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Synaptic proteomics as a means to identify the molecular basis of mental illness: Are we getting there?

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ABSTRACT

Synapses are centrally involved in many brain disorders, particularly in psychiatric and neurodevelopmental ones. However, our current understanding of the proteomic alterations affecting synaptic performance in the majority of mental illnesses is limited. As a result, novel pharmacotherapies with improved neurological efficacy have been scarce over the past decades. The main goal of synaptic proteomics in the context of mental illnesses is to identify dysregulated molecular mechanisms underlying these conditions. Here we reviewed and performed a meta-analysis of previous neuroproteomic research to identify proteins that may be consistently dysregulated in one or several mental disorders. Notably, we found very few proteins reproducibly altered among independent experiments for any given condition or between conditions, indicating that we are still far from identifying key pathophysiological mechanisms of mental illness. We suggest that future research in the field will require higher levels of standardization and larger-scale experiments to address the challenge posed by biological and methodological variability. We strongly believe that more resources should be placed in this field as the need to identify the molecular roots of mental illnesses is highly pressing.

1. Introduction

During the past fifteen years, proteomics research has exposed the molecular complexity of the synapse to a great level of detail (Bayés and Grant, 2009; Dieterich and Kreutz, 2015; Distler et al., 2014). This collective effort has resulted in a very comprehensive catalogue of proteins with a putative synaptic function. This is particularly true in the case of forebrain glutamatergic synapses. The current atlas of synaptic proteins makes it now much easier to move the field of synaptic neuroproteomics into the realm of functional systems biology and disease-oriented research. In our opinion, the future challenges in the field will deal with delineating the dynamics of the synaptic proteome rather than with the enumeration of its components. Developing the means to efficiently characterise the changes occurring to the synaptic proteome in the context of mental illnesses should importantly contribute identifying the key molecular alterations behind these conditions.

Unlike the genome, the proteome and the transcriptome are highly dynamic systems. The ultimate goal of proteomics and transcriptomics is to unravel the molecular mechanisms governing biological processes. While transcriptomics is much more of an 'omics' science, as it can provide quantitative information of all RNA molecules in a given sample, proteomics can still only identify a fraction of all proteins in a mixture (for review see, (O. T. Schubert et al., 2017). Unfortunately, as RNA and protein abundances are weakly correlated (Gry et al., 2009; Maier et al., 2009), it is not possible to get a bona fide view of the proteome on the basis of transcriptomic data. Thus, despite their current limitations, biochemical and mass spectrometry-based proteomic methods may stand as the best approach to directly study the effector mechanisms that operate in cellular systems.

Large-scale genomic projects are identifying many genes coding for proteins with prominent synaptic functions as strongly associated with mental disorders (Fromer et al., 2014; Kirov et al., 2011; Sullivan et al., 2012). Furthermore, our research, together with that of other groups, has shown that synaptic supramolecular protein complexes, such as the postsynaptic density (Bayés et al., 2011; Focking et al., 2015) and the complexes within it (Bayés et al., 2014; Fernandez et al., 2009), are highly enriched in proteins encoded by genes mutated in mental illnesses. This is particularly the case for genes related to intellectual

Abbreviations: ASD, Autism spectrum disorders; FXS, Fragile-X Syndrome; LC, liquid chromatography; MS, mass spectrometry; PPI, protein-protein interaction; PSD, postsynaptic density; 2D, two dimensions

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Table 1
Scientific articles included in the meta-analysis.

#	Disorder	Reference
1	Anxiety	(Szegő et al., 2010)
2	Anxiety	(Filiou et al., 2011)
3	Anxiety	(Kennedy et al., 2016)
4	Anxiety	(Mairesse et al., 2012)
5	Bipolar Disor./Schizophr./Depression	(Beasley et al., 2006)
6	Bipolar Disor./Schizophr./Depression	(Johnston-Wilson et al., 2000)
7	Bipolar Disorder/Schizophrenia	(Behan et al., 2008)
8	Bipolar Disorder/Schizophrenia	(Chan et al., 2010)
9	Bipolar Disorder/Schizophrenia	(Focking et al., 2011)
10	Bipolar Disorder	(Focking et al., 2016)
11	Bipolar Disorder/Schizophrenia	(Pennington et al., 2007)
12	Bipolar Disorder/Schizophrenia	(K. O. Schubert et al., 2015)
13	Schizophrenia	(Focking et al., 2015)
14	Depression	(Alexander et al., 2016)
15	Depression/Antidepressant treatment	(Bisgaard et al., 2012)
16	Depression	(Carboni et al., 2006)
17	Depression	(Han et al., 2015)
18	Depression	(Henningsen et al., 2012)
19	Depression	(Hu et al., 2013)
20	Depression/Antidepressant treatment	(Kedracka-Krok et al., 2010)
21	Depression	(Kim and Kim, 2007)
22	Depression	(Knapman et al., 2012)
23	Depression	(Li et al., 2013)
24	Depression	(Liu et al., 2011)
25	Depression/Antidepressant treatment	(Mallei et al., 2010)
26	Depression	(Mallei et al., 2015)
27	Depression/Antidepressant treatment	(Marais et al., 2009)
28	Depression	(Martins-de-Souza et al., 2012)
29	Depression	(Mu et al., 2007)
30	Depression	(Ning et al., 2017)
31	Depression	(Palmfeldt et al., 2016)
32	Depression	(Völgyi et al., 2016)
33	Depression	(Wei et al., 2015a, 2015b)
34	Depression	(Yang et al., 2013)
35	Depression	(Zhou et al., 2016)
36	Depression	(Piubelli et al., 2011b)
37	Depression	(Piubelli et al., 2011c)
38	Depression	(Piubelli et al., 2011a)
39	None//Antidepressant treatment	(Khawaja et al., 2004)
40	None//Antidepressant treatment	(Wesseling et al., 2015)
41	ASD	(Györffy et al., 2016)
42	ASD	(Reim et al., 2017)
43	ASD	(Wei et al., 2015a, 2015b)
44	FXS	(Klemmer et al., 2011)
45	FXS	(Liao et al., 2008)
46	FXS	(Tang et al., 2015)

disability, Autism Spectrum Disorders and Schizophrenia. Thus, the study of the synaptic proteome has become particularly relevant to those research projects directed at identifying the molecular pathophysiology underlying these conditions, key first step in the future development of pharmacological treatments. As several other scientific disciplines, synaptic proteomics aims at unravelling molecular mechanisms involved in disease. Its uniqueness resides in the fact that it does so by targeting hundreds of different proteins, in a non-aprioristic manner. This strategy allows identifying unexpected molecular alterations, being particularly useful in those fields of research where our understanding of the molecular pathophysiology is scarce, such as in mental illnesses. Detecting clinically relevant molecular mechanisms should have a tremendous impact in pharmacotherapy, as we would know which proteins or signalling pathways to interfere with in a given condition.

In this article we have reviewed the main proteomics research on mental illness, with a focus on those proteins known to play a synaptic role. We have specifically looked for synaptic proteins presenting altered expression levels in more than one study, with the ultimate goal of identifying the central molecular pathology related to these conditions. Importantly, it must be acknowledged that the outcome of this analysis is conditioned by the fact that the number of proteomics articles on mental illnesses is limited (we herein report 46, Table 1). Furthermore, very few of them, if any, strictly replicate previous work. Indeed, new articles always present changes over past research, including the brain region investigated, the animal model used, the tissue processing strategy used or the mass spectrometry method applied (see Supplementary Table 1). Yet, it is fair to reason that proteins found to be dysregulated in the same manner in independent studies are more likely to be pathophysiologically relevant than those that don't. Thus, the analysis presented in this review is sustained on the hypothesis that robust molecular alterations can be reproduced despite intrinsic experimental variation between studies.

2. Methodology

We selected a total of 46 articles performing high-throughput proteomics research on mental illnesses (Table 1). These spanned six different conditions that we have classified into Psychiatric Disorders (i.e. Anxiety, Bipolar Disorder, Depression and Schizophrenia) and Neurodevelopmental Disorders (i.e. Autism Spectrum Disorders and Fragile X-syndrome). Furthermore, we have also looked for articles on these six conditions that report the effect of drugs on the synaptic proteome. A sufficient number of these could only be found for Depression. Finally, we have also considered proteomics articles analysing the effect of

Table 2
Number of experiments and differentially expressed proteins for each mental illness.

	Experiments						Differentially expressed proteins			
	Whole tissue			Synapse			Whole tissue		Synapse	
	Human PM[a]	Mouse	Rat	Human PM[a]	Mouse	Rat	Up-regulated	Down-regulated	Up-regulated	Down-regulated
Psychiatric disorders										
Anxiety	0	1	1	0	2	0	48	58	203	113
Bipolar disorder	7	0	0	1	0	0	80	72	166	116
Depression	3	2	11	0	1	9	207	130	93	135
Depression (pharmacology)[b]	0	0	25	0	0	2	195	198	1	8
Schizophrenia	7	0	0	1	0	0	63	59	57	79
Neurodevelopmental disorders										
Autism spectrum disorders	0	1	0	0	2	1	53	66	72	114
Fragile-X syndrome	0	0	0	0	3	0	0	0	528	138
Drug effect on controls										
Antidepressants	0	0	5	0	0	2	53	29	6	7

[a] PM, post-mortem.
[b] Effect of antidepressant drugs in brain and synaptic proteomes.