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ORIGINAL PAPER

Endophenotype Approach to Developmental Psychopathology: Implications for Autism Research

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Abstract This paper discusses the utility of the endophenotype approach in the study of developmental psychopathology. It is argued that endophenotype research holds considerable promise for the study of gene-brain/cognition-behaviour pathways for developmental disorders. This paper outlines the criteria for determining useful endophenotypes. Possible endophenotypes for autism are discussed as an example of an area where endophenotype research on developmental disorders may be fruitful. It is concluded that although the endophenotype approach holds promise for the study of gene-brain/cognition-behaviour pathways, much work remains to be done in order to validate endophenotype measures. It is also noted that the changing nature of any developmental psychopathology poses a particular challenge to this type of research.

Keywords Intermediate phenotype · Cognitive development · Autism · Asperger syndrome · Theory of mind · Mentalising · Central coherence

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Introduction

It is now commonly accepted that most psychopathologies and many complex behaviours have genetic origins. A number of gene[1]-behaviour/gene-psychopathology associations have emerged from the field of behavioural genetics, for example associations between various dopamine system genes and ADHD (See Asherson and IMAGE consortium 2004 for a review). Initial excitement about a wealth of behavioural genetic findings, however, has been marred by variable success in terms of replication in independent samples. Part of the failure to replicate is likely to reflect a lack of statistical power due to small sample sizes. The genes affecting any measured phenotype (psychopathology/trait/behaviour) usually only account for a small proportion of variance of that phenotype (e.g. Plomin et al. 1994; Plomin 2005). Other reasons for non-replication may lie in the different ethnic origins of the samples, inconsistency in the methods employed for genotyping and the different measures used to quantify the phenotype of interest in different samples. Whether any risk effects of a gene manifest themselves can also be conditional on environmental factors (Moffitt et al. 2005).

A further reason for the failure to replicate candidate gene-phenotype associations may be that a myriad of biological and cognitive processes take place between genes and an observable phenotype. There are multiple routes to the same behaviour/psychopathology and, thus, even if a psychometrically reliable

[1] For simplicity's sake, in this paper we use the singular term gene when referring to gene-behaviour/gene-psychopathology pathways. We note, however, that it is unlikely that most psychopathologies are associated with just a single gene.

rating scale is used to quantify the behavioural/psychopathology phenotype, this often nevertheless yields an aetiologically heterogeneous group of individuals. This heterogeneous group represents a variety of causal pathways to behaviour/psychopathology (see Morton 2004, for an extensive discussion on this topic with regard to developmental psychopathology). Different pre-behavioural (e.g. brain/cognitive) phenotypes may form part of the causal chain and at least partly distinct genetic influences may be associated with various pre-behavioural phenotypes linked to the same behaviour.

As interdisciplinary research efforts have increased, so has the interest in optimising the use of pre-behavioural phenotypes to understand gene-behaviour pathways. This is perhaps where the greatest utility of studying pre-behavioural phenotypes lies. Once candidate genes for a particular psychopathology are suggested (either because of an observed association or neurobiological plausibility), it may be possible to strengthen candidate gene-behaviour associations by selection of pre-behavioural processes that are particularly plausible for mediating the genetic effects on behaviour. The psychopathology/behavioural ''pie'' can thus be divided into potentially more informative slices by selecting processes (and by default sub-groups characterised by those processes) that are the driving force in a particular gene-behaviour association.

Pre-behavioural phenotypes are commonly called *endophenotypes* (Gottesman and Shield 1972; Gottesman and Gould 2003; De Geus and Boomsma 2001; *endo* meaning ''inside'' or ''within''; *pheno* meaning ''show''). Commonly conceptualised endophenotypes include neurophysiological, biochemical, endocrinological, neuroanatomical, and cognitive processes.

It is notable that endophenotype research has only recently taken off within the behavioural genetic framework. At least part of the explanation for this can be found in the different approaches to the study of human behaviour prevalent in behavioural genetics and modern day cognitive science. Cognitive psychologists and neuroscientists (both groups doing research at the endophenotype level) have generally been interested in 'species universals' i.e. how people (or animals) in general process certain information, or the universal brain signal for a particular cognitive process. Behaviour genetic research, on the other hand, has focussed on the effects of genetic polymorphisms (i.e. individual differences in the genome) on individual differences in behaviour. In line with this, behavioural genetic studies have traditionally relied on psychometrically well-validated rating scale measures. As the basis of genetic epidemiology is the study of individual differences, any measure of interest needs to have demonstrated sensitivity, as well as reliability and validity, in the assessment of individual differences. In contrast, endophenotype measures (be they performance on a cognitive task or brain activity in response to certain stimuli) are not, as a rule, normed for large populations, nor is their reliability, validity, and sensitivity to individual differences always tested.

Recently, while behavioural geneticists have started to focus on endophenotypes, ''endophenotype researchers'' have become interested in molecular genetics. There has been a flurry of activity in conducting cognitive- or imaging-genetics studies (e.g. Hariri et al. 2002; 2003; Mattay et al. 2003; Meyer-Lindenberg et al. 2006a, b; Tunbridge et al. 2006). Researchers who have traditionally conducted research on a variety of psychopathologies at an endophenotype level of analysis are now starting to capitalise on molecular genetics information as a source for ''extra signal'' in their studies.

Ohnishi et al. (2006) recently studied the effects of both genotype (COMT val/met) and schizophrenia diagnosis on brain morphology. The COMT val allele has been associated with both poorer executive functions and higher fMRI BOLD response in the frontal cortex, including in anterior cingulate cortex (ACC), during working memory and attention tasks (Blasi et al. 2005; Bruder et al. 2005). The val allele has also been associated with schizophrenia in some previous studies (see Roffman et al. 2006 for a review). Ohnishi and colleagues found a significant genotype-diagnosis interaction effect in brain areas including the left ACC. ACC was smaller in the val-allele carriers with schizophrenia. This is interesting as ACC abnormalities have been implicated in several studies on schizophrenia (see Blakemore and Frith 2000 for review), but the Ohnishi et al. (2006) study suggests that this abnormality may be present only in people with schizophrenia who also carry the val-allele.

In summary, there are multiple routes to the same behavioural phenotype (Morton 2004). Behavioural rating scales exist that pick up individuals with pathological patterns of behaviour with a considerable level of reliability and accuracy. However, the route from genes to behaviour is complex. Different risk genes, each possibly reacting differently to environmental variables or to the presence of other genes, may predispose an individual to similar outcomes at the behavioural level. In between genes and behaviour, a variety of endophenotypes may be associated with the same behavioural outcome. Failing to take into account different endophenotypes signalling heterogeneity within a single psychopathology is likely to make it more difficult to replicate candidate gene-behaviour

associations, especially as the proportion of individuals with endophenotype ''A'' or ''B'' is likely to vary from study to study. In addition, endophenotypes are crucial for a full understanding of gene-behaviour pathways.

In this paper we outline criteria for determining suitable endophenotypes. We also discuss why well-selected endophenotype measures may be useful for understanding gene-behaviour relationships in developmental psychopathologies. We illustrate our case using the example of potential endophenotypes for autism. Finally, we outline the limitations and considerations for the future of the endophenotype approach to the study of developmental psychopathology.

Criteria for determining useful endophenotypes

Here we draw on the criteria for selecting endophenotypes put forward by De Geus and Boomsma (2001).

(1) Endophenotypes must be reliable. This assumes that the endophenotype measure should represent either a reliable trait or state that is persistently and consistently a marker for the phenotype. If we use cognitive task performance or brain activation pattern as an endophenotype, there should be some indication from previous research that there is test–retest reliability for the measures used. Furthermore, the measures should be sufficiently sensitive to pick up individual differences at the endophenotype level of analyses and meaningfully relate to individual differences in the behavioural phenotype of interest (See criterion 3).

(2) Endophenotypes must ultimately show evidence of genetic influences (heritability).[2] This criterion relies on data from twin or adoption studies. For example, a comparison of identical twins who share 100% of their polymorphic genetic material, and fraternal twins who share, on average, 50% of their polymorphic genetic material in a maximum likelihood model-fitting framework will provide a heritability estimate of the endophenotype of choice. Ideally, reliability of a measure will have been established prior to estimating the heritability. Otherwise the relative importance of genes and environment becomes trickier to interpret.

(3) An endophenotype must be associated with the behaviour/psychopathology of interest. This demonstrates the validity of the endophenotype as a possible mediator of gene-behaviour relationships. Here, either a correlation between the endophenotype and the behaviour/symptom checklist measure, or a relationship between the endophenotype measure and psychopathology group membership, would be expected. In other words, the endophenotype should be plausible for the particular psychopathology in question. In addition, it has been proposed that a certain level of specificity between an endophenotype and a psychopathology would be expected (DeGeus and Boomsma 2001).

(4) The association between an endophenotype and behaviour must derive partly from shared genes. In other words, shared genes should be at least partially responsible for mediating the phenotypic association between the endophenotype measure and the behaviour/psychopathology of interest. If one wishes to understand gene-brain-cognition-behaviour pathways, it is important to establish that the effects of some of the genes involved will be retained from one level of analysis to the next. Note that it is possible for an endophenotype to be heritable *and* have a phenotypic relationship with a disorder, without this relationship being mediated by common genes.

(5) The association between an endophenotype and a particular behaviour must be theoretically meaningful (causality). Demonstration of causality is the biggest challenge of endophenotype research as it requires following up well-characterised longitudinal samples. Ideal demonstration of causality would involve taking an endophenotype measure at time-point 1 (T1), and demonstrating that it predates the emergence of pathological behaviour at time-point 2 (T2).[3] The source of the endophenotype effect should also be specified as closely as possible. For example, does a cognitive process that we measure at T1 require some developmental or maturational process in order to develop into a disorder at T2? Can we ascertain that the effect of such a developmental or maturational process

[2] Note that we accept that there may be pre-behavioural phenotypes that are not heritable. However, as our paper largely advocates increasing the understanding of gene-behaviour pathways, demonstrating the involvement of genetic influences is crucial.

[3] It is also reasonable to assume direction of causality from behaviour to endophenotype, especially in the context of developmentally changing constructs. However, this relationship would still be limited by the genetic background of the individual. The genetic background probably influences the range of behaviours and individual engages in. It also limits the range of possible endophenotypes and the developmental change that can result from behaviour-endophenotype interactions.

would occur only for those individuals with the predisposing endophenotype at T1? If longitudinal endophenotype-behaviour measurements took place in a genetically informative study design, such as a twin study, the overlap of genetic influences on the endophenotype measure at T1 with the behavioural outcome at T2 could be measured. Any other mediator data could also be incorporated in such a design that looks for common genetic effects across time.

If an endophenotype measure is reliably associated with a psychopathology, as described above, then this endophenotype can be investigated in relatives of the affected individual. Assuming the measures are sensitive, certain predisposing abnormalities could be detected at the endophenotype level even if ratings of behaviour/symptoms are not sensitive enough to pick up any psychopathology traits in the relatives of the affected individual. In this way, endophenotype measures could contribute to a sensitive measure of susceptibility to a particular psychopathology.

Endophenotypes in developmental psychopathology

In this section, we discuss possible endophenotypes in autism research. We have chosen autism because we wanted to highlight that, although it represents a significant public health and educational burden to society, and is highly heritable, the progress in validating the endophenotype steps for autism has been slow. Other developmental psychopathologies that are of equal interest in the context of endophenotypes include attention-deficit hyperactivity disorder (ADHD), dyslexia, conduct disorder, schizophrenia and specific language impairment. Endophenotype research is perhaps most advanced in ADHD (Kuntsi et al. 2005). However, in line with psychiatric genetics in general, in many cases the findings have not been reliably replicated (Asherson and IMAGE consortium 2004). Striving to define stringently different endophenotypes relevant to ADHD may yield power for replicating candidate gene associations specific to symptoms rather than the diagnostic category in general. This has already started to happen, with research into the cognitive or neural abnormalities associated with a particular symptom cluster, rather than ADHD as a diagnostic category (See Castellanos et al. 2006). Research on other psychopathologies, such as schizophrenia, is also beginning to focus on symptoms rather than diagnosis (c.f. Blakemore and Frith 2000).

As we discuss in the next section, the same symptom-based approach might apply to autism research. In fact there is recent evidence of genetic heterogeneity when it comes to different facets of the autistic symptom triad (Ronald et al. 2005). This suggests that at least partially distinct genetic effects on different endophenotypes within this psychopathology might be expected.

Developmental endophenotypes will aid in charting particular gene-brain/cognition-behaviour pathways. Endophenotype research may eventually help to refine diagnostic practice, which could come to rely on knowledge about specific gene-behaviour pathways. This type of research in the area of developmental psychopathology offers not only increased power to the investigation of genetic influences on behaviour by focusing on component processes that mediate behaviour, but also provides information about gene-brain/cognition-behaviour relationships that can be used to define subgroups within current diagnostic categories.

In the next section, we focus on how to measure endophenotypes in autism using cognitive and brain imaging methods. Our discussion selectively focuses on two of the potential endophenotypes associated with autism.

Endophenotypes for autism

Autism is a highly varied developmental psychopathology typically characterised by difficulties in communication and social interaction, and by restricted interests and inflexible behaviour. The signs and symptoms appear gradually, and can only be recognised from the second year of life at the earliest. Autism comes in many degrees, spanning a whole spectrum, and can occur with either low or high intelligence (Wing 1996).

Twin and family pedigree studies have provided evidence that there is a strong genetic predisposition to autism that may impact on brain development before birth (e.g. Ingram et al. 2000; Frith 2003). Although it is rare for families to have more than one child with an autistic psychopathology, the risk of a second child being affected by a form of autistic psychopathology has been estimated at 3% (for a review, see Rutter 2000; for a recent meta-analysis, see Wing and Potter 2002). This is much higher than the normal population risk of autism, recently estimated as 0.6% (Wing and Potter 2002; or higher according to a recent meta-analysis by Fombonne 2005). Twin studies have demonstrated a high heritability for autism spectrum disorders (ASD; around 90%; Bailey et al. 1995; Rutter 2000)

It is clear that genes play a critical role in the development of autism and the search for potentially predisposing genes has become a fast moving area of research. While certain genes (in particular on chromosomes 2, 7, 15, and 16) have been reported in more than one study of autism, the significance levels of the findings are low and there are many inconsistent results (see Lamb et al. 2000; 2002 for review). One reason for this may be the wide behavioural criteria that permit a diagnosis of autism. Trying to locate the genes underlying such a heterogeneous group of behaviours and severity is challenging, particularly as there may be considerable variability in the level of intelligence and general functioning of individuals with autism in a sample. Such variability may hamper the understanding of the gene-brain/cognition-behaviour pathway in autism. It is arguably more meaningful to look for genes that underlie a particular symptom, rather than the behavioural diagnosis of ''autism''.

Autism research: a symptom-based approach

Autism is now widely agreed to be a spectrum disorder, a heterogeneous diagnostic category, presenting a wide range of symptoms, and symptom severities (DSM-IV; APA 1994). In addition to autism, two distinct variants are listed under an ASD diagnosis in the DSM-IV: Asperger syndrome and pervasive developmental disorders not otherwise specified (PDDNOS). Individuals with Asperger syndrome exhibit many symptoms of autism, but lack the characteristic language delay. A diagnosis of PDDNOS serves as a catch-all category for any cases that cannot clearly be given another diagnosis (e.g. autism) but includes similar symptoms. This spectrum may extend beyond clinical diagnoses and could include normally functioning adults who possess traits associated with the autism spectrum (Baron-Cohen et al. 2001). The diversity of symptoms in ASD makes it unlikely that its pathophysiology can be accounted for by a single localised cognitive or brain dysfunction.

Each symptom may be associated with a different cognitive or brain abnormality. Studying groups of people defined by their ASD diagnosis may explain the inconsistent and equivocal results of cognitive and brain imaging studies on autism. It may be fruitful to examine symptom variability rather than ignore it. For example, it might be counter-productive to include someone with extreme repetitive behaviours and mild social impairments in the same group as someone else with severe social impairments and mild repetitive behaviours simply because they can both receive a diagnosis of ASD. Including such a heterogeneous sample in the ''clinical'' group will add noise to experimental data. In this case, investigating a cognitive model of reciprocal social interaction impairment, or restricted interests, may be more meaningful and carry more power than investigating only people who happen to have both symptoms. Of course, we have to be cautious of the possible circularity of defining a patient group by a cognitive impairment and using that impairment to explain the symptom. To avoid this, the symptom should be defined purely at the behavioural level (e.g. unintentional rudeness in autism), which can be explained by, but is not synonymous with, a cognitive model (impaired theory of mind; Frith 2003), or neural abnormality. The strategy of linking specific symptoms to specific cognitive or brain abnormalities has been attempted and is tending to yield fruitful results. Klin et al. (2002a, b), for example, recorded eye movements when subjects observed natural social scenes. They found that increased focus on mouths in the autism group predicted improved social adjustment and less social impairment, whereas more time spent looking at objects predicted the opposite relationship. Dapretto et al. (2006) found that activity in part of the brain's ''mirror system'' (the inferior frontal cortex) was significantly (inversely) correlated with reciprocal social interaction impairment in autism.

Here, we outline two neurocognitive models of autism: mind-blindness (an explanation of the social impairments) and weak central coherence (an explanation of the restricted interests).

Mentalising impairments in autism

The *mind-blindness* hypothesis proposes that the intuitive ability to understand that other people have minds (*mentalising*) is missing, or impaired, in autism (Baron-Cohen et al. 1985; Frith 2003). Mentalising (or theory of mind) is the ability implicitly and invariably to attribute mental states, such as intentions and beliefs, to others (Premack and Woodruff 1978). Normally developing children rapidly acquire the ability to mentalise and, by age five, have an understanding of complex social scenarios, such as beliefs, pretence and white lies (Wimmer and Perner 1983). Early work on the social impairments observed in children with autism focused on false belief, an understanding that people can hold beliefs that differ from reality (Wimmer and Perner 1983; Dennett 1987). Many children with autism are unable to understand that other people can have different beliefs from their own (Baron-Cohen et al. 1985; Yirmiya and Shulman

1996). In children with autism, social understanding and mentalising lags behind by about five years (Happé 1999).

However, some children and adults with a diagnosis of autism can pass not only basic false-belief tasks, but more complicated second-order false-belief tasks as well (Tager-Flusberg and Sullivan 1994). While mentalising impairment is an explanation of the social impairments in autism, the children and adults included in these studies had varying severity of social impairment. In other words, while they have a diagnosis of autism, they differ in terms of symptom severity. This will contribute to the variable and inconsistent results seen in mentalising research.

Neural basis of mentalising

Several neuroimaging experiments have revealed which brain regions are active when normal adults engage in mentalising. In non-autistic people, different tasks that involve inferring people's intentions, beliefs and desires activate three key regions of the brain: the medial prefrontal cortex (PFC), the superior temporal sulcus (STS) and the temporal poles adjacent to the amygdala (cf Frith and Frith 2003). The medial PFC is involved in monitoring internal mental states of both the self and other people (Frith 2006 ref). The STS is important for recognising and analysing people's movements and actions. The temporal pole is involved in understanding meaning and processing emotions. Their consistent activation in all sorts of mentalising tasks suggests that these three brain regions play key roles in mentalising.

In recent studies, able people with Asperger syndrome (at the high IQ end of the autism spectrum) have been scanned while they perform mentalising tasks. These studies have demonstrated that the three brain regions involved in mentalising are less active in people with Asperger syndrome when they perform the same mentalising tasks, and are more weakly connected (Castelli et al. 2002).

We have suggested that mentalising may be considered an endophenotype of the social impairments in autism. We will now evaluate mentalising against the criteria outlined above.

Reliability

There is some evidence for good test–retest reliability of mentalising task performance (Hughes et al. 2000). No adequate tests of sensitivity of mentalising measures have been performed, but there is some evidence that the extent of mentalising problems relate to the extent of autism symptoms, and that mentalising tasks show a good range of scores (Joseph and Tager-Flusberg 2004; A. Ronald et al. Submitted). The test–retest reliability or sensitivity of the brain imaging measures are not yet known.

Heritability

When investigating heritability, the developmental aspects of the endophenotypes under study must be considered. To emphasise this point, only two twin studies to date have employed experimental assessment of mentalising ability and found evidence of no or little heritability (Hughes et al. 2005; Ronald et al. 2006). However, in both studies the children were assessed after the age of four when most would have already been able to perform simple mentalising tasks. Little variation would be expected in the core component of mentalising in this age group and, as a consequence, the heritability/environmental estimates would reflect other abilities required for this task and which vary between individuals. To determine heritability of mentalising performance as it relates to autism, it may be crucial to investigate mentalising at a time point where developmental transition is likely to occur with regard to this ability (between three and four years of age; Wimmer and Perner 1983). This is when individual differences in mentalising performance might reflect individual differences in the timing of genetic effects that relate to mentalising ability "switching on".

Association with the behaviour/psychopathology of interest

Several studies have replicated the finding of mentalising deficit in autism. Joseph and Tager-Flusberg (2004) demonstrated that among children with autism, performance in a battery of mentalising tasks was related to communicative impairment in autism, even after cognitive and language ability was controlled for. On the other hand, when language ability was controlled for, mentalising performance was not significantly correlated with reciprocal social interaction impairment. A modest correlation was recently found between experimental assessment of mentalising ability and parental ratings of autism trait scores in the general population, even after verbal ability was controlled for (Ronald et al. 2005). In addition, several studies indicate that poor mentalising performance shows a strong relationship with autism diagnosis.

Genetic correlation

No studies to date exist investigating genetic mediation of the phenotypic relationship between autism and mentalising.

Causality

To date no genetically informative, longitudinal studies investigating early mentalising performance and later autism diagnosis exist.

Weak central coherence in autism

While having poor social skills, people with autism sometimes have talents in other areas. The mentalising impairment does not explain these so-called savant skills, such as a photographic memory, extraordinary memory for numbers and dates or perfect pitch. Instead, it has been proposed that weak central coherence might explain these talents. Central coherence describes the degree to which component parts are perceived as a whole and stimuli are processed within their context. It is proposed that there is a normal distribution of central coherence (Happé 1999; Happe and Frith 2006). Some people have strong central coherence (poor memory for detail, good gist recall, difficulty in perceiving component parts) and some people have weak central coherence (good memory for detail, poor gist recall, difficulty seeing the wood for the trees), but the majority of people have medium central coherence. The terms strong and weak central coherence map closely onto the terms field independence and dependence. The theory of weak central coherence in autism suggests that there is a bias towards feature processing, and an inability to take into account context or overall meaning (Happé 1999; Frith 2003). We now consider whether weak central coherence holds up against the criteria for endophenotypes outlined earlier:

Reliability

There is some evidence for good test–retest reliability of central coherence tasks (Rhonda Booth, personal communication). No adequate sensitivity data of central coherence tasks exist. The test–retest reliability and sensitivity of the brain imaging probes is not yet known.

Heritability

Although heritability research is still ongoing for central coherence, some recent data indicates familial origin of this endophenotype. A recent study assessed central coherence in the first-degree relatives of children with autism (Briskman et al. 2001; Happé et al. 2001). In 47 families with a son with ASD, dyslexia or typical development, a cognitive phenotype (endophenotype) was established for characterising 'affected' individuals in future molecular genetic findings. Approximately half the fathers and a third of the mothers of children with ASD in this sample showed consistent detail-focus (weak central coherence), typically resulting in superior performance on tasks that involve detecting or remembering details. Results from experimental tasks and questionnaire ratings of everyday life preferences and abilities converged. This demonstrated the potential usefulness of a cognitive approach to the broader autism phenotype, and opened the way for possible exploration of the genetic predisposition, not for autism per se, but for dissociable aspects of autism such as weak coherence. The resulting measures have already been taken up for ongoing molecular genetic and imaging studies of relatives of individuals with ASD (Lamb et al. 2002).

Association with the behaviour/psychopathology of interest

Several studies have replicated the finding of weak central coherence in autism indicating validity of this construct (Joliffe and Baron-Cohen 1999; Pellicano et al. 2006; but see Burnette et al. 2005; Lopez and Leekam 2003 for equivocal results).

Genetic correlation

No studies to date exist investigating genetic mediation of the phenotypic relationship between autism and central coherence.

Causality

To date no genetically informative, longitudinal studies investigating early weak central coherence and later autism diagnosis exist.

Considerations for the future of the endophenotype approach in developmental psychopathology

At this point it becomes important to highlight possible lack of one-to-one mapping between levels of analyses. As any endophenotype is a result of genetic and environmental input, it follows that a continuum of genetic risk is not necessarily yoked seamlessly to a

continuum of risk in other levels of analysis. The continuum of genetic risk is no doubt correlated with the continuum of risk in some other, prebehavioural (endophenotype), level that relies on genetic input – but the strength of this correlation may vary considerably depending on the chosen endophenotype.

An endophenotype may only be a valid marker for a psychopathology once a certain threshold has been exceeded. In other words, the concept of endophenotypes might be particularly useful for psychopathologies where certain dysfunctional brain or cognitive processes, for example, become a limiting factor on performance, and where the phenotype can also be ascertained confidently given the severity of behavioural markers. In this case, the endophenotype-behavioural phenotype association may only manifest itself at the severe levels of both endophenotype and behavioural phenotype. A related point concerns the developmental genetic effects that may severely restrict or prohibit development of full cognitive capabilities (e.g. possibly the case of mentalising and autism). In this case the ''machinery'' used by normal population to perform the endophenotype task, after reaching a developmental milestone, would be vastly different from that used by people with autism, who failed to reach that milestone. Thus, any heritability estimate gauged from a population sample regarding that endophenotype, measured after a developmentally sensitive period, would have to be interpreted with caution. A complementary approach should involve studies combining candidate gene and endophenotype measurement (as exemplified by Ohnishi et al. 2006). As a case in point, when we look at very able individuals with autism and controls performing a brain imaging task, we can see that the two groups employ different areas of the cortex to process the same information (e.g. Castelli et al. 2002; Williams et al. 2006). The pattern of brain activation in individuals with autism could be thought of as a compensatory route to equivalent task performance, necessitated by an earlier, genetically influenced, developmental anomaly.

Using behavioural rating scales alone to select individuals with an endophenotype carries a certain level of circularity. If we can successfully use behavioural criteria to sub-type individuals, are endophenotype measures really necessary? Sub-typing at the behavioural level can be useful, but such sub-types may still be comprised of heterogeneous groups of individuals. Endophenotypes can be informative in defining homogeneous subgroups within symptom criteria. In addition, endophenotype measures allow the investigation of family members with possibly no overt signs of the psychopathology, and for whom behaviour ratings would thus be less informative. In this case the endophenotype would have been validated on individuals with a psychopathology and will not necessarily be associated with overt behavioural signs in the family members.

A final consideration is that we know very little about what happens to endophenotypes during development. Do they look the same across development or is there considerable change in what is a sensitive endophenotype index at different points in development? For example, simple, first-order theory of mind task may be adequate for assessing mentalising difficulties in young children with autism. More complex mentalising tasks, those including assessment of 'faux pas' or second-order theory of mind, for instance, may be required to index mentalising difficulties in adolescents or adults with autism. Investigating these developmental issues will be a challenge for endophenotype research and well-planned longitudinal research will be crucial to resolve these issues.

Conclusion

In summary, endophenotype research for developmental psychopathologies is still at early stages. This approach holds considerable promise for the study of gene-brain/cognition-behaviour pathways, particularly when conducted within longitudinal framework. It may also serve to clarify some tentative gene-phenotype associations by parcelling heterogeneous disorders into subtypes sharing endophenotype features. However, much work remains to be done validating the endophenotype measures. In addition, the changing nature of any developmental psychopathology poses particular challenge for endophenotype research.

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