



**New Knowledge about of the Genetics of Personality:
Implications for Clinical Practice**

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Outline



- Background
- New Facts about Character
 - ✓ Genetics, Environments, Learning Mechanism
- New Facts about Temperament
 - ✓ Genetics, Environments, Learning Mechanisms
- How are Temperament and Character Integrated?
 - ✓ 3 networks: gene-environment interactions
 - ✓ Prototypes of 3 different systems of learning
- Implications for Assessment and Precision Medicine
 - ✓ Ternary perspective, Person-centered care
 - ✓ Precision from genotyping + developmental history
- Implications for Clinical Practice
 - ✓ Evolution of Learning Networks & Well-being
 - ✓ Need for Integrated Learning & Unified Outlook


What is Personality



Personality is...


- the way people learn and adapt
- the self plus the internal and external forces that pull on the self
- the "dynamic organization within the individual of the psychological systems by which the person both shapes and adapts uniquely to an ever-changing internal and external environment" (Cloninger 2004)

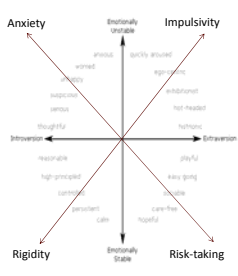
Key Features of Personality



- ❑ **Dynamical** – non-linear and adaptive, not linear or fixed
- ❑ **Psychobiological** – involves body (soma), analytical mind (thought), and intuitive and creative mind (psyche)
- ❑ **Organized** – there is a universal structure shared by human beings that allows us to understand one another and to communicate
- ❑ **Personal (Intrapyschic)** – adaptive processes occur WITHIN the individual, not between persons
- ❑ **Idiographic** – each person is unique in the development of their life narrative

Learning to adapt to pain & pleasure are independent






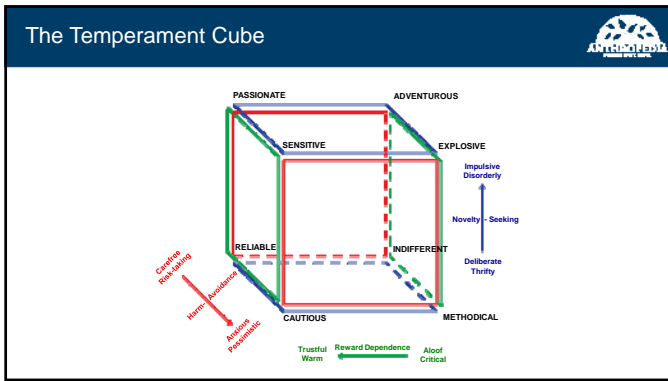
January 2012

- Learned responses to pain are independent of those to pleasure.
- Jeffrey Gray showed that the slopes of the response rates are along the diagonals of Eysenck's Neuroticism and Extraversion.
- Genetic Vulnerability to Anxiety and to Impulsivity correspond to the sensitivity to pain and the seeking of rewards also.
- These and other findings suggested basis for **Harm Avoidance** and **Novelty Seeking** instead of Neuroticism and Extraversion (Cloninger 1987).

Descriptors of 4 Extreme Temperaments



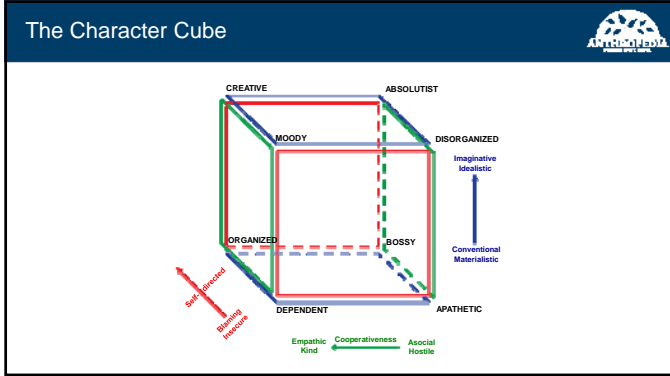
Temperament	High Scorer	Low Scorer
Harm Avoidance	Pessimistic Fearful Shy Fatigable	Optimistic Risk-taking Outgoing Vigorous
Novelty Seeking	Exploratory Impulsive Extravagant Quick-tempered	Reserved Rigid Thrifty Slow to anger
Reward Dependence	Sentimental Open Warm Approval-seeking	Critical Aloof Detached Independent
Persistence	Industrious Determined Ambitious Perfectionistic	Underachieving Flexible Happy-go-lucky Easy-going

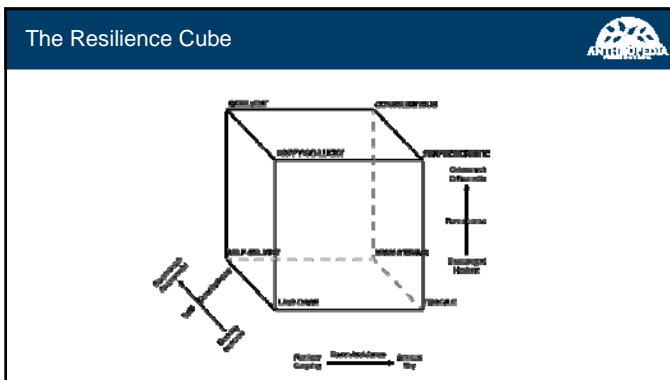


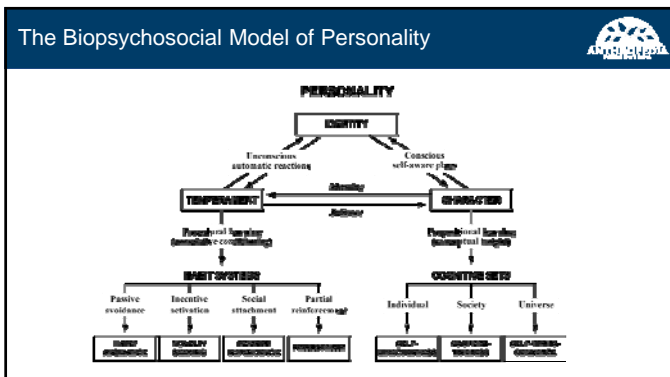
- ### Key Features of Personality
- Executive Functions (*Self-directedness*)
 - Resourceful, purposeful, self-accepting, responsible, self-actualizing
 - Legislative Functions (*Cooperativeness*)
 - Tolerant, helpful, empathic, principled, compassionate
 - Judicial Functions (*Self-transcendence*)
 - Idealistic, self-forgetful, joyful, contemplative, spiritual

Descriptors of Extreme Character Traits

Character	High Scorer	Low Scorer
Self-Directedness	Responsible Purposeful Resourceful Self-accepting Spontaneous	Blaming Aimless Helpless Defensive Conflicted
Cooperativeness	Tolerant Empathic Helpful Forgiving Principled	Prejudiced Insensitive Hostile Revengeful Opportunistic
Self-transcendence	Idealistic Self-forgetful Altruistic Contemplative Spiritual	Pragmatic Self-preoccupied Individualistic Conventional Skeptical



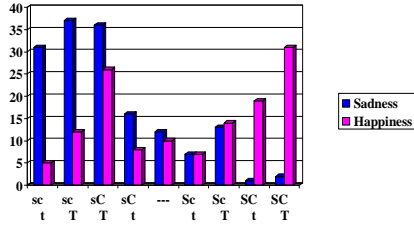




Character and Subjective Well-Being

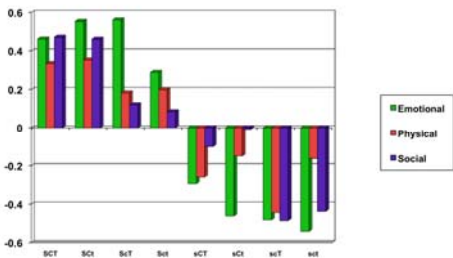


- Happiness and Sadness depend on all 3 TCI character dimensions



Cloninger, *Feeling Good: The Science of Well-Being*, 2004

Emotional, Physical, and Social Well-being depend on Character Profiles



Cloninger & Zohar, JAD 2011

Complexity is typical of living or adaptive processes



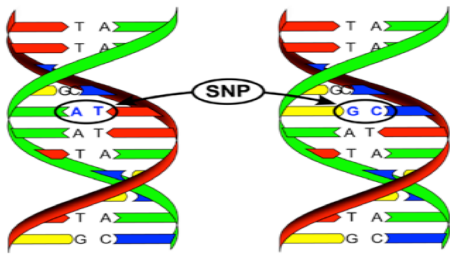
- ✓ Complexity results whenever there are functional connections among multiple variables, particularly positive or negative feedback interactions
- ✓ As a result complexity is typical of most functions of living systems (personality, psychosis, susceptibility to medical problems like disorders of heart disease, hypertension, skin disorders, etc.)
- ✓ People and their disorders operate like complex adaptive systems, not as machines with separate parts
- ✓ Consequently, there are no linear (one to one) relationships between genotype and phenotype - instead phenotypic-genotypic relations are "many to many"

Describing "Many to Many" Relationships



- ✓ There are no linear (one to one) relations of genotype and phenotype
 - ✓ Multi-finality ("pleiotropy") is common: the same antecedent causes may lead to many different phenotypes
 - ✓ Equi-finality ("heterogeneity") is common: many different antecedent causes may have the same phenotypic outcome
- ✓ Genes operate in functional sets in which they act in concert
 - ✓ The same gene may operate in combination with different sets of genes for distinct functions ("pleiotropy")
 - ✓ Different gene combinations may carry out similar functions by different pathways ("redundancy", "heterogeneity")
- ✓ Phenotypes are distinguished by different clinical syndromes
 - ✓ Each trait is likely to be affected by many genes and environmental variables (multifactorial inheritance)
 - ✓ Each gene or environmental variable is likely to affect many traits, leading to comorbidity

Single Nucleotide Polymorphisms (SNPs)



- Human Genome has 3.3 billion base pairs & 10-30 million are variable (= SNP)
- Microchip Arrays measure about 1 million that are highly variable & well-dispersed

Environmental Variables in Young Finns Study

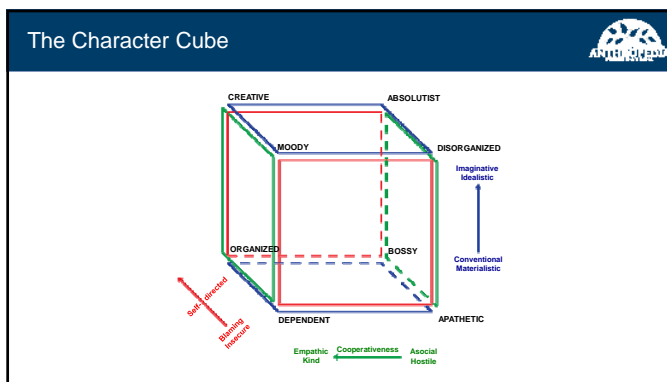


- Longitudinal study with assessments in home during childhood in 1980 (ages 3 to 18) and 1983
 - Parental Tolerance (acceptance of child)
 - Parental Emotional warmth
 - Parental Strict discipline
 - Parental Socioeconomic status
 - Urban vs rural residency during childhood
- Also measures were obtained during adulthood in 2001 (ages 24 to 39)
 - Stressful Life events
 - Years of Education
 - Urban vs rural residency during adulthood

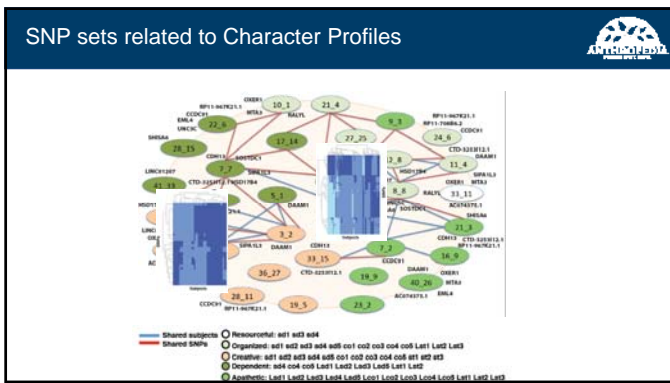
3 Independent Studies

Study Site	Subject Numbers	Personality Assessment	SNP Platform	Type of Sample
Healthy Finns	2159	TCI (Likert)	Illumina 670K Custom Chip	Epidemiological/longitudinal data
Healthy Koreans	1052	TCI-R (Likert)	Affymetric 6.0 Illumina 350K	Unrelated subjects from twin-family sample
Healthy Germans	1000	TCI-R (true-false)	Affymetric 6.0 Illumina Quad	Healthy people, exclude any exclude any mental disorder disorder

Zwir 1... Cloninger CR, Molecular Psychiatry 2018



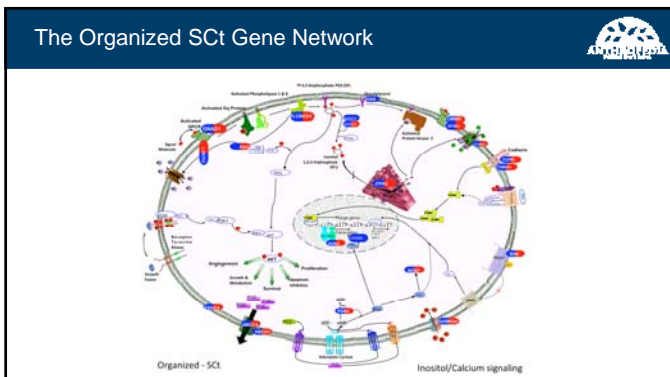
- ### Overview: Facts About Character
- ❑ 5 profiles of Character were distinct (Creative, Organized, Resourceful, Apathetic, Dependent)
 - ❑ 42 SNP sets associated with temperament in Finns (95% replicated in other two samples)
 - ❑ 727 genes mapped to these SNP sets
 - ❑ Genes code for profiles in whole person, not for single character traits
 - ❑ Genes and subjects were in 3 clusters related to 3 different systems of learning and memory with different brain circuitry
 - ❑ Heritability explained by character was 50 to 58% in the three samples
 - ❑ Some associated Environmental sets but effects are weak



727 Genes are most often unique for only one character Profile

Profile	Resource	Organized	Creative	Depend	Apathetic	Total #
Resource-ful	[0]	18	4	16	16	18
organized	2%	[208]	67	55	103	349
creative	1%	9%	[89]	60	99	235
Depend-ent	2%	8%	8%	[70]	67	172
apathetic	2%	14%	14%	9%	[130]	302

█ Red = # of genes unique to each profile
█ Blue = overlap between two profiles
█ Green = % of overlap based on grand total of 727 genes

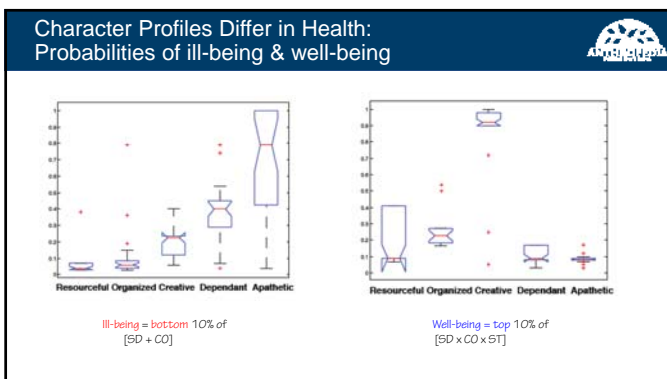


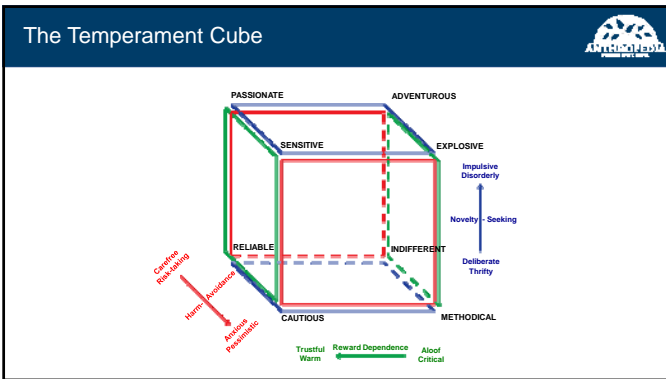
Genes Unique to Creative Profile

Function	Gene Symbol	Biological Processes
Episodic Learning	SLC14A2, CAMTA1, CCDC39, ID5, IARS	Regulate energy and transcription in regions for episodic learning
Neurogenesis	CCDC39, PGLYRP4, AXOXL, RUNX1	Regulate neurogenesis in hippocampal formation
Longevity, Resilience to stress	PAPPA, SAMD3, DDRGK1, FTMT, IARS, KYNU	Reduce insulin-like growth factor; maintain protein assembly under stress
Neuroprotection against injury or degeneration	RUNX1, MTMR14, ID5, FTMT, MAGEA11	Promote anti-oxidation, autophagy, and repair
Regulation of neuronal excitability & sensitivity	GLRA2, OR5L1, PGLYRP4, MAGEA11	Regulate neuroexcitation and sensory transduction
Regulation of growth and development	PTPRT, MAGEA11, SAMD12, GLRA2, PAPPA	Ras signaling pathway, regulate cell adhesion

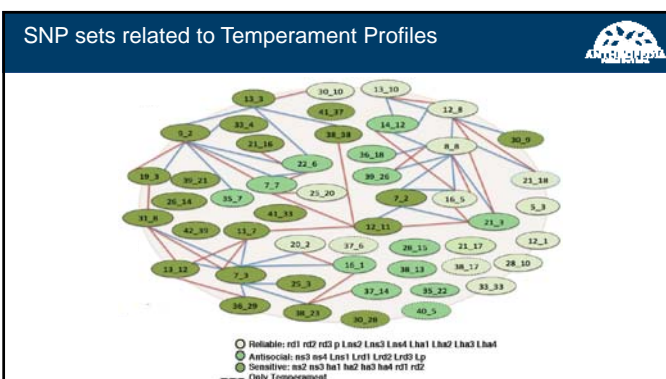
Genes Unique to Apathetic Profile

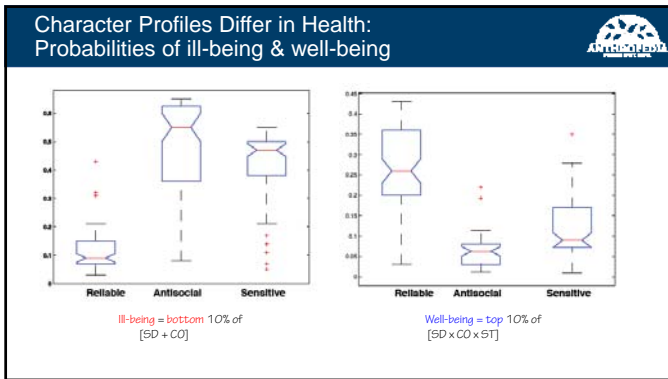
Neuronal Function	Gene Symbol	Biological Process
Stress Reactivity	NR3C2	Encoded mineralocorticoid receptor is trigger for the stress response system
Stress Reactivity	PKCB	Protein Kinase C beta regulates stress reactivity
Stress Reactivity	ATP6V1A	Neurotransmitter storage and release in Hypothalamic-Pituitary-Adrenal axis
Induction of Apathy and Anxiety	PDGFB	Reduced motivation from dopaminergic and vagal neurons
Down-Regulation of energy production	PIWIL2	RNA-mediated gene silencing of oxidation of fatty acids for entry into Krebs Cycle reduces energy

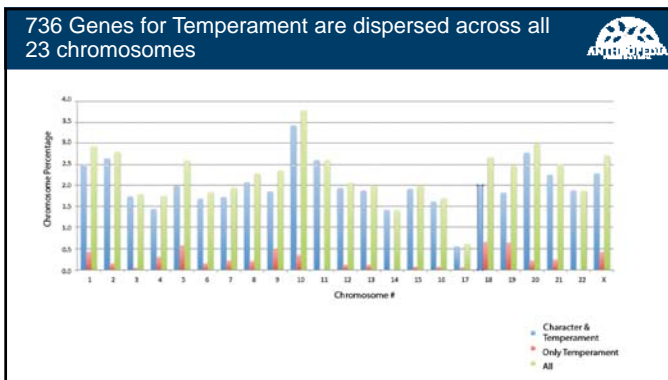


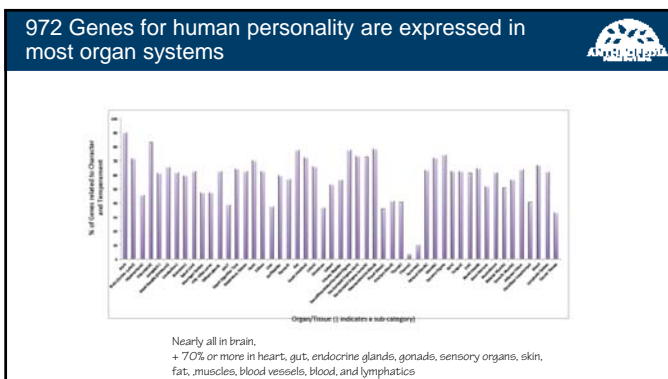


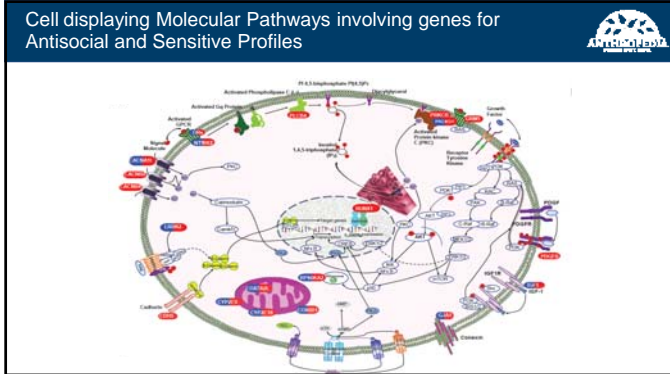
- ### Overview: Facts About Character
- ❑ 3 profiles of Temperament were distinct (Reliable, Sensitive, Antisocial)
 - ❑ 51 SNP sets associated with temperament in Finns (all but 1 replicated in other two samples)
 - ❑ 736 genes mapped to these SNP sets
 - ❑ Genes code for multidimensional temperament: profiles of whole person, not for individual TCI dimensions
 - ❑ Genes are mostly in two main pathways that respond to extracellular stimuli – Ras-MEK-ERK and PI3K-AKT-mTOR pathways
 - ❑ Heritability explained by SNPs was 48% in Finns, 53% in Germans, and 37% in Koreans
 - ❑ Some associated Environmental sets but effects are weak











New Facts About How Temperament & Character are Organized Together

- ☐ There are 3 nearly separate networks of people with different combinations of temperament and character
 - ✓ Creative/reliable, organized/reliable, Emotional/unreliable
 - ✓ There is marked complexity within each network in temperament-character relations
- ☐ There are 3 nearly separate genetic networks corresponding one-to-one with the phenotypic networks
 - ✓ 3 nearly separate networks of SNP sets related to systems of learning
 - ✓ 3 nearly separate networks of genes (67% unique to only one network)
- ☐ There are also 3 nearly separate networks of environmental influences
 - ✓ They correspond one-to-one with the phenotypic networks
 - ✓ Some are directly related to the phenotypic networks and many indirectly through associated SNP sets

Evolution of Human Brain Functions

Planes of Functioning	Sexual Subplane	Physical Subplane	Emotional Subplane	Intellectual Subplane	Spiritual Subplane
Spiritual					Unity
Intellectual			Intentional Socializing	Intentional Symbolizing	
Emotional					
Physical		Physicality			
Sexual	Mating				

Cloninger 2010

Emergence of Ancestors of Human Emotional-Cognitive Functions

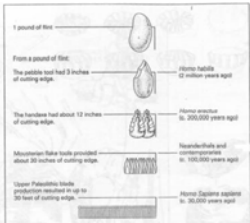


Anthropoid primates (e.g., Chimpe) kissing to reconcile after fight
Miocene - 24 mya



Anthropoid primates (e.g. Macaques) learning to intentionally wash potatoes in salt water
Miocene - 24 mya

Emergence of Long-term Planning in pre-modern Humans



Increasing cutting ability of Mode 1-3 stone tools, 2000 (1), 800 - 300 (2), 100 (3) kya



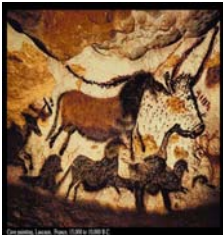
Shelter with hearth, Terra Amata, France, 400 kya

Neandertals lived in small isolated bands



- Studies of DNA from Neandertal genomes shows lower genetic diversity than seen in modern Homo sapiens
- Low genetic diversity indicates they lived in small isolated bands of 12 to 25 people with little mating between bands
- Members of bands were purposeful and resourceful hunters
- Members of one band cooperated with one another for mutual benefit in activities like hunting and caring for the injured of their band, but not with members of other bands

Emergence of Science, Art, and Perception of Unity in H. sapiens

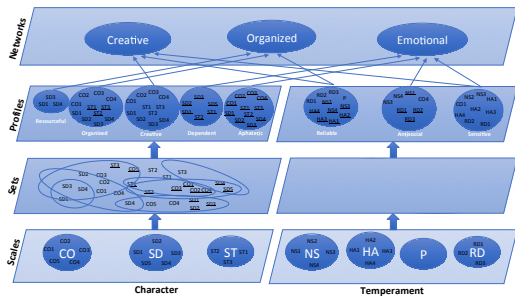


Cave Paintings
Lascaux, France
32-16 kya

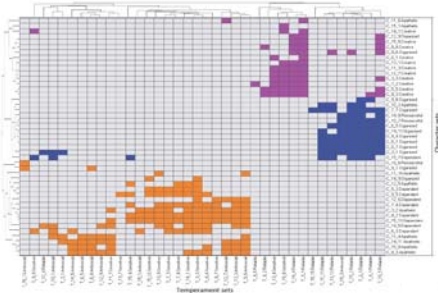


Plato
(in Raphael's School of Athens)
470 -399 B.C

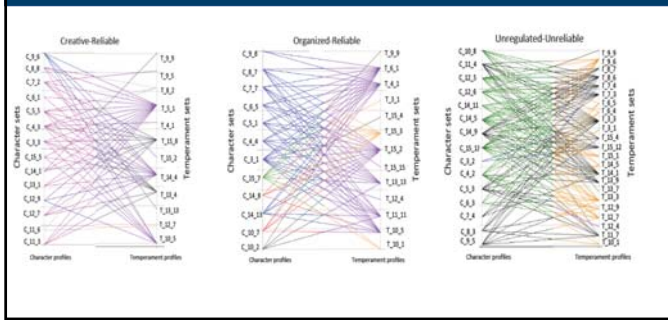
Uncovering 3 Integrated Temperament-Character Networks



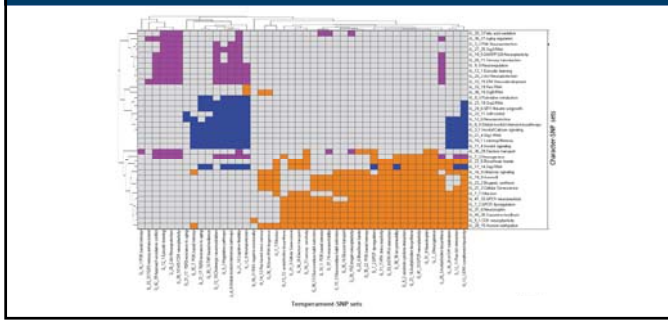
Three Nearly Separate phenotypic Networks (Temperament + Character)



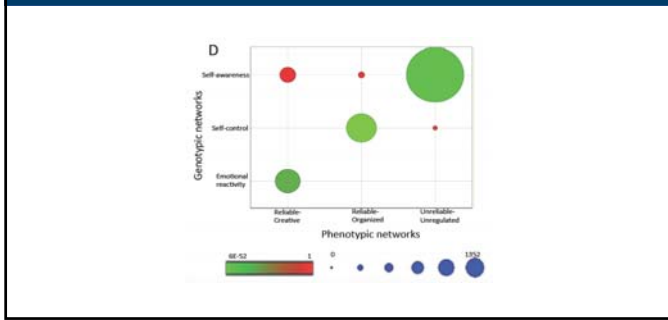
Complex Character - Temperament Relations within each Phenotypic Network



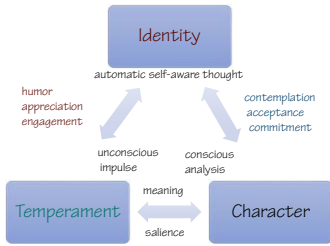
Three Nearly Disjoint GENOTYPIC Networks of Temperament and Character



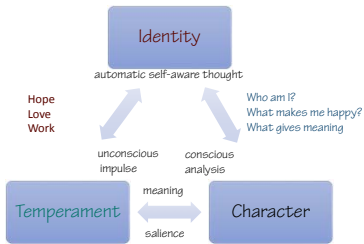
Strong Correspondence of Phenotypic and Genotypic Networks



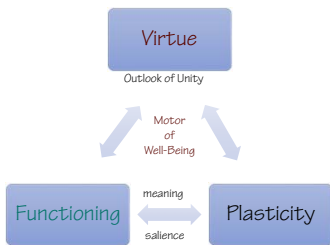
Ternary Processes of Health Promotion (1)



Ternary Processes of Developing Personality (2)



The Virtuous Circle Leading to Flourishing of Health



Well-Being depends on 3 Creative Life Practices



- 3 practices of living in well-being:
 1. Working in service of others
 - Enjoy giving of yourself
 - Be respectful & kind
 2. Letting go
 - Don't fight or worry
 - Be empathic & reflective
 3. Growing in awareness
 - Be happy to adapt and to learn constantly
 - Be genuine & humble



Diver of Paestum

The Creative Process: the experience of being "in – between"


Foresee the opportunity in change

For a trapeze artist to grab the next bar, she must let go of the last one.

Open hands

Questions



Rodin's 'The Cathedral' (two clasping right hands)

?

Key Method References

- 1) For TCI - Cloninger et al, *Arch Gen Psychiatry* 1993, 50:973-990.
- 2) For evolution of brain systems - Cloninger, *ANZJP*, 2009, 43:994-1006.
- 3) For genetics - Ziser...Cloninger, *Molecular Psychiatry*, 2018 x 2, 2019 x 2
- 4) For Clinical Psychobiology - Cloninger et al, *Transactional Psychiatry* 2019
