Review

Convergent Functional Genomics approach to prioritize molecular targets of risk in early life stress-related psychiatric disorders

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ABSTRACT

There is an overwhelming evidence proving that mental disorders are not the product of a single risk factor – i.e. genetic variants or environmental factors, including exposure to maternal perinatal mental health problems or childhood adverse events - rather the product of a trajectory of cumulative and multifactorial insults occurring during development, such as exposures during the foetal life to adverse mental condition in the mother, or exposures to adverse traumatic events during childhood or adolescence.

In this review, we aim to highlight the potential utility of a Convergent Functional Genomics (CFG) approach to clarify the complex brain-relevant molecular mechanisms and alterations induced by early life stress (ELS). We describe different studies based on CFG in psychiatry and neuroscience, and we show how this 'hypothesis-free' tool can prioritize a stringent number of genes modulated by ELS, that can be tested as potential candidates for Gene x Environment (GxE) interaction studies.

We discuss the results obtained by using a CFG approach identifying *FoxO1* as a gene where genetic variability can mediate the effect of an adverse environment on the development of depression. Moreover, we also demonstrate that *FoxO1* has a functional relevance in stress-induced reduction of neurogenesis, and can be a potential target for the prevention or treatment of stress-related psychiatric disorders.

Overall, we suggest that CFG approach could include trans-species and tissues data integration and we also propose the application of CFG to examine in depth and to prioritize top candidate genes that are affected by ELS across lifespan and generations.

1. Stress-related psychiatric disorders

Stress-related psychiatric disorders are multifactorial diseases characterized by an atypical response to short or long-term physical, mental, or emotional stress (Slavich and Irwin, 2014). Despite research indicates that their pathogenesis has a genetic basis, this is not sufficient to explain the underlying pathological mechanisms and also, genetic loci that substantially account for disease heritability have not been identified yet (Bohacek et al., 2013; Maul et al., 2019; McIntosh et al., 2019; Meier et al., 2019; Shadrina et al., 2018; Smoller, 2016). The missing component able to explain disease vulnerability has been identified in the environmental factors. Indeed, it has been demonstrated that physiological and psychological stressors in the presence of a specific genetic background represent a phenomenon called 'gene-environment (GxE) interaction'. Thus, the individual genotypic background may increase the risk for stress-related psychiatric disorders only in the presence of exposure to life stressors and other adverse environmental circumstances. Indeed, adverse and traumatic events, especially when experienced early in life, as in the pre-natal period, infancy and/or childhood have been suggested to affect brain developmental trajectories, leading to an enhanced risk of developing stress-related psychiatric disorders later in life (Agorastos et al., 2019; Rosa et al., 2018).

To complicate the picture, several studies have suggested that traumatic and stressful events experienced early in life can affect individuals across several generations, highlighting the transgenerational effects of these exposures (Razoux et al., 2017). For instance, an overall positive

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association between a mother's history of child maltreatment and her child's experience of emotional and behavioural difficulties across childhood and adolescence has been observed (Plant et al., 2018), with maternal psychological distress and poorer parenting practices among the key mediating pathways underlying this association (Plant et al., 2018).

Although several studies, mainly built up on hypothesis-driven approaches, have been conducted to identify the mechanisms underlying stress-related psychiatric disorders, they have failed to identify top significant genes (Culverhouse et al., 2018; Dunn et al., 2016; Otowa et al., 2016; Uher et al., 2011). Most notably, there is, up to now, a lack of concerted integration across molecular/transcriptomic and genetic studies, across human and animal model studies, and also across generations, resulting in missed opportunities to depict a clear picture.

On this basis, as we have recently articulated (Cattaneo and Pariante, 2018), 'mixing apples and oranges' (that is, integrating trans-species and trans-tissues omics data) may help in identifying mechanisms that recur across different experimental and clinical models relevant to the same phenomenon – in this case, depression.

2. Convergent functional genomics

'Convergent functional genomics' (CFG) is not a new topic in psychiatry. Indeed, with the aim to integrate multiple lines of evidence coming from human and animal model studies in a Bayesian fashion, Niculescu and colleagues have been one of the first authors developing this approach (Niculescu and Kelsoe, 2001; Niculescu et al., 2000). This tool, initially applied to identify the most significant biological processes and related biomarkers associated with bipolar disorder (Le-Niculescu et al., 2009; Ogden et al., 2004), schizophrenia (Le-Niculescu et al., 2007), mood (Le-Niculescu et al., 2009) and anxiety disorders (Le-Niculescu et al., 2011), alcohol abuse (Rodd et al., 2007)), finds recent application also in suicidality (Le-Niculescu et al., 2013; Niculescu et al., 2017), major depression disorder (Li et al., 2019), short-term memory dysfunction, as early feature of Alzheimer's disease (AD) (Niculescu et al., 2019b), pain (Niculescu et al., 2019a), stress related disorders (Le-Niculescu et al., 2019), as well as in cocaine misuse (Forero and Gonzalez-Giraldo, 2020).

The principle behind all these studies – which we also advocate (Cattaneo and Pariante, 2018) – is that current scientific development is somehow hindered by the struggle between the 'hypothesis-driven' approach, which can be slow in identifying novel, hitherto unknown mechanisms, and the 'omics' approaches (transcriptomics, genomics, metabolomics), which produce a plethora of novel findings and ideas, but require enormous clinical samples and stringent statistical adjustments to prioritize the most important findings. The 'convergent' approach, instead, uses a different model, where findings derived from omics analyses are prioritized not only through statistical and bioinformatics tools, but also by identifying mechanisms operating across species in different context characterized by similar clinical or experimental phenotypes (for example, depression in humans and chronic stress in rats) and regulated in the same direction across tissues (for example, in blood and brain). Such an approach may lead to discoveries that tap into fundamental mechanisms that are associated with a specific phenotype (because conserved across species) and that can also be used to make inferences from the peripheral blood to central brain processes (an essential requisite when studying humans).

It might be informative to discuss examples of such studies in psychiatry, in order to show how this approach can be successfully applied at the interface between psychiatry and neuroscience. For example, as previously mentioned, for the first time Niculescu's group has integrated genome wide association studies (GWAS) data with transcriptomics data from human post-mortem brain and blood, and from animal models, to identify relevant molecular markers for bipolar disorders and schizophrenia (Ayalew et al., 2012; Niculescu and Kelsoe, 2001; Niculescu et al., 2000; Patel et al., 2010). The same group has also integrated

changes in gene expression induced by antidepressants in the worm, C. elegans, with genes involved in depression vulnerability coming from a GWAS study, and genes that, in the literature, had independent published evidence of association with mood or stress disorders (Rangaraju et al., 2016). Another group has attempted to identify genes associated with antidepressant response investigating convergent findings from blood transcriptomic of mice with good or poor response to antidepressants and from a clinically relevant human cohort (Carrillo-Roa et al., 2017). Using a similar approach, another group has considered both the genetic variability and brain transcriptomic profiles in mice with a range of cognitive, affective and sleep traits, and then used publicly available humans transcriptomic datasets to demonstrate how cortex-specific gene networks are affected by depression (Scarpa et al., 2018).

Other studies have provided CFG findings that are relevant to the effects of childhood adverse events. For example, one study has identified epigenetic changes in three genes (the DNA-binding protein inhibitor (*ID-3*), the Tubulin polymerization promoting protein (*TPPP*), and the NMDA receptor subunit NR1 (*GRIN1*) using saliva DNA samples of a cohort of maltreated children; moreover, the mRNA levels of the same three genes have been found altered in the medial prefrontal cortex of mice subjected to maternal neglect (Montalvo-Ortiz et al., 2016). A second study has integrated DNA methylation data obtained using four experimental models of early life stress: the prefrontal cortex of rats exposed to prenatal stress, cells from the umbilical cord of human newborns exposed to stress in pregnancy, and peripheral blood and prefrontal cortex samples of rhesus monkeys exposed to stressful rearing conditions (Luoni et al., 2016). By using this convergent and integration approach, the authors found Ankyrin-3 (*Ank3*) gene as regulated by stress across all models, with methylation status affected in the same direction in the whole blood and buccal cells from monkeys. The authors also found that a functional polymorphism in the *Ank3* gene able to influence the effects of obstetric complications on brain functional connectivity, that has been assessed by using functional magnetic resonance imaging, fMRI (Luoni et al., 2016).

Taken together, these findings further confirm the usefulness of this convergent approach not only to analyze easily collectable tissues (i.e. saliva) as a proxy for not accessible tissues in psychiatric patients (such as brain), but also to identify targets that are functionally relevant to complex brain processes (i.e. fMRI connectivity).

The potential of using such a 'convergent' approach is now further potentiated by public access to incredible resources, like the recently published human brain genomic data from embryonic development through adulthood (Li et al., 2018), the Neurophenomics database of all the human and animal gene expression and genetics studies relevant to psychiatric disorders (Rangaraju et al., 2016), and the Psychiatric Cell Map Initiative, mapping the networks of interactions among relevant proteins and genes in psychiatry (Willsey et al., 2018).

3. Our experience with transcriptomics and trans-species functional genomics

3.1. Integrating data from in vivo and in vitro models of early life stress

We have first used a CFG approach by integrating data from two established experimental models in our laboratory: the aforementioned prenatal stress (PNS) model in rats and our 'depression in a dish' in vitro model, based on a human foetal hippocampal neuronal precursors cell line exposed to "high stress-levels" concentrations of cortisol (Fig. 1) (Anacker et al., 2011, 2013a, 2013b; Borsini et al., 2017, 2018; Horowitz et al., 2014; Klengel et al., 2013; Zunszain et al., 2012).

In particular, we have integrated the transcriptome profile obtained from the hippocampus of adult rats exposed to PNS with the transcriptome profile from hippocampal precursor cells exposed to cortisol, and found two molecular pathways that are inhibited in both models, the Hedgehog pathway and the *TGF-beta Receptor* - SMAD2/3 (Anacker et al., 2013a). In further mechanistic experiments, we have found that the
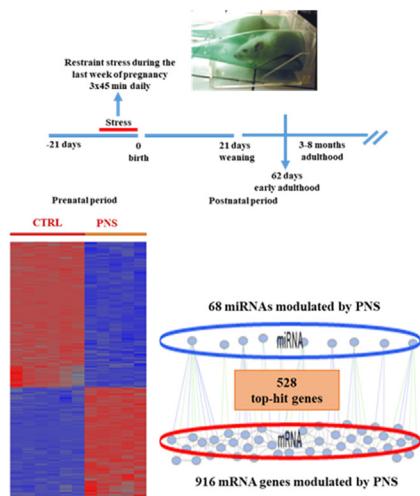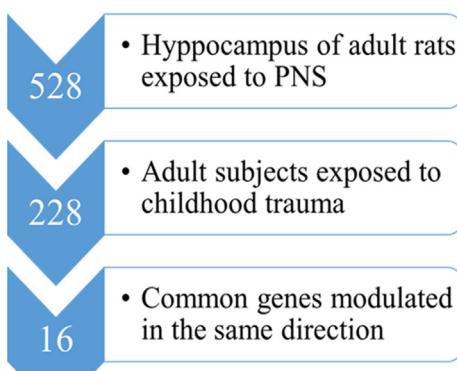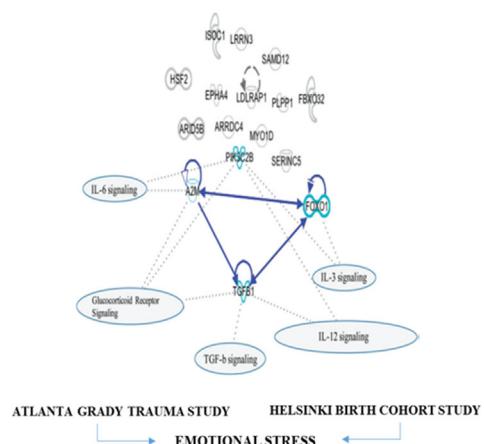
Fig. 1. A step-by-step description of our recently published trans-species CFG study (Cattaneo et al., 2018) where we integrated the transcriptome with the miRNOme from the hippocampus of adult rats exposed or not to the PNS model (Panel 1) and with the transcriptome from the blood of adult subjects characterized by early life trauma (Panel 2), and conducting a Gene x Environment association study in two independent clinical cohorts where information on childhood adversity and depressive symptoms were available (Panel 3).

Hedgehog pathway inhibition is relevant to the cortisol-induced reduction in neuronal differentiation, a putative crucial step by which stress induces depression (Egeland et al., 2015), as we co-treated cells with cortisol and a specific Hedgehog signaling activator, purmorphamine, and we were able to prevent the negative effects of cortisol on neurogenesis (Anacker et al., 2013a).

In another and most recent paper, we have found overlapping DNA methylation changes induced by dexamethasone treatment in the human hippocampal progenitor cells and in human blood cells (Provencal et al., 2019). We have examined in our in vitro model how exposure to glucocorticoids (GCs) at different stages, including proliferation, differentiation and post-differentiation, affects DNA methylation and gene expression profiles across lifespan and whether this interconnection changes during different developmental periods. Finally, we have overlapped the observed epigenetic alterations in human hippocampal progenitor cells with epigenetic profiles in developing human tissues (cross-tissues relevance; peripheral and cord blood) and assessed their potential as biomarkers for prenatal GCs exposure (Provencal et al., 2019). By using this CFG approach, we suggest that GC exposure can induce long-lasting changes in DNA methylation in mature tissues, not only altering neurodevelopmental trajectories but also priming the stress reactivity of adult tissues.

### 3.2. Cross-species and tissues approach: the key role of FoxO1

In a subsequent study (Cattaneo et al., 2018), we have integrated the transcriptome profile obtained from the hippocampus of adult rats exposed to PNS with the transcriptome profile from the blood of adult subjects characterized for early life trauma, and then we tested the mechanistic role of our findings both in our in vitro model and also in two independent clinical cohorts (Fig. 1).

In particular, as we have illustrated in Fig. 1, we first have measured the transcriptomics profile in the hippocampus of male adult rats exposed or not to PNS, finding a significant modulation of 916 mRNA genes (fold changes >1.4, FDR *q*-value <0.05) and 68 micro RNAs (miRNAs; an additional epigenetic regulator of the final expression of a target gene) in association with PNS exposure. We have then performed an mRNA-miRNA combining analysis, allowing the identification of genes that are both modulated by PNS exposure and targeted by the miRNAs that are significantly modulated by the same paradigm of PNS. This mRNA-

miRNA integration approach restricted the list of 916 genes to 528 significant genes (Fig. 1, Panel 1).

Subsequently, we have compared whole blood mRNA transcriptomics of adult subjects characterized for a history of exposure to severe childhood adverse events, and we have identified 250 genes that were differentially modulated (fold changes > 1.2, FDR *q*-value <0.05). In the next step, we have integrated the 528 genes obtained by the combined mRNA/miRNA analyses in the hippocampus of PNS rats with the 250 genes significantly modulated in blood samples of adult subjects exposed to childhood trauma, and we have identified 22 common genes that are present in both lists. Out of these 22 genes, 16 genes were also modulated in the same direction both in animals and in humans (Fig. 1, Panel 2).

Next, taking into account these 16 genes, we have applied a gene network analysis to identify those genes that interact with each other through physical interaction, co-expression or involvement in common pathways. We have observed only one cluster of interacting genes, represented by *alpha-2 macroglobulin (A2M)*, *Forkhead Box O1 (FoxO1)* and *Transforming growth factor beta 1 (TGF-β1)*, and we have focused on these three genes for the subsequent validation studies. From a mechanistic point of view, it is also worth mentioning that all three genes are functionally related to the immune system, with A2M being an acute phase protein, and both FOXO1 and TGF-β1 functionally interacting with the immune system (Cattaneo et al., 2018), confirming the crucial role of this biological system in psychiatry, as we and others have argued (Cattaneo et al., 2016; Dantzer et al., 2018; Hepgul et al., 2016; Miller and Raison, 2016; Nettis et al., 2019; Raison et al., 2006, 2013, 2018; Stilo et al., 2017; Wetsman, 2019).

For subsequent analyses we have used two independent clinical cohorts where GWAS data, childhood adversity information and depressive symptoms were available, represented by the Grady Trauma Project and the Helsinki Birth cohort. We have tested the interaction between all the SNPs located in these three genes and emotional stress in childhood in predicting depressive symptoms in adulthood. Then, we have assessed the combined effect over both cohorts and performed a meta-analysis, which reported as main finding that 6 SNPs, all located within the *FoxO1* gene, are significantly associated with emotional stress in predicting depressive symptoms, in both cohorts (Fig. 1, Panel 3). This data indicate *FoxO1* as a novel gene where its genetic variability can mediate the effect of the environment on the development of depressive symptoms.

Finally, we have validated the molecular action of *FoxO1* gene using the aforementioned in vitro model. We found that cortisol treatment increases *FoxO1* mRNA levels and decreases neurogenesis via a FOXO1-dependent effect, as the negative effects of cortisol were prevented and counteracted by a FOXO1 inhibitor given in co-treatment with cortisol.

3.3. The role of miRNOme analyses in implementing the CFG approach

Thanks to the improvement of techniques for miRNOmics, hundreds of endogenous miRNAs from different tissue samples, cell cultures as well as body fluids can now be measured in a hypothesis-free manner. In the context of psychiatry and neuroscience, miRNAs can be used to implement the CFG approach, in order to contribute in a better identification and prioritization of complex brain-relevant molecular mechanisms and alterations induced by ELS. For instance, last year, we have conducted a miRNOme analysis in blood samples of human adults characterized for childhood trauma, the hippocampus of rats exposed or not to prenatal stress, and the human hippocampal precursors cells treated with cortisol or vehicle (Cattane et al., 2019).

As we were interested in the identification of the biological processes regulated by miRNAs differentially modulated by ELS, we performed an individual pathway analysis on the three lists of miRNAs obtained in the three different samples (blood samples, rodent hippocampus and cells). Interestingly, we observed the modulation of several common biological systems, including those associated with neurodevelopment, such as FoxO and Mammalian Target Of Rapamycin (mTOR) signaling pathways, with immunity and inflammation, such as the TGF-β signaling, and with the intracellular signal transduction, such as Mitogen-Activated Protein Kinase (MAPK), Ras-Related Protein Rap-1A (Rap1) and Ras signaling pathways. All these findings suggest that stressful experiences, especially early in life, can affect neurodevelopmental and inflammatory-related systems, rendering the exposed individuals more vulnerable to develop a stress-related psychiatric disorder (Cattane et al., 2019). Interestingly, FoxO signaling pathway emerged as one of the most significant pathways regulated by differentially expressed miRNAs in the three different datasets all characterized by ELS exposure.

Subsequently, in order to identify a miRNAs signature associated with a stress exposure across different models and tissues, we intersected the list of miRNAs significantly modulated in the three datasets and we identified one miRNA, miR-125b-1-3p, as the only common miRNA significantly down-regulated in association with a stress-related condition. Interestingly, we also observed a significant down-regulation of miR-125b-1-3p in peripheral blood samples of a different group of patients affected by schizophrenia and exposed to childhood trauma. Our data, obtained by combining different miRNAs datasets across different tissues and species, allowed us to identify miR-125b-1-3p as a key marker associated with the long-term effects of stress early in life and with the enhanced vulnerability of developing schizophrenia (Cattane et al., 2019).

4. Conclusions

In this review, by bringing together epidemiological, clinical, biological and molecular findings, we have summarized several studies that successfully used the CFG approach, a 'hypothesis-free' tool to identify a stringent number of genes implicated in the effects of ELS, and possible novel candidates for GxE interaction studies.

CFG has opened the street towards the precision medicine in psychiatry, where there are no objective clinical laboratory blood tests able to identify a particular psychiatric condition or to predict depressive symptoms. For instance, Kurian et al., 2011 (Kurian et al., 2011) and Le-Niculescu et al., 2009 (Le-Niculescu et al., 2009) provided a proof of principle for how such a combined approach, integrating functional and genetic data together with phenotypic clinical information can be used for the development of objective laboratory tests to measure illness severity and response to treatment.

Other studies (Le-Niculescu et al., 2013; Levey et al., 2016; Niculescu et al., 2015) reported comprehensive data for discovery, prioritization, validation, and testing of next-generation broad-spectrum blood biomarkers for suicidal ideation and behaviour, across psychiatric diagnoses. They described two clinical information questionnaires in the form of apps, one for affective state (Simplified Affective State Scale, SASS) and one for suicide risk factors (Convergent Functional Information for Suicide, CFI-S), showing their utility in predicting suicidality. The combination of top biomarkers (from discovery, prioritization and validation), along with CFI-S, and SASS, permitted to predict state (suicidal ideation), and to predict trait (future hospitalizations for suicidality). Similarly, Niculescu et al., 2019 (Niculescu et al., 2019a) have recently applied the same integration approach, opening the door for precision medicine also for pain, with objective diagnostics and targeted novel therapeutics.

The results that we obtained by using a CFG approach have identified *FoxO1* gene as involved in the long-term effects of ELS on depression vulnerability as we found that genetic variability within *FoxO1* gene interacts with the adverse environment in mediating the development of depressive symptoms. Moreover, we have also demonstrated in vitro its functional relevance in causing a reduction in neurogenesis in the presence of high concentration of cortisol. Thus, this gene may represent a potential novel target for the development of pharmacological therapies, for the prevention of disorders caused by an exposure to stress early in life or for their treatment. It has been demonstrated that FoxO1 can act on several targets, not only genes involved in apoptosis and autophagy, anti-oxidative enzymes and cell cycle arrest processes, but also genes engaged in metabolic and immune systems (Murtaza et al., 2017; Wang et al., 2016), known to be involved in the biological mechanisms underlying the development of mood disorders (Kowalczyk et al., 2019). Considered this, if we are able to specifically target FoxO1 in relation to inflammation-related pathways, than FoxO1 might represent a novel pharmacological target for different psychiatric disorders characterised by an enhanced pro-inflammatory status.

The involvement of FOXOs family, including FOXO1, in the regulation of different biochemical processes and organs can explain the high potential of the FOXO1 modulation. Literature data have mainly shown the key role of FOXO1 inhibition rather than its over-expression in different context and disorders. For instance, although FOXO1 inhibitors have not reached clinical trials yet, numerous preclinical in vitro and in vivo studies have recently demonstrated their potential efficacy and safety for the treatment of type 2 diabetes. According to a growing body of evidence, when FOXOs are inhibited, glucose production decreases, with a potential benefit for diabetes treatment; however, hepatic lipid synthesis increases, predisposing to steatosis (Pajvani and Accili, 2015). In order to identify new potential therapeutic molecules for type 2 diabetes, Langlet and colleagues tested small molecules with the ability to fine-tune the FOXO1 activator/repressor balance in primary hepatocytes for their ability to modulate the expression of glucose-6-phosphatase (G6pc), the enzyme of glucose production, and of glucokinase (Gck), the enzyme of glucose utilization. They expected that a pan-FOXO1 inhibitor could decrease the former and increase the latter (Langlet et al., 2017). Among all tested molecules, they identified a group of compounds, which demonstrated selective inhibition by decreasing G6pc without affecting Gck expression levels. To assess the functional consequences of these selective inhibitors, the compounds were tested for glucose production and for de novo lipogenesis assays in primary hepatocytes. One compound was able to increase lipogenesis, as expected from a full FOXO1 inhibitor, whereas another one decreased it. To establish a potential mechanism for the differential actions of these two compounds on Gck versus G6pc expression levels, the authors tested their effects by performing chromatin immunoprecipitation assays in cAMP/dex hepatocytes. The results indicated that the differential actions of the two compounds were associated with different effects and mechanisms of action on the FOXO1 transcriptional complex.

Unfortunately, the authors did not test the compounds in vivo due to

their pharmacokinetic properties. However, concerning the therapeutic aspect, this study demonstrates that FOXO1 can be selective pharmacological targeted and suggests its key role in the regulation of glucose production. Moreover, in a clinical setting, this can reduce the hepatic glucose production without increasing triglyceride accumulation.

Among the FOXO1-antagonists/inhibitors, AS1842856, which initially was discovered to repress FOXO1 dependent transcription of the gluconeogenic enzymes G6pc and phosphoenolpyruvate carboxykinase (PEPCK), represents the compound that has been tested for the treatment of different illnesses, including i) metabolic disorders such as type 2 diabetes, obesity and insulin resistance, ii) cancer, including lymphoma, and iii) inflammatory/immune disorders, including viral infections.

Here below we describe evidences on the potential role of AS1842856 compound for the treatment of several diseases.

AS1842856 has been suggested to regulate adipogenesis (Zou et al., 2014) and, as an excess adipogenesis contributes to obesity development, AS1842856 may represent an anti-obesity candidate that warrants further investigation. Indeed, a persistent inhibition of FoxO1 with AS1842856 has been widely reported by several studies to completely suppress adipocyte differentiation, while a selective inhibition in specific stages of adipogenic regulation has differential effects on adipogenesis.

Similarly, recent studies have shown that AS1842856 is able to potentiate the regeneration of pancreatic β-cells and restore insulin secretion in diabetic mice (Chera and Herrera, 2016), suggesting the inhibition of FOXO1 as a key target mechanism in the treatment of diabetes.

In addition to the key role of FoxO1 in the glucose regulation and in adipogenesis, this transcription factor drives the proliferation and survival of B cells at several stages of their differentiation. Gehringer and colleagues (Gehringer et al., 2019) demonstrated that the pharmacological repression of FOXO1, due to the inhibition of AS1842856, induced both cell cycle arrest and apoptosis in an aggressive B cell lymphoma, the Burkitt lymphoma (BL) cell lines. The authors found that AS1842856 is toxic for BL, showing that the treatment with the FOXO1 inhibitor had similar effects to those obtained from the shRNA-mediated FOXO1 knockdown on gene transcription. However, the authors suggested that RNA interference decreases the FOXO1 levels, whereas AS1842856 does not modulate FOXO1 expression or localization, instead, it binds to the transactivation domain, interfering with the FOXO1 transactivation activity, represented by the crosstalk of signaling cascades or the activation of G protein–coupled receptor subunits (Gehringer et al., 2019). Moreover, it is possible that not all interactions of FOXO1 with other proteins, including up-stream or down-stream regulators, might be blocked by AS1842856. Therefore, the inhibition of other molecules involved in the FOXOs signaling might explain the stronger effects observed with the pharmacological compound as compared to those observed with the genetic FOXO1 inhibition.

The development of new potent FOXO1 inhibitors could help in increasing the efficacy, and in decreasing the toxicity of treatment of FOXO1-dependent tumors, including BL.

Among the functions of FOXO1, several studies have suggested that it actively maintains quiescence of human T lymphocytes. It is now well established that the mechanisms controlling the state of quiescence of naive T cells are essential for regulating their permissiveness to HIV infection (Pan et al., 2013), suggesting that FOXO1 can be involved in controlling HIV-1 infection in T cells. Indeed, literature data show an increase of viral replication after the inhibition of FOXO1 in quiescent T cells treated with Interleukin (IL)-7 (Trinite et al., 2014). Because FOXO1 is a master regulator of T cell functions, Roux and colleagues investigated the effect of its inhibition on T cell/HIV-1 interactions. By using the FOXO1 pharmacologic antagonist AS1842856, they observed that FOXO1 inhibition induced a metabolic activation of T cells with a G0/G1 transition in the absence of any stimulatory signals, as well as a significant increase of both the bioenergetics and transcriptional activity of human T cells, together with a significant increase in their size, without any cell division. One parallel outcome of this change was the

inhibition of the activity of one of the HIV restriction factor and the activation of the NFAT pathway. According to their findings, the authors suggested that FOXO1 has a central role in the HIV-1/T cell interaction and that inhibiting FOXO1 with drugs such as AS1842856 is sufficient to induce a profound reprogramming of human T lymphocytes, regulating their exit from quiescence and representing a new therapeutic shock-and-kill strategy to eliminate the HIV-1 reservoir in human T cells (Roux et al., 2019).

In the context of psychiatry disorders, we have previously demonstrated a cause-effect relationship between the effects of ELS and FoxO1 expression levels, as we observed that cortisol treatment increased FoxO1 mRNA levels and that, in parallel, decreased neurogenesis levels via a FoxO1-dependent effect. Interestingly, the negative effects of cortisol were prevented and counteracted by AS1842856, the FoxO1 inhibitor, given in co-treatment with cortisol. Moreover, as we found higher expression levels of FoxO1 in different tissues and species in association with stress exposures, including cortisol treatment, and that a reduction of FoxO1 mRNA levels could be related to an improvement of the molecular alterations induced by ELS, such as the neurogenesis levels, we can hypothesize a worsening of the biological and molecular negative outcomes due to an over-expression of FoxO1 mRNA levels even in control subjects, never exposed to ELS. Therefore, according to all these findings, FoxO1 and the modulation of its expression levels, together with its up-stream or down-stream regulators could represent interesting targets for the development of novel pharmacological treatments for stress-related psychiatric disorders.

Finally, recent studies have highlighted the contribution of epigenetic mechanisms, such as miRNAs, in the modulation of FoxO1 gene expression. Indeed, previous studies have demonstrated that the 3′-untranslated region of FOXO1 possesses a conserved target sequence for miRNAs, including miR-9, miR-135a, miR-223, miR-1288, miR-3188, miR-215 and the miR-183-96-182 cluster, which can inhibit FoxO1 expression levels (Xing et al., 2018), suggesting these small non coding RNAs as interesting modulators of the FoxO1 activity. Of course, further studies are needed to better understand the molecular mechanisms underlying miRNAs regulation of FOXO1 also in psychiatric disorders.

Based on our experience, we suggest that the CFG approach could include not only trans-species and tissues studies, but also transgenerational analyses, in the pursuit of clarifying brain-relevant molecular mechanisms underpinning the effects of ELS and their transgenerational transmission. Indeed, to our knowledge, no studies that neither integrate omics data coming from animal models, human cohorts nor from different generations are still available. Therefore, further studies to examine in depth and prioritize top candidate genes underlying a GxE interaction and modulated by the effects of ELS even across lifespan, and also across generations will be fundamental.

Finally, in our CFG approach, we have often used human hippocampal cells as a brain-based biological validation model, akin to what other studies have done using post-mortem human brain samples. Of course, more clinically-relevant, brain-based biological validation models, like brain fMRI connectivity, are closer to the psychiatric phenotypes associated with stress, especially considering the recent emphasis on circuit-based approaches for delineating brain-relevant molecular mechanisms related to early adversity and psychopathology (Cancel et al., 2017; Grant et al., 2014). Nevertheless, it is important to underline how cellular models, as the one we present here, can offer mechanistic insights into dynamic processes such as neurogenesis or transcriptomics/epigenetics, as well as provide proof-of-concept evidence with pharmacological activators or inhibitors leading to the development of novel therapeutic strategies.

All together, we accept that this review offers more questions than answers, and, as such, we hope that it will stimulate further conversation in the biological psychiatry research community on how to address the complexity of the bio-psycho-social and transgenerational nature of mental disorders, above all depression.

Declaration of competing interest

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References

Agorastos, A., Pervanidou, P., Chrousos, G.P., Baker, D.G., 2019. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Front. Psychiatr. 10, 118.

Anacker, C., Cattaneo, A., Luoni, A., Musaelyan, K., Zunszain, P.A., Milanesi, E., Rybka, J., Berry, A., Cirulli, F., Thuret, S., Price, J., Riva, M.A., Gennarelli, M., Pariante, C.M., 2013a. Glucocorticoid-related molecular signaling pathways regulating hippocampal neurogenesis. Neuropsychopharmacology 38, 872–883.

Anacker, C., Cattaneo, A., Musaelyan, K., Zunszain, P.A., Horowitz, M., Molteni, R., Luoni, A., Calabrese, F., Tansey, K., Gennarelli, M., Thuret, S., Price, J., Uher, R., Riva, M.A., Pariante, C.M., 2013b. Role for the kinase SGK1 in stress, depression, and glucocorticoid effects on hippocampal neurogenesis. Proc. Natl. Acad. Sci. U. S. A. 110, 8708–8713.

Anacker, C., Zunszain, P.A., Cattaneo, A., Carvalho, L.A., Garabedian, M.J., Thuret, S., Price, J., Pariante, C.M., 2011. Antidepressants increase human hippocampal neurogenesis by activating the glucocorticoid receptor. Mol. Psychiatr. 16, 738–750.

Ayalew, M., Le-Niculescu, H., Levey, D.F., Jain, N., Changala, B., Patel, S.D., Winiger, E., Breier, A., Shekhar, A., Amdur, R., Koller, D., Nurnberger, J.I., Corvin, A., Geyer, M., Tsuang, M.T., Salomon, D., Schork, N.J., Fanous, A.H., O'Donovan, M.C., Niculescu, A.B., 2012. Convergent functional genomics of schizophrenia: from comprehensive understanding to genetic risk prediction. Mol. Psychiatr. 17, 887–905.

Bohacek, J., Gapp, K., Saab, B.J., Mansuy, I.M., 2013. Transgenerational epigenetic effects on brain functions. Biol. Psychiatr. 73, 313–320.

Borsini, A., Alboni, S., Horowitz, M.A., Tojo, L.M., Cannazza, G., Su, K.P., Pariante, C.M., Zunszain, P.A., 2017. Rescue of IL-1beta-induced reduction of human neurogenesis by omega-3 fatty acids and antidepressants. Brain Behav. Immun. 65, 230–238.

Borsini, A., Cattaneo, A., Malpighi, C., Thuret, S., Harrison, N.A., Consortium, M.R.C.I., Zunszain, P.A., Pariante, C.M., 2018. Interferon-alpha reduces human hippocampal neurogenesis and increases apoptosis via activation of distinct STAT1-dependent mechanisms. Int. J. Neuropsychopharmacol. 21, 187–200.

Cancel, A., Comte, M., Boutet, C., Schneider, F.C., Rousseau, P.F., Boukezzi, S., Gay, A., Sigaud, T., Massoubre, C., Berna, F., Zendjidjian, X.Y., Azorin, J.M., Blin, O., Fakra, E., 2017. Childhood trauma and emotional processing circuits in schizophrenia: a functional connectivity study. Schizophr. Res. 184, 69–72.

Carrillo-Roa, T., Labermaier, C., Weber, P., Herzog, D.P., Lareau, C., Santarelli, S., Wagner, K.V., Rex-Haffner, M., Harbich, D., Scharf, S.H., Nemeroff, C.B., Dunlop, B.W., Craighead, W.E., Mayberg, H.S., Schmidt, M.V., Uhr, M., Holsboer, F., Sillaber, I., Binder, E.B., Muller, M.B., 2017. Common genes associated with antidepressant response in mouse and man identify key role of glucocorticoid receptor sensitivity. PLoS Biol. 15, e2002690.

Cattane, N., Mora, C., Lopizzo, N., Borsini, A., Maj, C., Pedrini, L., Rossi, R., Riva, M.A., Pariante, C.M., Cattaneo, A., 2019. Identification of a miRNAs signature associated with exposure to stress early in life and enhanced vulnerability for schizophrenia:

new insights for the key role of miR-125b-1-3p in neurodevelopmental processes. Schizophr. Res. 205, 63–75.

Cattaneo, A., Cattane, N., Malpighi, C., Czamara, D., Suarez, A., Mariani, N., Kajantie, E., Luoni, A., Eriksson, J.G., Lahti, J., Mondelli, V., Dazzan, P., Raikkonen, K., Binder, E.B., Riva, M.A., Pariante, C.M., 2018. FoxO1, A2M, and TGF-beta1: three novel genes predicting depression in gene X environment interactions are identified using cross-species and cross-tissues transcriptomic and miRNomic analyses. Mol. Psychiatr. 23, 2192–2208.

Cattaneo, A., Ferrari, C., Uher, R., Bocchio-Chiavetto, L., Riva, M.A., Consortium, M.R.C.I., Pariante, C.M., 2016. Absolute measurements of macrophage migration inhibitory factor and interleukin-1-beta mRNA levels accurately predict treatment response in depressed patients. Int. J. Neuropsychopharmacol. 19.

Cattaneo, A., Pariante, C.M., 2018. Integrating 'omics' approaches to prioritize new pathogenetic mechanisms for mental disorders. Neuropsychopharmacology 43, 227–228.

Chera, S., Herrera, P.L., 2016. Regeneration of pancreatic insulin-producing cells by in situ adaptive cell conversion. Curr. Opin. Genet. Dev. 40, 1–10.

Culverhouse, R.C., Saccone, N.L., Horton, A.C., Ma, Y., Anstey, K.J., Banaschewski, T., Burmeister, M., Cohen-Woods, S., Etain, B., Fisher, H.L., Goldman, N., Guillaume, S., Horwood, J., Juhasz, G., Lester, K.J., Mandelli, L., Middeldorp, C.M., Olie, E., Villafuerte, S., Air, T.M., Araya, R., Bowes, L., Burns, R., Byrne, E.M., Coffey, C., Coventry, W.L., Gawronski, K.A.B., Glei, D., Hatzimanolis, A., Hottenga, J.J., Jaussent, I., Jawahar, C., Jennen-Steinmetz, C., Kramer, J.R., Lajnef, M., Little, K., Zu Schwabedissen, H.M., Nauck, M., Nederhof, E., Petschner, P., Peyrot, W.J., Schwahn, C., Sinnamon, G., Stacey, D., Tian, Y., Toben, C., Van der Auwera, S., Wainwright, N., Wang, J.C., Willemsen, G., Anderson, I.M., Arolt, V., Aslund, C., Bagdy, G., Baune, B.T., Bellivier, F., Boomsma, D.I., Courtet, P., Dannlowski, U., de Geus, E.J.C., Deakin, J.F.W., Easteal, S., Eley, T., Fergusson, D.M., Goate, A.M., Gonda, X., Grabe, H.J., Holzman, C., Johnson, E.O., Kennedy, M., Laucht, M., Martin, N.G., Munafo, M.R., Nilsson, K.W., Oldehinkel, A.J., Olsson, C.A., Ormel, J., Otte, C., Patton, G.C., Penninx, B., Ritchie, K., Sarchiapone, M., Scheid, J.M., Serretti, A., Smit, J.H., Stefanis, N.C., Surtees, P.G., Volzke, H., Weinstein, M., Whooley, M., Nurnberger Jr., J.I., Breslau, N., Bierut, L.J., 2018. Collaborative meta-analysis finds no evidence of a strong interaction between stress and 5-HTTLPR genotype contributing to the development of depression. Mol. Psychiatr. 23, 133–142.

Dantzer, R., Cohen, S., Russo, S.J., Dinan, T.G., 2018. Resilience and immunity. Brain Behav. Immun. 74, 28–42.

Dunn, E.C., Wiste, A., Radmanesh, F., Almli, L.M., Gogarten, S.M., Sofer, T., Faul, J.D., Kardia, S.L., Smith, J.A., Weir, D.R., Zhao, W., Soare, T.W., Mirza, S.S., Hek, K., Tiemeier, H., Goveas, J.S., Sarto, G.E., Snively, B.M., Cornelis, M., Koenen, K.C., Kraft, P., Purcell, S., Ressler, K.J., Rosand, J., Wassertheil-Smoller, S., Smoller, J.W., 2016. Genome-wide association study (gwas) and genome-wide by environment interaction study (gweis) of depressive symptoms in african American and hispanic/latina women. Depress. Anxiety 33, 265–280.

Egeland, M., Zunszain, P.A., Pariante, C.M., 2015. Molecular mechanisms in the regulation of adult neurogenesis during stress. Nat. Rev. Neurosci. 16, 189–200.

Forero, D.A., Gonzalez-Giraldo, Y., 2020. Convergent functional genomics of cocaine misuse in humans and animal models. Am. J. Drug Alcohol Abuse 46, 22–30.

Gehringer, F., Weissinger, S.E., Swier, L.J., Moller, P., Wirth, T., Ushmorov, A., 2019. FOXO1 confers maintenance of the dark zone proliferation and survival program and can Be pharmacologically targeted in Burkitt lymphoma. Cancers 11.

Grant, M.M., White, D., Hadley, J., Hutcheson, N., Shelton, R., Sreenivasan, K., Deshpande, G., 2014. Early life trauma and directional brain connectivity within major depression. Hum. Brain Mapp. 35, 4815–4826.

Hepgul, N., Cattaneo, A., Agarwal, K., Baraldi, S., Borsini, A., Bufalino, C., Forton, D.M., Mondelli, V., Nikkheslat, N., Lopizzo, N., Riva, M.A., Russell, A., Hotopf, M., Pariante, C.M., 2016. Transcriptomics in interferon-alpha-treated patients identifies inflammation-, neuroplasticity- and oxidative stress-related signatures as predictors and correlates of depression. Neuropsychopharmacology 41, 2502–2511.

Horowitz, M.A., Wertz, J., Zhu, D., Cattaneo, A., Musaelyan, K., Nikkheslat, N., Thuret, S., Pariante, C.M., Zunszain, P.A., 2014. Antidepressant compounds can be both pro- and anti-inflammatory in human hippocampal cells. Int. J. Neuropsychopharmacol. 18.

Klengel, T., Mehta, D., Anacker, C., Rex-Haffner, M., Pruessner, J.C., Pariante, C.M., Pace, T.W., Mercer, K.B., Mayberg, H.S., Bradley, B., Nemeroff, C.B., Holsboer, F., Heim, C.M., Ressler, K.J., Rein, T., Binder, E.B., 2013. Allele-specific FKBP5 DNA demethylation mediates gene-childhood trauma interactions. Nat. Neurosci. 16, 33–41.

Kowalczyk, M., Szemraj, J., Blizniewska, K., Maes, M., Berk, M., Su, K.P., Galecki, P., 2019. An immune gate of depression - early neuroimmune development in the formation of the underlying depressive disorder. Pharmacol. Rep. : PR 71, 1299–1307.

Kurian, S.M., Le-Niculescu, H., Patel, S.D., Bertram, D., Davis, J., Dike, C., Yehyawi, N., Lysaker, P., Dustin, J., Caligiuri, M., Lohr, J., Lahiri, D.K., Nurnberger Jr., J.I., Faraone, S.V., Geyer, M.A., Tsuang, M.T., Schork, N.J., Salomon, D.R., Niculescu, A.B., 2011. Identification of blood biomarkers for psychosis using convergent functional genomics. Mol. Psychiatr. 16, 37–58.

Langlet, F., Haeusler, R.A., Linden, D., Ericson, E., Norris, T., Johansson, A., Cook, J.R., Aizawa, K., Wang, L., Buettner, C., Accili, D., 2017. Selective inhibition of FOXO1 activator/repressor balance modulates hepatic glucose handling. Cell 171, 824–835 e818.

Le-Niculescu, H., Balaraman, Y., Patel, S., Tan, J., Sidhu, K., Jerome, R.E., Edenberg, H.J., Kuczenski, R., Geyer, M.A., Nurnberger Jr., J.I., Faraone, S.V., Tsuang, M.T., Niculescu, A.B., 2007. Towards understanding the schizophrenia code: an expanded convergent functional genomics approach. Am. J. Med. Genet. Part B,

Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 144B, 129–158.

Le-Niculescu, H., Balaraman, Y., Patel, S.D., Ayalew, M., Gupta, J., Kuczenski, R., Shekhar, A., Schork, N., Geyer, M.A., Niculescu, A.B., 2011. Convergent functional genomics of anxiety disorders: translational identification of genes, biomarkers, pathways and mechanisms. Transl. Psychiatry 1, e9.

Le-Niculescu, H., Levey, D.F., Ayalew, M., Palmer, L., Gavrin, L.M., Jain, N., Winiger, E., Bhosrekar, S., Shankar, G., Radel, M., Bellanger, E., Duckworth, H., Olesek, K., Vergo, J., Schweitzer, R., Yard, M., Ballew, A., Shekhar, A., Sandusky, G.E., Schork, N.J., Kurian, S.M., Salomon, D.R., Niculescu 3rd, A.B., 2013. Discovery and validation of blood biomarkers for suicidality. Mol. Psychiatr. 18, 1249–1264.

Le-Niculescu, H., Patel, S.D., Bhat, M., Kuczenski, R., Faraone, S.V., Tsuang, M.T., McMahon, F.J., Schork, N.J., Nurnberger Jr., J.I., Niculescu 3rd, A.B., 2009. Convergent functional genomics of genome-wide association data for bipolar disorder: comprehensive identification of candidate genes, pathways and mechanisms. Am. J. Med. Genet. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 150B, 155–181.

Le-Niculescu, H., Roseberry, K., Levey, D.F., Rogers, J., Kosary, K., Prabha, S., Jones, T., Judd, S., McCormick, M.A., Wessel, A.R., Williams, A., Phalen, P.L., Mamdani, F., Sequeira, A., Kurian, S.M., Niculescu, A.B., 2019. Towards precision medicine for stress disorders: diagnostic biomarkers and targeted drugs. Mol. Psychiatr.

Levey, D.F., Niculescu, E.M., Le-Niculescu, H., Dainton, H.L., Phalen, P.L., Ladd, T.B., Weber, H., Belanger, E., Graham, D.L., Khan, F.N., Vanipenta, N.P., Stage, E.C., Ballew, A., Yard, M., Gelbart, T., Shekhar, A., Schork, N.J., Kurian, S.M., Sandusky, G.E., Salomon, D.R., Niculescu, A.B., 2016. Towards understanding and predicting suicidality in women: biomarkers and clinical risk assessment. Mol. Psychiatr. 21, 768–785.

Li, H., Chang, H., Song, X., Liu, W., Li, L., Wang, L., Yang, Y., Zhang, L., Li, W., Zhang, Y., Zhou, D.S., Li, X., Zhang, C., Fang, Y., Sun, Y., Dai, J.P., Luo, X.J., Yao, Y.G., Xiao, X., Lv, L., Li, M., 2019. Integrative analyses of major histocompatibility complex loci in the genome-wide association studies of major depressive disorder. Neuropsychopharmacology 44, 1552–1561.

Li, M., Santpere, G., Imamura Kawasawa, Y., Evgrafov, O.V., Gulden, F.O., Pochareddy, S., Sunkin, S.M., Li, Z., Shin, Y., Zhu, Y., Sousa, A.M.M., Werling, D.M., Kitchen, R.R., Kang, H.J., Pletikos, M., Choi, J., Muchnik, S., Xu, X., Wang, D., Lorente-Galdos, B., Liu, S., Giusti-Rodriguez, P., Won, H., de Leeuw, C.A., Pardinas, A.F., BrainSpan, C., Psych, E.C., Psych, E.D.S., Hu, M., Jin, F., Li, Y., Owen, M.J., O'Donovan, M.C., Walters, J.T.R., Posthuma, D., Reimers, M.A., Levitt, P., Weinberger, D.R., Hyde, T.M., Kleinman, J.E., Geschwind, D.H., Hawrylycz, M.J., State, M.W., Sanders, S.J., Sullivan, P.F., Gerstein, M.B., Lein, E.S., Knowles, J.A., Sestan, N., 2018. Integrative functional genomic analysis of human brain development and neuropsychiatric risks. Science 362.

Luoni, A., Massart, R., Nieratschker, V., Nemoda, Z., Blasi, G., Gilles, M., Witt, S.H., Suderman, M.J., Suomi, S.J., Porcelli, A., Rizzo, G., Fazio, L., Torretta, S., Rampino, A., Berry, A., Gass, P., Cirulli, F., Rietschel, M., Bertolino, A., Deuschle, M., Szyf, M., Riva, M.A., 2016. Ankyrin-3 as a molecular marker of early-life stress and vulnerability to psychiatric disorders. Transl. Psychiatry 6, e943.

Maul, S., Giegling, I., Fabbri, C., Corponi, F., Serretti, A., Rujescu, D., 2019. Genetics of resilience: implications from genome-wide association studies and candidate genes of the stress response system in posttraumatic stress disorder and depression. Am. J. Med. Genet. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics.

McIntosh, A.M., Sullivan, P.F., Lewis, C.M., 2019. Uncovering the genetic architecture of major depression. Neuron 102, 91–103.

Meier, S.M., Trontti, K., Purves, K.L., Als, T.D., Grove, J., Laine, M., Pedersen, M.G., Bybjerg-Grauholm, J., Baekved-Hansen, M., Sokolowska, E., Mortensen, P.B., Hougaard, D.M., Werge, T., Nordentoft, M., Breen, G., Borglum, A.D., Eley, T.C., Hovatta, I., Mattheisen, M., Mors, O., 2019. Genetic variants associated with anxiety and stress-related disorders: a genome-wide association study and mouse-model study. JAMA Psychiatry.

Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34.

Montalvo-Ortiz, J.L., Bordner, K.A., Carlyle, B.C., Gelernter, J., Simen, A.A., Kaufman, J., 2016. The role of genes involved in stress, neural plasticity, and brain circuitry in depressive phenotypes: convergent findings in a mouse model of neglect. Behav. Brain Res. 315, 71–74.

Murtaza, G., Khan, A.K., Rashid, R., Muneer, S., Hasan, S.M.F., Chen, J., 2017. FOXO transcriptional factors and long-term living. Oxidative medicine and cellular longevity 2017, 3494289.

Nettis, M.A., Pergola, G., Kolliakou, A., O'Connor, J., Bonaccorso, S., David, A., Gaughran, F., Di Forti, M., Murray, R.M., Marques, T.R., Blasi, G., Bertolino, A., Pariante, C.M., Dazzan, P., Mondelli, V., 2019. Metabolic-inflammatory status as predictor of clinical outcome at 1-year follow-up in patients with first episode psychosis. Psychoneuroendocrinology 99, 145–153.

Niculescu 3rd, A.B., Kelsoe, J.R., 2001. Convergent functional genomics: application to bipolar disorder. Ann. Med. 33, 263–271.

Niculescu 3rd, A.B., Segal, D.S., Kuczenski, R., Barrett, T., Hauger, R.L., Kelsoe, J.R., 2000. Identifying a series of candidate genes for mania and psychosis: a convergent functional genomics approach. Physiol. Genom. 4, 83–91.

Niculescu, A.B., Le-Niculescu, H., Levey, D.F., Phalen, P.L., Dainton, H.L., Roseberry, K., Niculescu, E.M., Niezer, J.O., Williams, A., Graham, D.L., Jones, T., Venugopal, V., Ballew, A., Yard, M., Gelbart, T., Kurian, S.M., Shekhar, A., Schork, N.J., Sandusky, G.E., Salomon, D.R., 2017. Precision medicine for suicidality: from universality to subtypes and personalization. Mol. Psychiatr. 22, 1250–1273.

Niculescu, A.B., Le-Niculescu, H., Levey, D.F., Roseberry, K., Soe, K.C., Rogers, J., Khan, F., Jones, T., Judd, S., McCormick, M.A., Wessel, A.R., Williams, A.,

Kurian, S.M., White, F.A., 2019a. Towards precision medicine for pain: diagnostic biomarkers and repurposed drugs. Mol. Psychiatr. 24, 501–522.

Niculescu, A.B., Le-Niculescu, H., Roseberry, K., Wang, S., Hart, J., Kaur, A., Robertson, H., Jones, T., Strasburger, A., Williams, A., Kurian, S.M., Lamb, B., Shekhar, A., Lahiri, D.K., Saykin, A.J., 2019b. Blood biomarkers for memory: toward early detection of risk for Alzheimer disease, pharmacogenomics, and repurposed drugs. Mol. Psychiatr.

Niculescu, A.B., Levey, D.F., Phalen, P.L., Le-Niculescu, H., Dainton, H.D., Jain, N., Belanger, E., James, A., George, S., Weber, H., Graham, D.L., Schweitzer, R., Ladd, T.B., Learman, R., Niculescu, E.M., Vanipenta, N.P., Khan, F.N., Mullen, J., Shankar, G., Cook, S., Humbert, C., Ballew, A., Yard, M., Gelbart, T., Shekhar, A., Schork, N.J., Kurian, S.M., Sandusky, G.E., Salomon, D.R., 2015. Understanding and predicting suicidality using a combined genomic and clinical risk assessment approach. Mol. Psychiatr. 20, 1266–1285.

Ogden, C.A., Rich, M.E., Schork, N.J., Paulus, M.P., Geyer, M.A., Lohr, J.B., Kuczenski, R., Niculescu, A.B., 2004. Candidate genes, pathways and mechanisms for bipolar (manic-depressive) and related disorders: an expanded convergent functional genomics approach. Mol. Psychiatr. 9, 1007–1029.

Otowa, T., Kawamura, Y., Tsutsumi, A., Kawakami, N., Kan, C., Shimada, T., Umekage, T., Kasai, K., Tokunaga, K., Sasaki, T., 2016. The first pilot genome-wide gene-environment study of depression in the Japanese population. PloS One 11, e0160823.

Pajvani, U.B., Accili, D., 2015. The new biology of diabetes. Diabetologia 58, 2459–2468.

Pan, X., Baldauf, H.M., Keppler, O.T., Fackler, O.T., 2013. Restrictions to HIV-1 replication in resting CD4+ T lymphocytes. Cell Res. 23, 876–885.

Patel, S.D., Le-Niculescu, H., Koller, D.L., Green, S.D., Lahiri, D.K., McMahon, F.J., Nurnberger Jr., J.I., Niculescu 3rd, A.B., 2010. Coming to grips with complex disorders: genetic risk prediction in bipolar disorder using panels of genes identified through convergent functional genomics. Am. J. Med. Genet. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics 153B, 850–877.

Plant, D.T., Pawlby, S., Pariante, C.M., Jones, F.W., 2018. When one childhood meets another - maternal childhood trauma and offspring child psychopathology: a systematic review. Clin. Child Psychol. Psychiatr. 23, 483–500.

Provencal, N., Arloth, J., Cattaneo, A., Anacker, C., Cattane, N., Wiechmann, T., Roh, S., Kodel, M., Klengel, T., Czamara, D., Muller, N.S., Lahti, J., team, P., Raikkonen, K., Pariante, C.M., Binder, E.B., 2019. Glucocorticoid exposure during hippocampal neurogenesis primes future stress response by inducing changes in DNA methylation. Proc. Natl. Acad. Sci. U. S. A.

Raison, C.L., Capuron, L., Miller, A.H., 2006. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 27, 24–31.

Raison, C.L., Knight, J.M., Pariante, C., 2018. Interleukin (IL)-6: a good kid hanging out with bad friends (and why sauna is good for health). Brain Behav. Immun. 73, 1–2.

Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 70, 31–41.

Rangaraju, S., Levey, D.F., Nho, K., Jain, N., Andrews, K.D., Le-Niculescu, H., Salomon, D.R., Saykin, A.J., Petrascheck, M., Niculescu, A.B., 2016. Mood, stress and longevity: convergence on ANK3. Mol. Psychiatr. 21, 1037–1049.

Razoux, F., Russig, H., Mueggler, T., Baltes, C., Dikaiou, K., Rudin, M., Mansuy, I.M., 2017. Transgenerational disruption of functional 5-HT1AR-induced connectivity in the adult mouse brain by traumatic stress in early life. Mol. Psychiatr. 22, 519–526.

Rodd, Z.A., Bertsch, B.A., Strother, W.N., Le-Niculescu, H., Balaraman, Y., Hayden, E., Jerome, R.E., Lumeng, L., Nurnberger Jr., J.I., Edenberg, H.J., McBride, W.J., Niculescu, A.B., 2007. Candidate genes, pathways and mechanisms for alcoholism: an expanded convergent functional genomics approach. Pharmacogenomics J. 7, 222–256.

Rosa, M.J., Lee, A.G., Wright, R.J., 2018. Evidence establishing a link between prenatal and early-life stress and asthma development. Curr. Opin. Allergy Clin. Immunol. 18, 148–158.

Roux, A., Leroy, H., De Muylder, B., Bracq, L., Oussous, S., Dusanter-Fourt, I., Chougui, G., Tacine, R., Randriamampita, C., Desjardins, D., Le Grand, R., Bouillaud, F., Benichou, S., Margottin-Goguet, F., Cheynier, R., Bismuth, G., Mangeney, M., 2019. FOXO1 transcription factor plays a key role in T cell-HIV-1 interaction. PLoS Pathog. 15, e1007669.

Scarpa, J.R., Jiang, P., Gao, V.D., Fitzpatrick, K., Millstein, J., Olker, C., Gotter, A., Winrow, C.J., Renger, J.J., Kasarskis, A., Turek, F.W., Vitaterna, M.H., 2018. Cross-species systems analysis identifies gene networks differentially altered by sleep loss and depression. Sci Adv 4, eaat1294.

Shadrina, M., Bondarenko, E.A., Slominsky, P.A., 2018. Genetics factors in major depression disease. Front. Psychiatr. 9, 334.

Slavich, G.M., Irwin, M.R., 2014. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol. Bull. 140, 774–815.

Smoller, J.W., 2016. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology 41, 297–319.

Stilo, S.A., Gayer-Anderson, C., Beards, S., Hubbard, K., Onyejiaka, A., Keraite, A., Borges, S., Mondelli, V., Dazzan, P., Pariante, C., Di Forti, M., Murray, R.M., Morgan, C., 2017. Further evidence of a cumulative effect of social disadvantage on risk of psychosis. Psychol. Med. 47, 913–924.

Trinite, B., Chan, C.N., Lee, C.S., Mahajan, S., Luo, Y., Muesing, M.A., Folkvord, J.M., Pham, M., Connick, E., Levy, D.N., 2014. Suppression of Foxo1 activity and down-modulation of CD62L (L-selectin) in HIV-1 infected resting CD4 T cells. PloS One 9, e110719.

Uher, R., Caspi, A., Houts, R., Sugden, K., Williams, B., Poulton, R., Moffitt, T.E., 2011. Serotonin transporter gene moderates childhood maltreatment's effects on persistent

but not single-episode depression: replications and implications for resolving inconsistent results. J. Affect. Disord. 135, 56–65.

Wang, S., Xia, P., Huang, G., Zhu, P., Liu, J., Ye, B., Du, Y., Fan, Z., 2016. FoxO1-mediated autophagy is required for NK cell development and innate immunity. Nat. Commun. 7, 11023.

Wetsman, N., 2019. Finding narrative in a scientific field: understanding the relationship between the immune system and psychiatric illness. Brain Behav. Immun. 77, 1–2.

Willsey, A.J., Morris, M.T., Wang, S., Willsey, H.R., Sun, N., Teerikorpi, N., Baum, T.B., Cagney, G., Bender, K.J., Desai, T.A., Srivastava, D., Davis, G.W., Doudna, J., Chang, E., Sohal, V., Lowenstein, D.H., Li, H., Agard, D., Keiser, M.J., Shoichet, B., von Zastrow, M., Mucke, L., Finkbeiner, S., Gan, L., Sestan, N., Ward, M.E., Huttenhain, R., Nowakowski, T.J., Bellen, H.J., Frank, L.M., Khokha, M.K., Lifton, R.P., Kampmann, M., Ideker, T., State, M.W., Krogan, N.J., 2018. The psychiatric cell Map initiative: a convergent systems biological approach to illuminating key molecular pathways in neuropsychiatric disorders. Cell 174, 505–520.

Xing, Y.Q., Li, A., Yang, Y., Li, X.X., Zhang, L.N., Guo, H.C., 2018. The regulation of FOXO1 and its role in disease progression. Life Sci. 193, 124–131.

Zou, P., Liu, L., Zheng, L., Liu, L., Stoneman, R.E., Cho, A., Emery, A., Gilbert, E.R., Cheng, Z., 2014. Targeting FoxO1 with AS1842856 suppresses adipogenesis. Cell Cycle 13, 3759–3767.

Zunszain, P.A., Anacker, C., Cattaneo, A., Choudhury, S., Musaelyan, K., Myint, A.M., Thuret, S., Price, J., Pariante, C.M., 2012. Interleukin-1beta: a new regulator of the kynurenine pathway affecting human hippocampal neurogenesis. Neuropsychopharmacology 37, 939–949.