Using endophenotypes to examine molecules related to candidate genes as novel therapeutics: the “Endophenotype-associated surrogate endpoint (EASE)” concept

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Abstract

In this article, a new concept of an “endophenotype-associated surrogate endpoint (EASE)” is proposed. To examine effect of a novel therapeutic molecule on a target phenotype of a genotype associated with the molecule, state-dependent aspect of an endophenotype can be used as a surrogate endpoint. Desired characteristics for EASE are 1) a close relationship to the endophenotype associated with therapeutics, 2) longitudinal changes in illness severity, while the original “endophenotype” is primarily state independent, 3) a physical sign or laboratory measurement that occurs in association with a pathological process and has putative diagnostic and/or prognostic utility, and 4) serves as a substitute for a clinically meaningful endpoint. Advantages are expected for both surrogate endpoints in drug development and endophenotypes in uncovering pathogenesis. EASE are closer to molecules than clinically meaningful endpoints and can respond to administration of the molecule in a more direct manner. Therefore, a statistically significant effect is likely to be observed in clinical trials with smaller sample sizes and shorter durations. As with endophenotypes, reduced heterogeneity might be expected especially in heterogeneous syndromes such as psychiatric disorders. Potential interactions (e.g., elucidating biological mechanisms underlying novel treatments) can be further expected. (193 words)

Keywords: Autism spectrum disorder; Dopamine; Neuroimaging; Obsessive-compulsive disorder; Oxytocin; Schizophrenia; Serotonin

Introduction

Highly prevalent and currently untreatable disease symptoms, such as negative symptoms in schizophrenia or socio-communicational deficits in autism spectrum disorder (ASD), are considered to be huge unmet medical needs that lead to a heavy burden on people with the disorders, their families, and society as a whole. Clinical research should essentially be aimed at satisfying these unmet needs, regardless of using a direct or indirect approach. However, although research in this field is increasing, the research findings accumulating do not necessarily contribute to satisfying these unmet needs.

The multifactorial and polygenic genetic origin of psychiatric disorders complicates attempts to uncover the neurobiological mechanisms and develop novel effective treatments for the symptoms. These disorders, clinically defined as syndromes based on phenotypes at the behavioral level, are biologically heterogeneous. To resolve this issue, endophenotypes are used in clinical research with expectation reducing heterogeneity in these clinically defined syndromes, although the notion has recently been criticized (Flint et al., 2014). The term “endophenotype” was provided by John and Lewis in 1965, and further developed in psychiatry by Gottesman and Shields in 1973. Endophenotypes were originally defined as measurable components unseen by the unaided eye along the pathway between disease and distal genotype. Gottesman and Gould (2003) stated that “Endophenotypes for psychiatric disorders must meet certain criteria, including association with a candidate gene or gene region, heritability that is inferred from relative risk for the disorder in relatives, and disease association parameters.” Their criteria for an endophenotype were:

1. The endophenotype is associated with illness in the population.

2. The endophenotype is heritable.
3. The endophenotype is primarily state independent (manifests in an individual whether or not illness is active).
4. Within families, the endophenotype and illness co-segregate.
5. The endophenotype found in affected family members are found in nonaffected family members at a higher rate than in the general population.

In addition to heterogeneity in the pathogenesis of disorders, lack of objective and quantitative assessment of symptoms makes it difficult to sensitively and appropriately identify the effect of new therapeutic candidates, and impedes development of new therapeutics. Ellenberg and Hamilton (1989) wrote that “investigators use surrogate endpoints when the endpoint of interest is too difficult and/or expensive to measure routinely and when they can define some other, more readily measurable, endpoint, which is sufficiently well correlated with the first to justify its use as a substitute.” Originally, “surrogate endpoint” was proposed as a substitute concept for a clinically meaningful ‘true’ endpoint. Wittes, Lakatos, and Probstfield (1989) simply defined a surrogate endpoint as “an endpoint measured *in lieu* of some other so-called “true” endpoint.” Hillis and Seigel (1989) defined a surrogate observation as “an observed variable that relates in some way to the variable of primary interest, which we cannot conveniently observe directly”. Advantages of surrogate outcomes over final outcomes are that they may occur more rapidly and are easier to assess, thereby shortening the duration, size, and cost of trials. Sometimes biomarkers are used as surrogate endpoints, namely “surrogate endpoint biomarkers” (Dunn and Akpa, 2012; Fleming and Powers, 2012).

In this review, I conceptualize and discuss “endophenotype-associated surro-

gate endpoints (EASE)” to resolve the above mentioned issues efficiently and simultaneously by combining “endophenotype” and “surrogate endpoint”.

Concept of EASE

It is reasonably expected that the state-dependent aspect of an endophenotype can be used as a surrogate endpoint for assessing the effect of a molecule associated with a genotype on a target phenotype. Individual differences in the regional brain volume of certain brain regions is trait rather than state dependent. However, functional brain measurement of the same brain region is likely to reflect state aspects of the disease process as well, therefore the measurement may be associated with a heritable trait marker overlapped with endophenotypic brain volume. In such case, while the functional measurements of brain region are associated with the endophenotype, the measurements can also have a role as surrogate endpoint to reflect time-course change in disease process substitute for clinically meaningful true endpoint. In the next section, several examples from previous studies are discussed.

Examining the effect of oxytocin administration on social behavior using limbic and paralimbic brain regions associated with the oxytocin receptor genotype at the structural level (Figure 1)

ASD is a prevalent and highly heritable neurodevelopmental disorder. Although a number of studies have investigated ASD pathogenesis, its etiology remains unclear. Previous studies have identified significant association between ASD and oxytocin-related genes, such as the oxytocin receptor gene (*OXTR*) (reviewed in (Yamasue 2012; LoParo and Waldman, 2015). Studies have shown that in typically developed individuals, *OXTR*

is associated with individual differences in function and structure of limbic and paralimbic brain regions including the amygdala, medial prefrontal cortex (mPFC), and insula (Inoue et al., 2010; Tost et al., 2010; 2011; Furman et al., 2011; Yamasue et al., 2011; Saito et al., 2013). Therefore, the structure and function of these brain regions can be considered an endophenotype between oxytocin-related genes and social behavior and its pathological deviations such as ASD.

Efficient pharmacological treatment for core ASD symptoms has not yet been developed. Recent studies show the therapeutic effect of oxytocin on social communication and interaction deficits in ASD, through improvement of emotion recognition using direct emotional cues such as facial expression and voice prosody (Hollander et al., 2003; 2007; Guastella et al., 2010; Andari et al., 2010; Domes et al., 2013; Gordon et al., 2013). In my own research group, we have used limbic and paralimbic brain region function as a surrogate endpoint for the effect of exogenous oxytocin administration in subjects with ASD (Watanabe et al., 2014; Aoki et al., 2014; Aoki et al., 2015; Aoki and Yamasue, 2015). In addition, in typically developed people, a number of studies have consistently reported that intranasal oxytocin administration modulates social cognition and function of limbic and paralimbic brain structures (reviewed in Yamasue et al., 2012; van Ijzendoorn and Bakermans-Kranenburg, 2012; Veening and Olivier, 2013; Shahrestani et al., 2013; Bethlehem et al., 2013).

Sociocommunicational deficits make understanding communication content with conflicting verbal and nonverbal information such as humor or irony difficult for individuals with ASD. To directly determine if oxytocin has a beneficial effect on these sociocommunicational deficits, my own research group at The University of Tokyo Hospital, conducted a randomized, double-blind, placebo-controlled, within-subject–

crossover, single-site experimental trial with both behavioral and neural measures after administration of intranasal single-dose oxytocin (24 IU) and placebo. In total, 40 highly functioning men with ASD participated in the trial. Using functional magnetic resonance imaging (fMRI), we examined the effect of oxytocin on participants' behavioral and neural responses during a social psychological task (Watanabe et al., 2013). In our previous case-control study using the same psychological task, when making decisions about social information with conflicting verbal and nonverbal content, participants with ASD made judgments based on nonverbal content less frequently and with longer reaction times, and did not sufficiently activate the mPFC (Watanabe et al., 2012). Therefore, our main outcomes and measures reflect the frequency of nonverbal information-based judgments (NVJs), response time for NVJs, and mPFC brain activity during NVJs. Intranasal oxytocin enabled participants to make more frequent NVJs with shorter response times. During the mitigated behavior, oxytocin increased the originally diminished brain activity of the mPFC. Moreover, oxytocin enhanced functional coordination in the mPFC, and the magnitude of these neural effects was predictive of the behavioral effect. These findings provide neurobiological evidence for the beneficial effect of oxytocin on sociocommunicational deficits in ASD, and provide an initial account of the neurobiological mechanisms underlying the beneficial effects of the neuropeptide (Watanabe et al., 2014).

As described above, oxytocin mitigates autistic behavioral deficits by restoring mPFC activity, demonstrated using fMRI during the sociocommunication task. However, it is not known if oxytocin exhibits effects at the neuronal level, which was outside the focus of the specific task examined. Nevertheless, in the same clinical trial, N-acetylaspartate (NAA) levels, a marker for neuronal energy demand (Aoki et al.,

2012), were measured in the mPFC using ^1H -magnetic resonance spectroscopy (^1H -MRS). Here, oxytocin-induced changes in NAA levels were associated with mPFC changes in the fMRI signal. Furthermore, path analysis found that NAA changes in the mPFC trigger increases in task-dependent fMRI signal in the mPFC, which consequently leads to improvements in sociocommunication difficulties associated with ASD. This suggests that the beneficial effects of oxytocin are not limited to the autistic behavior elicited by our psychological task, but may be generalized to other autistic behavioral problems associated with the mPFC (Aoki et al., 2015).

Difficulty in understanding others' social emotions and beliefs in conditions without direct emotional cues also plays an important role in ASD. Thus, we sequentially performed both a case-control study and a clinical trial to investigate the potential effects of oxytocin on this deficit at the behavioral and neural level, measured using fMRI during a psychological task. This task was modified from the Sally-Anne Task, a well-known first-order false-belief task. The task was optimized for investigation of abilities to distinctly infer another person's social emotions and beliefs, so as to test the hypothesis that oxytocin improves deficits in inferring social emotions rather than beliefs under conditions without direct emotional cues. In the case-control study, 17 high-functioning men with ASD showed significant behavioral deficits in inferring social emotions but not beliefs compared with 17 typically developed, demographically matched male participants. They also showed significantly less activity in the right anterior insula and posterior superior temporal sulcus when inferring social emotions, and in the dorsomedial PFC when inferring beliefs. Next, to investigate the potential effect of oxytocin on these behavioral and neural deficits, we performed a double-blind, placebo-controlled, crossover within-subject trial using a single dose of intranasal 24 IU oxyto-

cin in an independent group of 20 ASD male patients. Behaviorally, oxytocin significantly increased the correct rate for inferring social emotions. At the neural level, the peptide significantly enhanced the originally diminished brain activity in the right anterior insula when inferring social emotions, but not in the dorsomedial PFC when inferring beliefs (Aoki et al., 2014).

Although a limited number of pioneering studies have attempted to identify associations between oxytocin related genes such as *OXTR* and *CD38*, and function of limbic brain regions in TD subjects (Sauer et al., 2012; 2013; Montag et al., 2013), further research examining the association between oxytocin-induced changes in these surrogate endpoints and oxytocin-related genes is needed in clinical trials of ASD subjects. Nevertheless, the above summarized studies support the view that function and structure in limbic and paralimbic brain regions are associated with oxytocin-related genes as well as with response to oxytocin administration. These indices, which were measurable in experimental setting, were surrogate endpoints in lieu of clinically meaningful endpoint such as ASD core symptoms evaluated in real-life social situations. Therefore, these neuroimaging indices can be considered examples of EASE to detect the effect of oxytocin administration.

Examining the potential effect of the COMT inhibitor tolcapone or a dopamine antagonist on dopamine-associated clinical symptoms associated with the COMT genotype using working memory performance, prepulse inhibition, and prefrontal activity

Studies of dopaminergic transmission provide another good example for EASE. The brain dopaminergic system is implicated in the pathophysiology of neuropsychiatric

disorders such as schizophrenia and Parkinson disease. Catechol O-methyltransferase (COMT) is associated with dopamine inactivation and is related to several neuropsychiatric disorders.

Weinberger and his co-researchers suggested that deficits in working memory and PFC function are important outcome measures in schizophrenia, and both are associated with dopamine dysregulation and a *COMT* gene functional polymorphism (Val108/158Met) (Bertolino et al., 2004). To examine the effect of the *COMT* genotype on symptom variation, working memory performance, and PFC physiology, response to an atypical antipsychotic drug was examined in patients with schizophrenia. Thirty patients with acute unmedicated schizophrenia were clinically evaluated using the Positive and Negative Syndrome Scale, then genotyped for the *COMT* Val/Met polymorphism, and underwent 8 weeks of treatment with olanzapine, an atypical antipsychotic drug. Twenty patients completed fMRI scans during n-back working memory tasks, twice at 4 and 8 weeks. They found a significant interaction between the *COMT* genotype and olanzapine effect on PFC function. Met allele load predicted an improvement in negative symptoms, working memory performance, and prefrontal physiology after 8 weeks of treatment. These results suggest that a genetically determined variation in PFC dopamine catabolism impacts upon the therapeutic profile of olanzapine, and can be considered an endophenotypic surrogate endpoint of antipsychotic effects.

Roussos and colleagues examined the interaction between the *COMT* rs4818 C/G polymorphism and effect of the COMT inhibitor, tolcapone, on working memory and prepulse inhibition (PPI) (Roussos et al., 2009). Thirteen healthy G/G male individuals (low PFC dopamine) and 12 C/C male individuals (high PFC dopamine), entered and completed the study. Subjects participated in two weekly sessions associated

with either acute oral tolcapone (200 mg) or placebo, according to a counter-balanced, crossover, double-blind design. PPI was assessed with 5 and 15 dB above background prepulses at 30-, 60-, and 120-ms intervals. Subjective mood and working memory performance (n-back and letter-number sequencing) were also assessed. In the placebo condition, lower PPI and slower n-back reaction times were detected in the G/G group compared with the C/C group. Tolcapone increased PPI and improved performance in both working memory tasks in the G/G group only. Baseline startle was greater in the C/C group, and not affected by tolcapone. The mood profile was worse in the C/C group, and tended to deteriorate with tolcapone. Val158Met status alone cannot explain these results. PPI and working memory may both relate to PFC dopamine levels according to an inverted U-shaped curve function. Tolcapone may potentially be useful in the treatment of conditions with deficient sensorimotor gating and working memory (such as schizophrenia and prodromal states), but only in a genotype-specific manner.

The same research group also examined the interaction between the *COMT* Met158Met polymorphism and effect of tolcapone on working memory and PPI (Giakoumaki et al., 2008). Tolcapone (200 mg) was administered in two weekly sessions according to a counter-balanced, crossover, double-blind, placebo-controlled design in 12 Val/Val and 11 Met/Met healthy male individuals. In the placebo condition, PPI was lower in the Val/Val group compared with the Met/Met group. Tolcapone increased PPI significantly in the Val/Val group, and tended to have the opposite effect in the Met/Met group. Baseline startle was not affected by tolcapone in the Val/Val group but was slightly increased in the Met/Met group. Tolcapone improved working memory performance (n-back and letter-number sequencing) in only the Val/Val group. These results suggest that early information processing indexed by PPI and working memory

may both depend on PFC dopamine signaling and relate to PFC dopamine levels according to an inverted U-shaped curve function.

Farrell and colleagues (2012) reported their results of a randomized double-blind trial examining the effect of tolcapone on working memory and its neural correlates, by testing the interaction between the *COMT* genotype and pharmacological response. In a randomized, double-blind, between-subjects design, a single dose of tolcapone (200 mg) or placebo was administered to 34 men with the *COMT* Met158Met genotype and 33 men with *COMT* Val158Val. Participants completed the n-back working memory task and a gambling task. In the placebo group, Met/Met subjects performed better than Val/Val subjects on the n-back working memory task, and were more risk averse. Tolcapone had opposite effects in both genotype groups, worsening n-back performance in Met/Met subjects and enhancing it in Val/Val subjects. Tolcapone caused Met/Met subjects to be less risk averse, and Val/Val subjects more so. Thus, tolcapone reversed baseline genotype differences in both tasks. As the authors noted, the data clearly demonstrate that the direction of a drug's effect can be influenced by a polymorphism in its target gene. These results can be interpreted as further support for the inverted-U model of dopamine function.

In a double-blind crossover study, Ashare and colleagues performed 8 days of treatment with tolcapone and a placebo in 20 smokers (Ashare et al., 2013). In both medication periods, smokers completed fMRI scans during the n-back task after 24 h of abstinence. Smokers were genotyped prospectively for the *COMT* Val158Met polymorphism. Compared with placebo, tolcapone modestly improved accuracy and enhanced suppression of activation in the ventral mPFC. There were no medication effects in other *a priori* regions of interest (dorsolateral PFC, dorsal cingulate/medial prefrontal cor-

tex, or posterior cingulate cortex). They further suggested that tolcapone leads to decreased fMRI signal in several brain regions of smokers with Val/Val genotypes, but increased or remained unchanged among Met allele carriers. Tolcapone did not attenuate craving, mood, or withdrawal symptoms compared with placebo.

Although the tolcapone studies described above were performed in non-clinical populations, the findings have translational relevance because COMT inhibitors are used in adjunct treatment of Parkinson's disease, and are under evaluation in schizophrenia and other disorders (Marsala et al., 2012). Previous literature has supported a role for dopaminergic system brain function as a surrogate endpoint to evaluate the effect of dopaminergic drugs such as COMT inhibitors and dopamine antagonists. These measurements are substitute for clinical symptom measurements. Neuroimaging indices in dopaminergic systems show association with the *COMT* gene, therefore these indices can be considered good examples of EASE.

Striatum function and morphology to assess the effect of a selective serotonin reuptake inhibitor in obsessive-compulsive symptoms

Obsessive-compulsive disorder (OCD) is characterized by unwanted repetitive thoughts and behaviors. OCD occurs in 1–3% of the general population, and its often rather early onset causes major disabilities in the everyday lives of patients. Although heritability of OCD is between 35 and 65%, many linkage, association, and genome-wide association studies have failed to identify single genes that exhibit high effect sizes (Pauls et al., 2014). Several neuroimaging studies have identified structural and functional alterations, mainly in cortico-striato-thalamic loops, as intermediate OCD phenotypes (Nakao et al., 2014). However, there is also marked heterogeneity between studies. These in-

consistencies in genetic and neuroimaging studies may be because of the heterogeneous and complex phenotype of OCD. Considering that genetic variants may also influence neuroimaging in OCD, researchers have started to combine both domains in the field of imaging genetics.

A recent systematic review of genetic imaging in OCD and related disorders identified eight publications, which was extended to 43 by inclusion of related disorders (Grunblatt et al., 2014). The most promising findings point to involvement of gene variants in the serotonergic (*5-HTTLPR*, *HTR2A*), dopaminergic (*COMT*, *DAT*), and glutamatergic (*SLC1A1*, *SAPAP*) systems within cortico-striato-thalamic loops. However, the review emphasized that the field of imaging genetics in OCD must be further explored, best through investigations combining multimodal imaging techniques with genetic profiling, particularly profiling techniques that employ polygenetic approaches with much larger sample sizes.

As a recent example, the effect of selective serotonin reuptake inhibitors (SSRI), a first-line treatment for OCD, on the whole-brain functional network was reported (Shin et al., 2014). Resting-state fMRI was performed on 25 drug-free OCD patients. After 16 weeks, 17 patients receiving SSRI treatment were rescanned. In addition, 23 matched healthy controls were examined at baseline, with 21 rescanned after 16 weeks. Topological properties of brain networks were analyzed cross-sectionally and longitudinally using a graph-theory approach. At baseline, relative to healthy controls, OCD patients showed decreased small-world efficiency (including local clustering coefficients, local efficiency, and small worldness) and functional association between default-mode and frontoparietal modules, as well as widespread altered connectivity degrees in many brain areas. They observed clinical improvement in OCD patients after

16 weeks of SSRI administration, which was accompanied by significantly elevated small-world efficiency, modular organization, and connectivity degree. Improvement in OCD symptoms was significantly correlated with changes in connectivity degree in the right ventral PFC after treatment. These findings suggest that OCD phenomenology may be the outcome of a disrupted optimal balance in brain networks, and reinstating this balance with SSRI treatment is accompanied by significant improvement in symptoms.

Hoexter *et al.* (2012) sought to document structural brain abnormalities in treatment-naïve OCD patients, and determined the effect of SSRI and cognitive-behavioral therapy (CBT) on regional brain volumes. Thirty-eight treatment-naïve OCD patients underwent structural MRI before and after a 12-week randomized clinical trial with either SSRIs or group CBT. Thirty-six matched healthy controls were also scanned at baseline. Voxel-based morphometry was used to compare regional gray matter volume in regions of interest in the orbitofrontal, anterior cingulate, and temporolimbic cortices, striatum, and thalamus. Treatment-naïve OCD patients had smaller gray matter volumes in the left putamen, bilateral medial orbitofrontal, and left anterior cingulate cortices than controls at baseline. After treatment with either SSRI or CBT ($n = 26$), gray matter volume abnormalities in the left putamen were no longer detectable relative to baseline controls. Within-group comparisons found that gray matter volume in the left putamen significantly increased in 13 SSRI-treated patients, whereas no significant changes were observed in 13 CBT-treated patients. This supports involvement of the orbitofronto/cingulo-striatal loops in OCD pathophysiology, and suggests that SSRI and CBT may have distinct neurobiological mechanisms of action.

Several ^1H -MRS studies have investigated brain metabolic abnormalities in

OCD patients, and also metabolic changes after treatment. One study examined potential alterations in neurometabolites in a group of drug-naïve children and adolescents with OCD using *in vivo* ^1H -MRS to identify treatment effects on metabolite levels (Lazaro et al., 2012). Overall, 11 OCD children and adolescents and 12 healthy subjects of similar age, sex, and estimated intellectual quotient were studied. They placed three voxels, one bilaterally located (involving the anterior cingulate-medial frontal region) and one in each striatal region (involving the caudate and putamen regions). Concentrations of creatine (Cr), myo-inositol, total choline-containing compounds (Cho) (glycerophosphocholine + phosphocholine), NAA, and glutamate + glutamine were calculated. They found significantly lower total Cho concentrations in the left striatum in OCD patients compared with healthy subjects. This difference in left striatal Cho concentration did not change over time and persisted at follow-up assessment. Similar to controls, OCD patients undergoing pharmacological treatment and clinical recovery showed no significant changes in neurometabolic activity between the first and second evaluations.

Another ^1H -MRS study also investigated the SSRI effects on neurochemical levels in OCD patients (Tukel et al., 2014). Ratios of metabolite levels in three brain regions were compared between 19 unmedicated OCD patients (including 10 drug-naïve), at baseline and following 12 weeks of SSRI treatment, and 19 healthy control subjects. NAA/Cr levels were significantly lower in OCD patients at baseline than in healthy controls in the anterior cingulate and caudate. Conversely, no significant NAA/Cr differences were detected in the anterior cingulate, caudate, or putamen between OCD patients after 12 weeks of SSRI treatment and healthy controls. NAA/Cr levels were significantly higher in OCD patients after 12 weeks of SSRI treatment compared with those at baseline in the anterior cingulate and caudate. These results suggest

that NAA reductions can be reversed with SSRI treatment, which may indicate an improvement in neuronal integrity.

As overviewed above, previous studies support the notion that brain function and structure in serotonergic brain system in cortico-striato-thalamic loops can be used as an EASE to assess the effect of SSRIs in OCD patients.

Desired characteristics for EASE (Figure 2)

Taking together with the above-mentioned concepts and previous examples, the desired characteristics for EASE can be summarized as follows:

1. EASE has a close relationship with endophenotypes related to target therapeutic molecules.
2. EASE reflect longitudinal changes in illness severity, while endophenotypes are primarily state independent.
3. EASE are a physical sign or laboratory measurement that occur in association with a pathological process, and have putative diagnostic and/or prognostic utility.
4. EASE are intended to serve as a substitute for a clinically meaningful endpoint, and expected to predict the effect of a therapeutic intervention.

Conclusion: Advantage of EASE in clinical research

With successful examples of EASE, advantages are expected in both surrogate endpoints for drug development and endophenotypes for uncovering disease pathogenesis and their interactions.

It is reasonably expected that a surrogate marker, which is closer to the mo-

molecular level than a clinically meaningful endpoint, can be altered by administration of the molecule in a more direct manner. Therefore, with smaller sample sizes and shorter durations, statistically significant effects can be expected with surrogate endpoints of larger effect sizes. Indeed, the sample sizes in the discussed examples are relatively small ($n < 70$). Advantages resulting from a pharmacogenetic trait are further anticipated, because previous studies have shown larger effect sizes for single nucleotide polymorphisms on individual differences in responsiveness to a certain drug in patients with a disease, than on disease diagnosis (Cirulli and Goldstein, 2010).

Furthermore, EASE are expected to reduce heterogeneity and approach the neurobiological mechanisms underlying the effect of a candidate treatment, similar to the original endophenotype. As an interaction between surrogate endpoint and endophenotype advantages is also expected, developing new treatments that directly address target symptom etiology will be promoted. Successful findings revealed by EASE clearly support a direct link between clinical symptoms and candidate genotypes.

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Figure legends

Figure 1. An example of an endophenotype-associated surrogate endpoint (EASE): using medial prefrontal cortex function to examine the effect of intranasal oxytocin on autistic social behavior

Intranasal administration of oxytocin improves autistic social behavior and underlying brain function (Watanabe et al., 2014; Aoki et al., 2014a). Brain regions with recovered activity following intranasal oxytocin show significant association with oxytocin receptor genotypes in previous studies (Inoue et al., 2010; Tost et al., 2010; Yamasue et al., 2011; Furman et al., 2011).

Figure 2. Multimodal MRI as an endophenotype-associated surrogate endpoint (EASE) to assess candidate therapeutics on behavioral phenotypes of associated genes

Individual differences in genetically determined factors related to target molecules (e.g., SNPs) shape individual differences at the neural level (e.g., brain region function). Individual differences in brain functions may generate behavioral characteristics ranging from normal to extreme, and include various behavioral traits, personality, and clinical symptoms. It is expected that the therapeutic effect of exogenous target molecules or agonists will improve behavioral and neural phenotypes of related genes. In such models, part of the endophenotype (e.g., brain function) plays a role as a surrogate endpoint of target molecule administration, and can be considered an “endophenotype-associated surrogate endpoint (EASE)”.

Figure 1

Administration of oxytocin or placebo

40 min

Friend/foe
judgment task

MRI Scanning

Time

Oxytocin induced recovery
of non-verbal
communication use

Frequency of Judging other's
hostility based on non-verbal
communication cue

Oxytocin induced recovery of
non-verbal information based
judgment specific activity

From JAMA Psychiatry 2014 & Molecular Psychiatry 2014

Figure 2