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Phenotyping psychosis: Room for neurocomputational and content-dependent cognitive endophenotypes?

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Introduction. The endophenotype research strategy aims at reducing complex clinical phenomena to reveal a more tractable mapping to underlying genes. Cognitive dysfunctions have been widely pursued as target endophenotype in schizophrenia. We critically discuss the promise and limitations of this approach.
Methods. Relevant theoretical and empirical issues on genes and behaviour, neurocognitive structure and psychopathology were selectively reviewed and discussed.
Results. Some important inherent limitations of the current cognitive endophenotype approach were identified. These include reliance on (1) classic neuropsychology; (2) deficit measures; and (3) a general information processing approach with the use of content-independent, neutral stimuli. As a result, many current cognitive endophenotypes are likely to overlap and converge with general cognitive impairments, which may be shared with other disorders.
Conclusions. We propose three novel directions for further psychosis endophenotype research: (1) in addition to such content-independent computational processes, which operate in a similar way regardless of the stimuli, it is important to consider the potential roles of "content-dependent endophenotypes", which operate on different stimuli in consistently different manners. Advances in cognitive studies suggest there may be evolutionarily important aspects of cognition which are content-dependent. We propose that both content-independent and content-dependent processes should be addressed in psychosis research. (2) In line with the emphasis on content, close attention should be paid to the study of "psychopathological endophenotypes" in addition to cognitive endophenotypes. (3) "Neurocomputational endophenotypes" may be defined by parsing cognitive processes into "subsystems" with specific computational processing algorithms and considering key computational parameters suggested from these models. These potential "neurocomputational endophenotypes" (such as neuronal noise, synaptic

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learning algorithms) are potentially intermediate variables located between the levels of cognition and neurobiology.

Keywords: Psychosis; Endophenotype; Genotype; Cognitive structure; Content-dependent process.

INTRODUCTION: WHY ENDOPHENOTYPING IS IMPORTANT

Definition of the target behavioural phenotype is a crucial starting point in any attempt to map genes to behaviours. In the case where the target behavioural phenotype is the complex disorder schizophrenia, data so far suggest a polygenic mode of inheritance with each of the putative genes exerting only a small effect (Harrison & Owen, 2003). There are likely many non-linear gene–gene and gene–environment interactions (Gottesman & Shields, 1967; Meyer-Lindenberg & Weinberger, 2006), which may be further complicated by possible pleiotropic effects (Page, George, Go, Page, & Allison, 2003). This challenging scenario has led investigators to reconsider whether complex clinical categories (such as schizophrenia or psychotic disorders) are optimal phenotypes. As a result, researchers have attempted to reduce complex phenotypes to simpler endophenotypes in the hope that the latter represents putative "atomic" components which map more directly onto genes (Gottesman & Gould, 2003; Gould & Gottesman, 2006).

We critically evaluate this approach, particularly in relation to cognitive and psychopathological (as in descriptive psychopathology) phenotypes. After surveying the explanatory gap between genes and behaviour first from a bottom–up and then a top–down perspective, we propose that existing cognitive endophenotype research may have suffered from a relative lack of robust *a priori* considerations of search strategies and consequently may bias towards measuring general cognitive dysfunctions, resulting in likely findings of genetic mapping to nonspecific general cognitive capacity. While useful to some extent, this approach may not fully address the more specific pathways for psychosis. We then explore some current views on the structure of cognition in terms of cognitive subsystems and basic computational processes within a cognitive subsystem. This leads to the proposal of locating endophenotypes at the neurocomputational level, intermediate between cognition and neurobiology. At the same time we explore possible reasons why there has been a tendency to overlook content-dependent endophenotypes. This tendency was also apparent in empirical cognitive studies and psychopathology. Following works that suggest human cognitive processing may consist of content-specific modules, we propose that it is important to take into account "content-dependent" processes (different

stimuli are processed in consistently different manners by the same processing system) as potential endophenotypes in addition to "content-independent" processes (different stimuli being processed by the same operation). It is argued that while content-independent processes may partly underlie psychotic disorders, they are less likely to be specific. It is therefore proposed that it will be the content-dependent processes, which have been relatively neglected in traditional cognitive research, that are most promising in yielding endophenotypes relevant to a specific understanding of psychosis.

THE GAP BETWEEN GENOTYPE AND PHENOTYPE

Recent progresses in genotyping and sequencing technologies have resulted in a situation whereby gene-level information has outstripped our knowledge of how genes work at physiological and pathological levels. This discrepancy is particularly noted for brain mechanisms in relation to complex behavioural disorders.

Complexity of the "black box": bottom–up view

Current knowledge on processes that explain from the bottom–up how genes are expressed in behaviour is minimal. Still it is important to try to appreciate the complexity involved. Amongst possible direct expressions of genes, some may specify structural proteins in the nervous system (e.g., the axon and cytoskeleton dendritic trees) and some specify chemical transmission processes in synapses (e.g., receptors, neurotransmitters, second messengers, and metabolism of neurotransmitters). Apart from the structural genes, there may be genes that specify the physical location of particular cells, as well as those that mark specific temporal stages along development. Some genes may mediate specific environmental signals (e.g., the mating season, seasons in general, and food scarcity). Some genes may even specify fixed connectivity between neurons (e.g., instinctive perceptual patterns and instinctive sets of responses). There are also regulatory genes that directly modulate the expression of other genes; those that can be activated depending on the internal environment (i.e., responding to other components of the neural system) and those that respond to aspects of the external environment. Together, genes of the brain (estimated to comprise approximately a third of the human genome) drive the formation of different cell types, the axonal growth and tracking, the formation of neural connections, as well as the connection pattern between neurons (i.e., networks) and the timing of neural developmental events. Eventually after many levels of reduction, they constitute the material basis for the behavioural modules, with input–output mappings modulated by a large number of factors.

Challenges of the ''black box'': top–down view

The use of endophenotypes are intended as an initial top–down deconstruction (i.e., reduction) of complex behavioural phenomena into component processes (i.e., cognitive or neural), which presumably lie closer to the biological mechanisms that genetic information impacts on.

Currently there are at least three levels of reduction: the symptom/psychopathology level (i.e., units of subjective experience/behavioural categories); the cognition level (i.e., discrete cognitive processes or modules); and the neural level (i.e., brain physiological systems). It is implicitly assumed that these levels are hierarchically arranged so that phenomena at a higher level are reducible to combinations of ''atomic'' components at a lower level. For example, a symptom may be reducible to one or more basic cognitive processes, each of which in turn is reducible to one (or more) brain process(es). It is assumed that lower level ''atomic'' components are more directly determined by a smaller number of genes. There is however no clear guidance as to what might constitute the ''natural kinds'' or whether we are ''carving nature at its joints'' at lower levels. Whilst cognitive science has attempted to define the structure of cognition in the form of ''cognitive modules and subsystems'' (e.g., Kosslyn, 1994; Pylyshyn, 1984), it has been challenging to consider whether such conceptions are likely to be relevant in the search for psychosis endophenotypes (see later).

LIMITATIONS IN CURRENT COGNITIVE ENDOPHENOTYPE APPROACHES

Power to reduce complexity from clinical phenotypes

As endophenotypes are intended to be alternative behavioural dimensions that map better to genes than clinical categories (Gottesman & Gould, 2003), their success should be measured against this objective. It is contentious as to whether so far the application of cognitive endophenotypes to understanding psychosis specifically has resulted in a definitive reduction in complexity (Flint & Munafo, 2007; Keri & Janka, 2004).

Figure 1 illustrates two potential scenarios with endophenotypes. In Figure 1a, depicting the ideal situation, a clinical phenotype (diagnostic category) is completely reduced to two distinct endophenotypes. Each of these neatly maps onto a smaller number of genes. In this instance, the use of endophenotype has reduced the complexity of the genotype–phenotype mapping and made the subsequent analysis simpler. In another (more likely) situation, depicted by Figure 1b, the phenotypes are (1) not completely explained by the endophenotypes, and (2) the endophenotypes are not specific for the phenotypes. In this situation it is possible that the endophenotypes

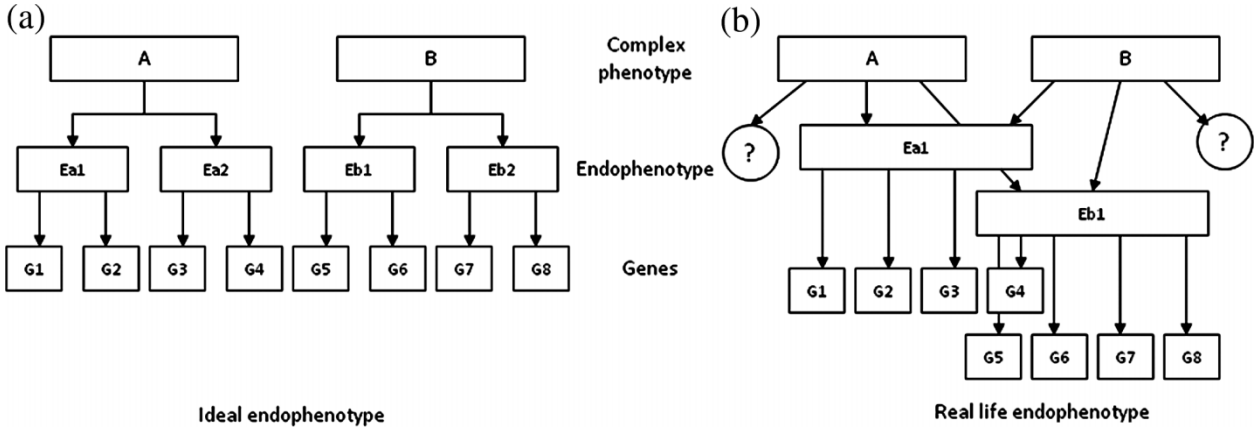

Figure 1. Schematic representation of ideal and real-life endophenotypes mappings. A and B Represent phenotypes (diagnostic categories). Ea1, Ea2, Eb1, Eb2 are putative endophenotypes (cognitive or biological measures). G1-8 are related genes. Figure 1a is the ideal situation when the endophenotype-to-gene mapping is less complex than the phenotype-to-gene mapping. Figure 1b is the real-life situation where the endophenotype-to-gene mapping may not be less complex as compared with the phenotype-to-gene mapping.

themselves may map onto an equally large set of genes, and not necessarily significantly reduce the complexity of the phenotype-to-gene mapping. Arguably the current situation for schizophrenia may be closer to the latter than the former instance.

Endophenotypes are "endo" because they may not be easily observable (John & Lewis, 1966). In the search for cognitive endophenotypes, dimensions that are relatively more accessible have been preferentially studied. Existing screening for potential cognitive endophenotypes has relied heavily on a convenient set of currently available measurements (Goldberg & Weinberger, 2004) – pre-existing assessment tools for memory, attention, executive function and general intelligence in psychosis dominated recent research, without necessarily providing richer insights on how the failure of these systems mediates psychotic symptoms. A fundamental limitation of current research is thus the lack of a coherent strategy to guide researchers in looking beyond what is conveniently available.

General (content-independent) cognition and psychosis

Although psychotic illnesses express themselves in very specific terms (i.e., in the highly specific range of symptoms, such as persecutory delusions, derogatory third-person auditory hallucinations), there is also evidence that a general reduction in cognitive capacity may contribute towards psychosis. Psychotic symptoms have been reported more frequently in populations suffering from a general reduction in cognitive processing capacities (e.g., learning disability, dementia and ageing) (Rosen & Zubenko, 1991; Turner, 1989; van Os, Howard, Takei, & Murray, 1995). Psychotic symptoms can also occur in acute illnesses that compromise brain function integrity (e.g., traumatic brain injury) (Koponen et al., 2002). Research in cognitive dysfunctions in schizophrenia has suggested a contribution of general cognitive impairment (Kraus & Keefe, 2007). In fact, there has been intense debate over whether there are specific impairments on top of the generalized impairments in cognitive functions (e.g., working memory, verbal memory, executive function) (Goldberg, Weinberger, Berman, Pliskin, & Podd, 1987; Goldman-Rakic, 1994; Saykin et al., 1994). Regardless of the specific cognitive impairments, there is broad agreement that a generalized component of a wide range of deficits in cognitive function is involved (Dickinson, Ragland, Calkins, Gold, & Gur, 2006; Kraus & Keefe, 2007). It has been suggested that general cognitive abilities are determined by a set of genes (the "generalist" genes) (Butcher, Kennedy, & Plomin, 2006; Kovas & Plomin, 2006). Because of the relationship between general intelligence and psychosis, we anticipate that some of these genes may eventually be found to be associated with psychotic disorders.

How general cognitive impairment could contribute to psychosis is still unknown. A number of theories have been proposed. Some examples are: (1) general cognitive capacity is related to reasoning and logical thinking, and psychosis is a consequence of failure in applying logic and sound reasoning in interpreting social events (MacCabe et al., 2008); and (2) reduced cognitive capacity increases the likelihood of spurious memories generated by the associative memory system, resulting in the clustering of bizarre features on a single representation (Chen, 1994, 1995; Hoffman, 1987).

Even though it appears that nonspecific cognitive processes play a role in psychotic disorders, it is unlikely that they are sufficient explanations. It is important also to note that in psychosis, generalized cognitive impairment is neither a necessary nor a sufficient condition: a significant proportion (over 20%) of psychosis patients are not cognitively compromised (on classical neuropsychological measures), while a significant proportion of cognitively compromised subjects do not experience psychotic symptoms (Keri & Janka, 2004). There is considerable overlap between the cognitive capacity of participants with psychosis and normal participants. This highlights the need to further identify cognitive and neurobiological processes specifically related to the mechanisms of psychosis.

Evidence from twin studies also suggest in addition to a genetic link for more general neuropsychological measures and schizophrenia, there are also additional genetic factors unrelated to these measures that influence the risk of schizophrenia via independent mechanisms (Toulopoulou et al., 2007). It is in the search for these specific cognitive endophenotypes that a novel approach to characterize cognition in psychosis, distinct from the deficit and the general information processing frameworks, holds promise in identifying more specific cognitive pathways to psychosis.

Why conventional cognitive endophenotypes may be limited?

Most of the cognitive endophenotypes considered so far have originated from conventional neuropsychological measures or from a cognitive psychology framework. There is a possibility that they may converge to tap general cognitive impairment rather than become candidates for more specific psychosis endophenotypes, for the following reasons:

1. *Reliance on classic neuropsychology:* conventional neuropsychological measurements based on gross brain lesions (e.g., head injury, tumour or cerebrovascular events) appear to have played a major role in the search for cognitive endophenotypes. Although readily measurable, there is no *a priori* reason why such deficits should map more simply onto genes.

As most neuropsychological functions were defined by lesion effects on specific areas of the brain (such as the frontal lobe), this approach does less well in describing more diffused effects affecting networks of multiple brain areas. Some more sophisticated studies using modern cognitive science methods may overcome this limitation.

2. *Reliance on deficit measures:* a second limitation with the conventional cognitive approach is the emphasis on deficit measurements. The standard paradigm is to define a cognitive function and to measure the decline of that function in abnormal states. This approach is structurally less suitable for addressing problems that arise from aberrant functions rather than losses of function. For instance, conventional memory measurements focus on the loss of memory (e.g., failure to recognize and recall items in working memory, verbal and spatial long-term memory), and have relatively neglected the study of spurious memories (e.g., the production of abnormal or distorted memories). This bias would result in research findings that focus on general losses of functions, but would be relatively inadequate in probing the mechanisms for anomalous experiences in psychotic disorders.
3. *Reliance on a general information processing framework:* another weakness arises from the alignment of cognitive psychology with a general information processing framework (Tooby & Cosmides, 1992). The general information processing approach views the human cognitive system as a general purpose computational system, which processes different inputs to the system according to the same, neutral, algorithm independent to the content of the input (content-independent). As pointed out below, this approach may overlook important aspects of human cognition and psychopathology specifically relevant to psychosis. This content-independent framework could at best address only issues pertaining to general processing capacity and the disorders that arise from a nonspecific failure of processing, which are likely to be shared amongst many different disorders. Some investigators have already commented on the need for more novel perspectives in searching for cognitive endophenotypes (Goldberg & Weinberger, 2004). We would like to propose several possibilities in the rest of this paper.

PROBING THE STRUCTURE OF COGNITION

Cognitive subsystems and modularity

Applying the endophenotype approach to cognition raises a need for a rigorous review of the structure of cognition (i.e., how "individual" cognitive processes are validly defined, and how they are likely to be organized in

relation to one another). Cognitive scientists have made several attempts at more rigorous conceptualizations of the structure of cognition. A commonly adopted framework conceives the cognitive system as consisting of a number of "subsystems". Each of the subsystem can receive an input, perform an operation on the input to generate an output, and then pass the output onto another subsystem. Operations within a subsystem are proposed to be relatively independent of processes occurring in other subsystems (e.g., Kosslyn, 1994). The concept of subsystems is akin to the notion of "cognitive modules" proposed by Fodor (1983). As such, these "cognitive modules" or "subsystems" naturally become candidates for the endophenotype approach, and an important task involves the identification and characterization of the key "subsystems" relevant to normal psychology as well as to psychosis. It is recognized however that the structure of cognition is unlikely to consist simply of a number of independent modules. Upon further consideration, the relationship between subsystems can be elaborated by a distinction between "strong modularity" and "weak modularity". In a metaphor used by Simon (1981) and adapted by Kossyln (1994), the cognitive system is compared to a house that is subdivided into rooms by walls (subsystems with strong modularity), and each room is subdivided into cubicles by thin walls (weak modularity). To regulate the room temperature there is a thermostat in each cubicle which can be set independently. This will result in each cubicle having different temperatures; however the temperatures in different cubicles within a room are more similar than that between rooms. Although such elaborations are important for retaining explanatory power over a wide range of phenomena, at the same time, they remind us that it may be simplistic to expect cognitive subsystems be "clean" endophenotypes.

Computation within cognitive subsystems

It is important to recognize that the conceptualization of cognition in terms of subsystems is only a first step. After defining the cognitive systems with their input and output, the crucial question is to understand how information is computed from input to output, and how information from one subsystem interacts with other subsystems. The interaction between subsystems can also take a number of forms: one subsystem may send output directly as input to another system, a subsystem's output might "prime" the processing in another subsystem so that it modulates the probability of a certain output in the target system; a subsystem may also affect the general operation of another subsystem (slowing or blocking it) (Kossyln, 1994). For the current discussion, we shall focus on computations within a cognitive subsystem.

Different accounts of cognitive computation exist, cognitive science makes a distinction between "symbolic" processes and "subsymbolic" processes (Smolensky, 1995). In symbolic processes, the input information is taken as an atomic unit, and the operation is defined at this level without further reduction (e.g., "STORE" stimulus "A", or "RETRIEVE" stimulus "A", thus maintaining a "black box" at this level). In "subsymbolic" processes the input information is further reduced to "dimensions" or "micro-features" (which may or may not be meaningful), and they are represented by multiple smaller units. Transformation from input to output is defined by parallel computation between these units using principles of associative learning. We shall consider one account of subsymbolic mental representation and operations (i.e., parallel distributed processing (PDP) or neurocomputational models). These models have been influential firstly because they adopt neurobiologically inspired basic structures: employing a large number of richly interconnected processing units (Rumelhart & McClelland, 1986). Secondly they offer a reduced level (sub-atomic level) of explanation compared with most conventional cognitive psychology models (typically articulated at the "symbolic" level with processes defined at this level without further reduction). Because of their unique roles, it is important to clarify the nature of neurocomputational models and the extent they impact on our thinking of endophenotypes. While most neurocomputational models are not aiming for detailed neuronal realism, and are certainly not complete explanations of either brain processes or cognition, but it is believed that their distributed structure allows their emergent behaviour to capture some important aspects of neurocognitive phenomena that are otherwise difficult to explain (e.g., graceful degradation and content addressability[1]). As mentioned above, in neurocomputational models the structure of a representation is defined by a large number of micro-feature dimensions (Churchland & Sejnowski, 1992). The "content" of a particular representation is specified by the array of "values" along the feature dimensions. In this perspective, the "structure" or "form" is related to the computational space defined by the feature dimensions, and this space is a platform that can be "filled" by specific contents in a particular instance. In a detailed model of cognitive schema,

[1] "Graceful degradation" refers to a pattern of loss of information in a computational system as a result of inactivation of part of its hardware components. In a conventional computer, the inactivation of a specific hardware location generally results in total loss of circumscribed information. In contrast, in distributed systems, inactivation of part of the hardware leads to global impairment affecting all information, and the initial effect of limited damage may be relatively small. "Content addressability" refers to the process of memory retrieval whereby presentation of part of the memory contents can be used to retrieve the entire memory representation. This process can be realized in some distributed networks (e.g., autoassociative networks) and is in contrast to conventional computer process of using a separate "address" to search and retrieve a piece of information.

Rumelhart, Smolensky, McClelland, and Hinton (1986) constructed a neural network where units represent features in a cognitive schema and the connection between units represents constraints between features. The network is allowed to evolve in such a way that each unit calculates its activation level based on the initial input (external evidence), according to a specified algorithm. Since the units are connected with most other units, the outputs then influence the activity level of the connected units. This process is repeated until the state of the network (i.e., the activity level of all the units) settles into a steady state. This state represents an optimal solution to a given input, in which the maximum number of internal constraints is satisfied. Rumelhart et al. (1986) illustrated this with an example using the schema for "rooms", where features of this schema would consist of size and shape of the space, the number and nature of furniture, the colour and patterns of the walls, the lighting, the inhabitants and so on. A particular permutation of final values for each of the features would then give rise to the interpretation of the kind of room encountered (e.g., whether this is a classroom, a restaurant, or a washroom). The schema for "rooms" can be filled in with specific contents (bathroom, living room, bedroom, etc.) according to external input. Importantly "contents" are not fixed entities, but are patterns specified by the strength of association between different feature dimensions, which could be adjusted based on previous encounter (e.g., according to a defined learning algorithm such as the Hebbian rule). Such systems are capable of adaptive learning, associative memory and handling ambiguous information. The contents are not actually stored; what is stored is the connection strengths, which encode the co-occurrence of features in the environment. The actualization of a particular "content" at any particular moment is therefore fluid, plastic, and adaptable.

This conceptualization has implications for the endophenotype approach: the models only need to define very few initial baseline structures, namely the feature dimensions and the computational algorithms. The actual "contents" are experience-dependent, modifiable representations. This distinction implicitly suggests that only the basic structure and the learning algorithm need to be specified biologically and are more likely to be genetically determined (hard-wired), whereas "content" can develop according to individual experience. The strength of PDP models is that they suggest innovative and interesting possibilities for key neurocomputationally relevant variables as putative endophenotypes (e.g., for size of computation network, strength of inhibitory processes, neuronal noise regulation, synaptic pruning, or synaptic learning algorithms). These variables are located between the levels of neurobiological and cognitive representations.

Neurocomputationally relevant endophenotypes are expected to be mediating processes that are generic rather than relating to specific contents.

''CONTENT'' IN COGNITION AND PSYCHOPATHOLOGY

The distinction between "form (or structure)" and "content" permeates much of cognitive and psychopathological research and requires a more focused exploration here.

How ''contents'' have escaped cognitive models

In our consideration of cognitive scientific approaches to cognition, we have reviewed how conventional information processing approaches were limited by a preference for generic, neutral stimuli. We then reviewed recent neurocomputational approaches, which attempt further reduction for computational processes within cognitive systems, and we found that in such systems "contents" are usually represented by experience-modifiable processes rather than genetically determined processes. While suggesting interesting possibilities for neurocomputational endophenotypes (see earlier), these models attribute content-dependent processes almost entirely to learning. Although neurocomputational models themselves place much emphasis on the role and nature of learning, they have necessarily focused on modelling systems where the important "contents" of cognitions are learnt rather than inherited. The latter are relevant in endophenotype considerations. In the following sections we also review the contexts in which "contents" have also been relatively overlooked in cognitive psychology and in psychopathology.

Content and form in cognition

In conventional cognitive psychology and neuropsychology, there is a tendency towards studying how the cognitive system responds to neutral stimuli. For instance, abstract shapes, colours, and forms are used in the Wisconsin card sorting test; "meaning-free" numbers or letters are used in the continuous performance tests. The use of such stimuli originates from a convention where the target of investigation implicitly focuses on general computational processes, which are presumed to operate in a similar fashion regardless of the specific "content" of the particular stimulus. Thus in the Wisconsin card sorting test, the colour "red" is presumed to be just one of the possible colours, without particular distinctive meanings. It is not anticipated that results would differ if another colour was used in substitution for the "red" colour. Findings from such studies led to insights about how the cognitive system operates "in general" regardless of the "content" of the stimulus (content-independent processes). In other words, this approach focuses on those cognitive operations which are invariant to meaning and content. Although subsequently there are also studies which

specifically investigated how particular "content" or emotional connotations may contribute towards processing, this important domain has not been emphasized and explored as intensively as the "content-independent" processes. As an example, this approach would look for whether the processing of, say the colour "red" can have an impact different from that of another colour (e.g., Elliot, Maier, Moller, Friedman, & Meinhardt, 2007). Taking this perspective, it is noteworthy that colour perception itself (as much as colour words) lead to semantic activation of concepts related to the colour (Nijboer, van Zandvoort, & de Haan, 2006). This example illustrates that much of cognitive processing is inherently content (semantics) dependent and this could affect even supposedly "neutral" information processing "tasks". Other approaches involve the "emotional Stroop task" where participants have to name the colour in which words are printed, where the words may contain contents relevant to the psychopathology. The emotional Stroop task has been extensively studied mostly in affective disorders with a general finding that words with connotations relevant to psychopathology are processed slower (Williams, Mathews, & MacLeod, 1996). Similarly, some studies of facial emotion processing suggest that the processing of specific affect might be impaired in patients with psychotic disorders (Kohler et al., 2003; Mandal, Pandey, & Prasad, 1998). While much of the data in this area are preliminary and await confirmation, these possibilities should call into question the assumption that content-independent processes should automatically be the main focus of cognitive investigations and are necessarily more biologically relevant.

Content and form in psychopathology

A similar dichotomy between "content-dependent" and "content-independent" dimensions also emerged as an important notion in descriptive psychopathology. The distinction between "content" and "form" in psychopathological phenomena can be traced back to the early descriptive psychopathologists. Karl Jaspers, in his classic textbook on psychopathology (Jaspers, 1918/1963, p. 58), remarked that the distinction between form and content is "constantly being made in psychopathology", that they should be kept separate, and that descriptive psychopathology is primarily interested in the "form" rather than the "content" of phenomena. The assumption underlying this perspective is that the "content" of a psychopathological phenomenon is more variable as it depends on individual experiences, whereas the "form" of the phenomenon may have less individual variations (e.g., a hallucination is an abnormal perception regardless of the actual content, such as what the voices actually said), and is presumably more related to the same abnormal brain processes that generate the experience in

different individuals. This emphasis on "form", or representational structure, has significantly impacted descriptive psychopathology and the methodology of symptom characterization, which became the foundation for modern definitions of diagnostic categories. Notwithstanding the above general principle it is noteworthy that consideration of content has been an important aspect of descriptive psychopathology (e.g., in the classification of delusions, and when considering mood-congruity in psychotic symptoms), and it has increasingly been recognized that some aspects of "content" are consistent across subjects and the specific "contents" are themselves interesting clues for the nature of these symptoms.

Content and cognitive modules

In considering the extent to which cognitive subsystems are involved in content-dependent processing, Pylyshyn (1984) makes the distinction between subsystems that operate at the semantic, intentional level (i.e., content-dependent) from others. According to this framework, content-dependent processing is proposed to be located at a "higher" level (Pylyshyn, 1984). More specifically, the theoretical notion of "cognitive penetrability" has been introduced to investigate whether a given phenomenon is independent of "high-level" beliefs and goals. If changes in contents alter the empirical phenomenon, the phenomenon is said to be "cognitively penetrable" (Figure 2).

This approach articulates some assumptions often made only implicitly in cognitive science, namely the tendency to divide cognition into "lower level" mechanistic processes on one hand (strongly modular subsystems, presumably closer to biology, mechanical, and content-independent), and "higher level" processing on the other hand (weakly modular subsystems, presumably influenced by individual experience and culture, hence content-sensitive). In the context of this dichotomy, it is expected that research efforts may underemphasize the role of biological determination in "higher-level", content-dependent behaviours and illnesses.

RELEVANCE OF CONTENT-SPECIFIC COGNITIVE SUBSYSTEMS

The need to consider content-specific cognitive subsystems

Recent developments in cognitive science have however challenged the assumption that biologically important subsystems are necessarily content-independent (Duchaine, Cosmides, & Tooby, 2001). These authors challenged the general information processing model in which psychology tended

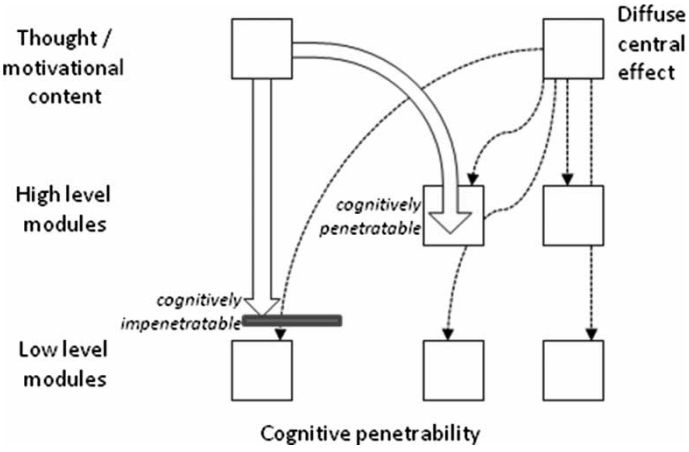

Figure 2. Cognitive penetrability and postulated hierarchy in the cognitive system. According to Pylyshyn (1984), thought/motivational content would affect only high-level modules, whereas low-level modules are unaffected, or cognitively impenetratable, by these contents. This model is shown on the left. An example of cognitive impenetrable phenomena would be the Müller-Lyer visual illusion: higher-level knowledge about the illusion does not cause it to disappear. To the right of the figure an alternative model is depicted where thought/motivational contents exert diffuse central effects directly on both presumably "high" and "low" level modules.

to withdraw from explaining meaning-laden content-dependent phenomena. It was noted that cognitive experiments have been designed mostly to explore general, content- independent mechanisms, and "emotionally-laden" stimuli have often been regarded as "noise" in experiments (Tooby & Cosmides, 1992). They argued content-independent cognitive processes as only a weak explanation since most of human cognition and psychology will need to address content/domain-dependent processes. A growing body of evidence suggests that "contents" are not simply learned combinations of features expressed in a neutral biological hardware platform. In many respects, processing of everyday stimuli is far from neutral and is often dependent on the content. As a specific example, individuals perform logical operations in a significantly different manner depending on whether abstract symbols or real-life social scenarios are used in logically and structurally equivalent tasks that differ only in "content" (Cosmides, 1989). An example of this phenomenon is the Wason selection task (Figure 3). When presented with the letter–number version of the task (Figure 3a), only a small proportion of healthy participants are able to respond correctly in this task. However, when an alternative, "social interaction" task is presented (Figure 3b), most participants would be able to correctly respond.

Based on this and other findings, it has been proposed that the human cognitive system has evolved to solve specific problems (e.g., interactions of

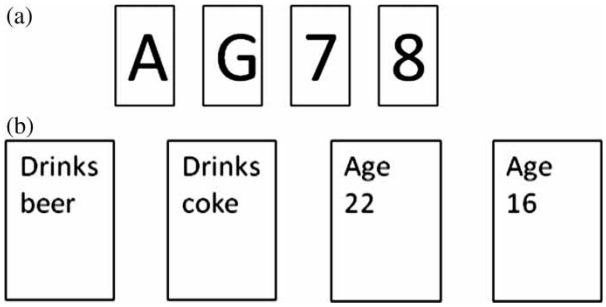

Figure 3. The Wason selection task. (a) Is a letter–number version of the task. Four cards are presented, each with a number on one side and a letter on the other. Two cards are presented letter-side up and two cards are presented number-side up. The subject is then presented with a rule: "If there is an A on one side, then there is a 7 on the other side", and then asked which cards they must turn in order to discover whether the rule is true. The correct answer is "A" and "8". (b) Is the social interaction version of the same task. The rule is "if a person is drinking a beer, then they must be over 18". The subject is asked which cards need to be turn to know if the rule has been violated.

a social nature) rather than for general abstract computation (Tooby & Cosmides, 1992). Proponents of this view suggest that the human brain handles information not in an abstract and neutral manner, but instead, in a manner relevant to potential evolutionary scenarios that early *Homo sapiens* encountered in their natural and social environment (Barkow, Cosmides, & Tooby, 1992). These observations implicitly suggest some contents will be more relevant than others with regards survival value in the environment of early hominids. Evolutionary pressure may have acted on the selection for some content-dependent cognitive functions resulting in genetically determined "hard-wiring" of the brain. For instance, returning to the example of the concept of rooms mentioned above, evolutionary pressure would have favoured a cognitive system that can discern specific types of spatial environment (e.g., an enclosed space from which there is no easy escape route, which maps closely to the stimulus that could trigger certain forms of agoraphobia).

Genetic determination of content-dependent behaviour

The biological organization of behaviours in terms of gene actions is unlikely to follow a simple hierarchical pattern. From animal studies, it is evident that certain highly complex behaviours can simply and directly map onto a small number of specific regulating genes (e.g., Drosophila sexual behaviour) (Manoli, Meissner, & Baker, 2006). Such behaviours may become highly conserved in evolution because of intense selection pressure (Hirth & Reichert, 1999). Similarly in humans, there may be behavioural sets that are

under considerable selection pressure and thus are highly conserved even at a complex behavioural level. Highly conserved processes may interact with specific stimuli in the environment and constitute content-dependent rather than general processing. Successful identification of such systems requires considerations from an evolutionary biological perspective. Thus, when considering endophenotypes for a specific behavioural set, it is important for investigators to take into account whether the "black box" is likely to include content-dependent elements. Some ideas about this can be generated from consideration of the highest level phenomena (i.e., symptoms and diagnostic categories).

Content-dependence in symptom and behaviour

Illnesses can be the result of dysfunction in either content-dependent or content-independent processing. For instance, most phobias are content-dependent phenomena elicited by a highly specific set of stimuli (e.g., an enclosed space with no escape, or small insects), whereas in generalized anxiety disorder, anxiety symptoms are experienced by patients "out of the blue" and do not appear to be restricted to specific stimuli (Stevens & Price, 2000). It is important to recognize that in phobia, a specific and narrow range of stimuli (usually small animals such as insects, but seldom large dangerous animals) are found in the majority of cases, which suggests that a general "learned threats" explanation is not adequate. For many patients with animal phobias, the exposure to the phobic stimulus is minimal or sometimes even absent. On the other hand, conditions such as dementia and learning disabilities appear content-independent, as they disrupt the processing of a wide range of information regardless of content. In contrast, many other disorders, such as obsessive compulsive disorder, affective disorders, as well as psychotic disorders, are content-dependent, in which symptoms are expressed in well-circumscribed and specific sets of themes. Adequate theories of these disorders must include an account of why particular theme contents are prominent.

With the general understanding that behaviour consists of a wide spectrum of adaptive components, it has often been assumed that responses to specific environmental stimuli are adaptively acquired (learned) and experience-dependent instead of biologically determined. This presumption has led to the tendency to consider content-dependent processes primarily in terms of cultural and social contexts, resulting in an overemphasis of content-independent processes in neurobiological illness theories and relative neglect of the potential biological underpinning and significance of content-dependent processes.

As content-dependent processing may constitute an important aspect of the cognitive system and may be of direct evolutionary biological relevance, it follows that potentially fruitful lines of enquiry may be suggested if human brain function and psychopathology are explored in the context where they have evolved to confront specific challenges for survival in unique physical and social environments, rather than as an all-purpose general information processing system (Barkow et al., 1992; Black, 1998). Application of an evolutionary framework in understanding the adaptive functions of symptoms and cognitive processes have been proposed in some areas of psychopathology. For instance, in an interesting discussion on the possible endophenotypes of dysthymia from an evolutionary perspective, it has been proposed that an "anergic" form of dysthymia, with the symptoms of loss of motivation, loss of interest, and loss of engagement with daily tasks, may have evolutionary selective advantage in the sense that it allows the individual to withdraw from a challenging situation where persistent engagement may not be the most advantageous strategy (Niculescu & Akiskal, 2001).

Given that some content-dependent disorders may have a prominent genetic basis (e.g., psychosis), it would be an important strategy to search for genes that map to content-dependent behavioural phenotypic expression, even though such systems may be less accessible and currently less well-defined. In contrast, while content-independent processes (e.g., general information processing capacity) may contribute to the explanation, they are on their own unlikely to provide adequate accounts for these disorders. To ignore content-dependence in cognitive processes and to focus exclusively on the more accessible content-independent endophenotypes as an account for content-dependent disorders is a mismatch that could compromise the eventual explanatory power.

Need to reconsider psychopathological endophenotypes in addition to cognitive endophenotypes

Before we embark on the challenge of exploring content-dependent cognitive processes underlying psychosis, it should be asked whether content-dependent approaches have been fully exploited at the level of symptom specifications. Current endophenotype research seldom capitalizes on symptoms as a possible level of analysis. Some accounts are even explicitly excluding symptoms in their consideration of endophenotypes, perhaps out of the belief that they are too closely related to the clinical categories and too complex or "experiential" (a notable exception is found in Gottesman & Gould, 2003, where subjective data were included as possible endophenotypes). Often research approaches bypass the level of symptom expression and attempt to relate clinical categories with more distal neurocognitive and

neurophysiological processes. Symptoms however remain one of the most content-dependent expressions of the disorder. This bypassing is potentially costly as it immediately reduces the clinical phenomenon of psychosis to something far less content-dependent (i.e., that of a general information processing deficit).

Arguably the study of symptoms and their structures should be a prime target of endophenotype research. At present, the complexity and descriptive methodology of symptoms may have been under-investigated. Although there are known possibilities of variability and measurement error in symptoms, given sufficient attention to methodology, these are not necessarily insurmountable. As discussed above, it is often assumed that the form of a symptom is more invariant than the content of a symptom. However, form variables are insufficient and may constraint an adequate account of psychopathology. For example, they fall short in explaining why delusions are often on a limited range of themes, and why hallucinations are usually verbal and derogatory. Theoretical explanations that account for the content of psychotic symptoms (content-relevant theories) are critical in understanding psychosis.

Because of the general tendency in cognition research to neglect specific content information contained in symptoms, current approaches may grossly understudy the richness in the psychosis phenomena. In addition, even for the content-independent symptoms, the current perspectives may be suboptimal. Psychiatric research, in the search for reliable diagnostic categories, may have trivialized the importance of symptom identification, characterization, and classification. It is often assumed that the ascertainment and characterization of symptoms are unproblematic, and focus has been more on how combinations of symptoms produce diagnostic categories (Berrios & Chen, 1993). In fact, the characterization of symptoms may represent a central challenge to psychiatric research in general, and to the endophenotype approach in particular. The current under-emphasis on symptoms has resulted in the widespread use of pragmatic symptom rating scales that may lack the sensitivity to measure potentially important symptom dimensions, as well as the capacity to capture subthreshold phenomena in non-clinical populations. This has resulted in a relatively unrefined symptom characterization, foregoing the opportunity to explore to what extent symptom dimensions reflect underlying neurobiological system dysfunctions.

CONCLUSIONS: BIOLOGICALLY RELEVANT ENDOPHENOTYPES

Based on the above discussion, it seems reasonable to expect endophenotypes for psychosis (and any content-dependent disorders) to be of two

important classes: generic cognitive endophenotypes and content-dependent endophenotypes. Generic endophenotypes are related to general cognitive performance and capacity and they are content-neutral. It is expected that generic endophenotypes may be shared by many different disorders (i.e., they may determine the general risk for a variety of mental conditions). There is a need for an optimal framework for studying these content-independent processes. In-depth consideration of cognitive processes (such as neurocomputational processes) may provide further insights and possibilities. In contrast, content-dependent endophenotypes are those that act to determine the content-dependent expression of disorders (such as psychotic symptoms). They account for the specific disorders expressed. Content-dependent endophenotypes, which are relatively under-explored due to relative lack of available measurements tools, are expected to be linked to evolutionary-relevant biological determinants of behaviour. Investigation of content-dependent processes and abnormalities may constitute one of the greatest challenges and opportunities in future psychosis research.

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