illness and treatment based on the phenotype. However, data regarding responses to pharmacological manipulation can inform an understanding of the specific neurobiological capacity and expand perspectives on possible treatments. The gathering and analysis of evidence using the neurobiological-associative model may also be useful in designing treatments and accommodations based on a systems perspective which could enable identification of specific subsystem dysfunction, and thus enable more targeted therapies, effective interventions, and refined diagnoses.

Further, current advancements in personalized medicine may include the acquisition of brain activity/connectome data as well as the analysis and application of genetic information. Using this data and information, the neurobiological-associative model could enable the identification of specific components involved in a dysfunction, and thus allow treatment of the problem's origins,rather than the targeting of symptoms. Further, this could supply additional information for and support the efficacy of diagnosis and treatment of neurological dysfunctions. An understanding of regulatory dynamics and flux limitations may also help inform medical interventions that are directly related to a patient's predispositions. An understanding of neurobiological system dynamics may be useful not only to better diagnose patients, but also to inform more targeted and efficient assignments of patients to downstream specialists.

In light of the implications of the neurobiological-associative model, it may be a useful tool for sociologists and historians in creating more comprehensive profiles of historical figures, groups, events and decisions. For example, dietary habits as well as food or nutritional shortages certainly limit flux into neurotransmitters, altering neurofunctionality. Applying this idea to the analysis of historical events may offer new perspectives on societal and individual behavior in different climates, cultural contexts and historical periods. Allele frequencies over time can also inform the neurobiological basis of national normalized associative models, allowing possible new insights into the traditions and philosophies that have dominated certain periods and locations. Further understanding the interplay between the different subsystems and their contribution to connectome structure and function may also help inform the analysis, structuring and development of social welfare campaigns.

It may also be possible to apply aspects of the neurobiological-associative model to education. There is no "one size fits all" solution to human behavior and interaction, and understanding the roles that various subsystems play in learning and teaching can further better communication via improved analysis of individuals' characteristics, the structuring of groups, and the development of applicable educational strategies. As with medicine and psychology, education could perhaps benefit from analyses supported by the model to provide a more differentiated perspective and

better focused systemic approach to confronting problems, adjusting social structures and better tailoring of learning situations.

The model could also be useful in the design and structuring of business hierarchies and subgroups, allowing better support for desired corporate and financial behaviors based on neurobiological factors and a normalized associative model. Application of the model could aid in the selection of individuals for positions with high responsibility, especially in regard to the identification of individuals who show neurobiological indications for impulsiveness, narcissism, borderline, and psychopathy. An understanding of the impact of the normalized associative model could also enable the rational design of factual and science-based prosocial normalized models useful in international situations, including in areas involving scientific cooperation, environmental regulation, and design and regulation of political and social systems.

Overall the neurobiological-model could better help organize the interactions of different systems at various levels with regard to human interaction, behavior, cognition, and decision-making. Although biology supplies the basis for understanding life, and thus brain structure as well, the connection between molecular interactions and complex system states has historically been explained in a reductionist fashion with attempts to reduce complex biological and neurological effects into a narrow interaction involving a single locus in a single gene. The neurobiological-associative model continues contemporary work being done in biology to develop a more systemic perspective, which, as with most other disciplines, will enable better, more focused, and more successful interdisciplinary cooperation, research and results beneficial to all areas of human endeavor.

Conflict of interest: None

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