Toward a conceptual framework for linking biological mechanisms to symptom clusters in cancer

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Development
social/emotional competence, brain maturation, puberty

Genetics

Physiology
alcohol metabolism, craving, reward, tolerance, withdrawal

Environment
peer influence, stress, availability

Behavior
personality/temperament, externalizing/internalizing disorders
Based on Wilson and Cleary (1995)

Molecular and genetic factors

Characteristics of the individual
E.g., Extraversion, loneliness, sociability

Molecular and genetic factors

Biological and physiological variables
Somatic malfunction
CNS malfunction

Symptom status
E.g., Fatigue, pain, reduced mobility
E.g., Mood disturbance, communication impairment, social fear

Functional status
Social functioning

General health perceptions

Overall quality of life

Characteristics of the environment
E.g., Social support, family structure, neighborhood
Genetics, Epigenetics and Pain

• Why do some people experience pain differently from other people?
  – Emerging data offer convergent evidence for the importance of ion channels in both pain sensitivity in normal populations and pathological pain states
  – Research suggests a SNP within the SCN9A gene that encodes the α subunit of the voltage gated sodium channel Na_v1.7 may play a role in determining risk for chronic pain conditions as well as variation in pain responding within normal populations.\textsuperscript{[91]} In a mixed cohort of sciatica, osteoarthritis, pancreatitis

• Why do some people get pain relief from a treatment and others do not?
Pro-inflammatory Pathway

IL-1β

- Fatigue
- Pain
- Depression
- Anti-depressant response
- General health
- Physical function
Anti-inflammatory Pathway

- Fatigue
- Pain
- Depression
- Social function
- General health
- Physical function
Dopaminergic Synapse

Emotional function:
- Positive affect

Social function

Fatigue

Pain
Amygdala and Neural Pathway
So what might help us put it together?

- Make advances helped by blurring research boundaries and using multi and trans disciplinary perspectives
- Examine pathways by placing questions on a theoretical modelssuch as Sprangers et al expansion of Wilson and Cleary or Lutgendorf as starting point
- Include important modifiers or confounders such as resilience and personality
- Add each subjective domain as a correlate individually or together in clusters, i.e., pain, depression, fatigue
PRO Measurement in the Pathways

• Use symptom and sign measures with clear concept and dimensionality

• Consider measures of personality and resilience (assessed with PROS or ?)
  • --Strengths and Difficulties Questionnaire for Infants and Youth
  • --Measures of Coping
  • --Optimism Pessimism
  • --Cognitive Reserve

• Measures of impact more distal but related
  • --Functional status
  • --Perceived quality of life
Cautionary Thoughts

• Missing heritability
  – Even when dozens of genes linked to a trait or behavior, cumulative effects disappointingly small
  – No surprise it isn’t one gene, one phenotype but more complex
  – Possibly 1000s of variants
  – GWAS and SNPS— to sequencing whole genomes

• Brain “plasticity” --brain changes with experience

• We can move along with basic science
Other challenges

• Difficulties of causal inference even with personalized risk profiles using genetics

• Findings “need” to be placed within structural determinants of population and individual health—the social patterning of health and illness

• Need for use of innovative research designs such regression discontinuity design, pretest post-test with thresholds